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Interrelations of the endocrine organs

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INTERRELATIONS OF THE ENDOCRINE ORGANS

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INTERRELATIONS OF THE ENDOCRINE ORGANS.

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INTERRELATIONS OF THE ENDOCRINE ORGANS.

Much has been asserted, but comparatively little proved, about the interdependence of the endocrine organs. That they are classified as of the same type does not necessarily signify that they have any definite relation; so most careful investigation has been needed to determine the exact bearing of one ductless gland on the others. Some of these relationships have been guessed at by the clinicians; perhaps the most exhaustive and reliable data, however, have come from the animal experimenters.

The endocrine system consists of an undetermined number of glands, some of which have other functions than the one of internal secretion. The endocrine activities of the glands are so varied that no distinct classification of functions can be made. In a general way, however, certain glands may be classified as those of growth and nutrition. These are: the pancreas, which secretes insulin from specialised cells to regulate the sugar mobilization from storage centers, or the sugar assimilation by the cells; the adrenal medulla, whose adrenalin is thought by some to influence the use of sugar; the thyroid, the thyroxin (Kendall), or iodin of which keeps up metabolism, especially that of protein; the anterior pituitary, whose secretion, tethelin, stimulates the metabolic and growth rate. Other glands are characterised by their influence on morphogenesis. Of these, the

interstitial sex secretion controls the development of the secondary sex characters, - the growth of the skeleton, hair, mature voice, etc. The thyroid also is associated with the development of the skeleton, the nervous system, and sex glands, and, in the lower animals at least, gives permanence to the secondary sex characters. The pituitary has to do with the growth of the skeleton and connective tissue, and the establishing of sex maturity. The thymus, though not distinctly an endocrine organ, prevents the premature development of the sex glands. The pineal also inhibits the growth and development of the gonads during the pre-pubertal years.
The third grouping of glands is those with regulating or stimulating functions. They are: the thyroid, which has a general stimulating effect on the gonads and other tissues; the posterior pituitary, whose pituitrin is said to stimulate the milk secretion; while it is known to cause contraction of the uterus, blood vessels, etc.; the gonads, either the interstitial of follicular portion of which in the female causes menstruation, and the interstitial cells in the male stimulate the bodily processes; the myometrial gland or fetus, which may have to do with milk secretion and prevention of ovulation; the adrenal cortex which is related to sex activities, especially in the female; and, more generally, the whole adrenal, which affects all the sympathetic nervous system, giving the physical expressions to the emotions. Then the glands classified as having anti-toxic functions are the liver, which transforms toxic products into non-toxic; the parathyroids, which take care

of the acid-base equilibrium; and the thyroid, whose detoxicating power is due to its quickening of body activites, etc.

These functions are to all appearances normally performed by the individual gland. But in special cases, normally or abnormally, there is some interrelation, - compensation or antagonism, - among the endocrine organs. It is with the more evident of these interactions that this paper essays to deal.

In general, some relation may be due to the fact that many of the endocrine glands have, through evolution, developed from the same source, - nephridia. In the higher animals, the excretory function being largely localized in the kidneys, some former nephridia have assumed endocrine functions and become the thyroid, parathyroids, thymus, pituitary, and pineal. (Brown). The most generally accepted belief of the derivation of the two latter glands is, however, that the pituitary is an outgrowth of the brain, with the outer portion derived from the ectoderm; and that the pineal is a similar outgrowth, and, biologically, a functionless third eye. All these changed nephridia have lost their ducts through the modifying effects of the new alimentary tract. (Brown). What part this fact may play in indicating the correlation of those glands we shall note in the treatment of the individual endocrines.

1. THYROID.

Biologically, the thyroid is a pair of modified nephridia of the mesosomatic region, in common with the tonsils, parathyroids, and thymus. Its former excretory func-

tion is still indicated by the presence of iodin in the thyroid secretion, - iodin is a modified excretory product.

a. Relation to parathyroids.

Vincent notes that in thyroidectomy, the parathyroids develop vesicles like the thyroid. Others have indicated that the parathyroids hypertrophy in thyroid removal. Howard has even reported that tetany, caused by parathyroidectomy, has been known to occur in thyroid diseases. These facts would all bear out the biological development theory of interrelation. No experiments, however, are sufficiently conclusive, as imperfect excision of the thyroid, or interference with the parathyroid blood supply, might bring about these results.

b. Relation to thymus.

The closeness of biological and embryological development may be significant in the connection between thyroid and thymus, if there is one. A mutual relation is thought by some investigators to exist. Experimentally, feeding thyroid to pregnant animals results in enlarged thymus in the fetus. (Schafer). Then, lack of thyroid secretion inhibits the thymus growth in albino rats. (Hammett, '23). Clinical observation by Cappelle, Pappenheimer, and others, has shown that in Grave's disease (hyperthyroidism), the thymus is often enlarged; while in simple congenital goiter, according to Birnbaum, the same condition may exist. In 73 percent of 74 studies of exophthalmic goiter, Markham and others found hypertrophy of the thymus. Dustin and Zung, in a recent study of war

victims, discovered that in case of reduced thyroid the thymus was enlarged, and vice versa. While most of these facts illustrate compensation, the relationship is by no means clearly defined.

c. Relation to pituitary.

Embryologically, both thyroid and posterior pituitary arise from the entoderm lining the floor of the pharynx, and are closely associated until the third month of fetal life. In the human system, there is also a close neural relation, the stimulation of the sympathetic nerves increasing the output of the thyroid, pituitary, and adrenals. (Faught and Ryan).

The endocrine relation has been the subject of much experimentation. When the thyroidectomy is performed on animals, the pituitary usually hypertrophies. In experiments on tadpoles, colloid masses like the thyroid developed in the anterior pituitary, and the secretions of all parts of the pituitary were increased. (Hoskins and Hoskins) Herring, however, found no change in the anterior lobe, but increase in the pars intermedia, with colloid formation. In other animals, dogs and goats, enlargement of the pituitary was reported by Kamo. Izumi ('23), too, discovered that in cats, thyroidectomy causes hypertrophy of the anterior and posterior lobes, but not of pars intermedia. The intimate compensatory effect of thyroid and pituitary is further borne out by the experiment of Hogben, '23, on Axolotls. These amphibians are found usually

in the larval stage, only in rare occasions metamorphosing. The conditions necessary for metamorphosis had been for a long time more or less of a puzzle, until recent work disclosed it of endocrine influence. The curiosity about the animals is that the gonads are functional while the body retains the larval appearance. On these sex-mature larvae, Hogben performed thyroidectomy, and then injected anterior lobe pituitary extract. They metamorphosed as quickly as though they had been given thyroid, developing into the salamander Ambystoma, a terrestrail form, without gills or fins. The reverse process was also tried. Hypophysectomized larvae, which had lost their pigment as a result of loss of pituitary, were fed thyroid of a cat, and metamorphosed. Smith, however, did not obtain these results in his experiments. Trautmann, also, had negative results on goats. In thyroidectomy, he could determine no hypertrophy of the pituitary, but on the other hand, indications of regression.

The inhibitory effect of thyroid on pituitary is indicated by Livingston , when thyroid feeding was shown to prevent increase in the size of the pituitary after thyroidectomy. The usual enlargement of the pituitary after thyroidectomy may, then, be the lack of the restraining influence of thyroid on pituitary, or the tendency of the hypophysis to try to compensate for thyroid deficiency.

d. Relation to adrenals.

Biologically, the thyroid has a common origin with

the adrenal cortex, both coming from nephridia. There is no evolutionary relation with the medulla, that being a mass of chromaffin cells, similar to cells in other parts of the body.

Experimentally a relation has been indicated between the thyroid and adrenals. Hoskins, Herring, and Hewitt recently discovered that thyroid feeding in animals caused an increase in the weight of the adrenals. Hoskins's guinea-pigs showed adrenal weight 25 percent more than normal, after thyroid feeding had proceeded from birth for 15 days. Herring, with cats, found the cortex more markedly hypertrophied. Herring, also, working on the epinephrin store, found it to be increased by thyroid feeding, and decreased by thyroidectomy. Other investigators have failed to support his discoveries, however. Carlson, for one, obtained in thyroidectomy hypertrophy of the adrenals. But Hammett ('23) found lack of thyroid secretion to inhibit the growth of the adrenals in albino rats of both sexes. So the question is still in the air. Cannon found by certain action currents that stimulation of the adrenal produced an action current in the thyroid, indicating secretion there also. That fact may explain some of the concomitant and supplementary activities of the two.

Clinically, Krause found that in exophthalmic goiter patients, the blood serum caused dilation of the pupil of the extirpated eye of a frog, while normal blood serum has no such effect. Furthermore the symptoms in hyperthyroidism, - over excitation of the sympathetic mechanism, - are similar to those

caused by adrenalin. In Grave's disease, for instance, there are indications of adrenalin disorders, - pigment, diarrhea, etc. The blood here contains, according to Fraenkel, four to eight times the amount of normal adrenalin. The whole relationship may exist, however, solely through the thyroid effect in stimulating the nervous system, and hence the secretion of adrenalin.

e. Relation to Gonads.

Biological evidence points to the fact that a close relationship formerly existed between the thyroid and sex glands, especially in the female. In paleostracans, for instance, the thyroid gland was the uterine gland. The relation is borne out experimentally. Long and Hofmeister performed thyroidectomy on animals with the result that it depressed sex functions. Ceni found that thyroidless hens laid less eggs. Albino rats, after removal of thyroids and parathyroids, indicate cessation of growth and loss of weight in the ovary and uterus; the testes and epididymis, however, are hardly affected. (Hammett, '23). Alquier and Theuvemy reported in the dog a diminished production of sperm after thyroidectomy. In the female the change in the ovary was not so marked, but there was less appearance of heat, and difficulty of conception. In most of these cases, however, the result may have come merely from lowered metabolism.

From the clinical angle, the evidence is perhaps more voluminous. The thyroid enlarges at puberty, and during

menstruation, sexual intercourse, and pregnancy. Deficiency of thyroid in youth prevents the normal sex development, as the Cretins so vividly illustrate; or with less severe hypothyroidism, sexual infantilism is the result. An enlarged thyroid is generally accompanied by precocious sex development, while thyroidectomy is followed by atrophy of the uterus. Hypo- and hyper-thyroidism both cause menstrual disturbances. That thyroid and sex are closely connected is further illustrated by the fact that thyroid diseases are several times more frequent in women than in men, and that the symptoms frequently begin in pregnancy, or during lactation. In exophthalmic goiter, atrophy of the gonads is found, or, in a goiter of long standing, subnormal genital development. The clinical contribution is sufficient to indicate an interrelation of thyroid and gonads, though the exact effect, whether through general metabolic stimulation, or other channels, is not clearly demonstrated.

f. Relation to pancreas.

The thyroid secretion has apparently an antagonistic effect on the pancreatic internal secretion. In Lorand's work, after excision of the pancreas, with its resulting glycosuria, the removal of the thyroid caused the sugar to disappear. The antagonism is further indicated in Grave's disease, where there is increased tendency to glycosuria, due, supposedly, to the inhibition of the pancreas by the thyroid. In the reverse condition, hypothyroidism, (myxoedema, etc.), there is increased tolerance for sugar.

THYROID

In disease of the pancreas there are symptoms of thyroid overactivity (eyes, etc.) which might indicate that the thyroid was at fault. However, the relation of the thyroid and pancreas is not at all well defined.

g. Relation to endocrine system.

The thyroid, then, has an effect on all the other endocrine organs; if not a specific reaction, at least the one of influencing their metabolism, and hence activity.

2. PITUITARY.

The pituitary secretions are of two, and perhaps three distinct natures, the anterior lobe, the posterior lobe, and the intermediate portion. Nevertheless, the pituitary acts as one body. The secretions may be measured histologically, the presence of certain kinds of cells signifying the amount of the secretion. In the anterior lobe, chromophobe cells are the active secretors; basophil cells are the storage variety, which, when they yield up their tethelin, become the eosinophils; these again begin to store until they are basophils, and so on. Injecting anterior pituitary in guinea-pigs results in over-secretion of the anterior lobe,- more chromophobe cells. Feeding pituitary gives more eosinophil cells, perhaps having caused the basophils to give up their storage. (Blair Bell).

a. Relation to thyroid.

A large amount of experimental work has been done in this field, the most fascinating of which has, perhaps, been with the amphibians. It has been possible with them to ex-

tirpate the pituitary at all stages of the embryo, where in mammals such procedure is out of the question until after birth, when the animal is well along in its development. Swingle, with about five millimeter frog embryos, removed the pituitary and reared the tadpoles. They never metamorphosed. Examination proved that the thyroid had never developed. Giving pituitary, however, caused their metamorphosis, because it stimulated the development of the backward thyroid. Smith, also removed the hypophysis in tadpoles, with a resulting underdevelopment of thyroid tissue, - the gland was five times smaller than usual, and inactive, so that metamorphosis never occurred. With the injection of bovine pituitary substance, the beginning of metamorphosis occurs within twenty-four hours. Feeding does not give these results. When a small amount of hypophysis is injected, the thyroid develops to its normal size. When much additional gland is given, the thyroid becomes greatly enlarged. When the thyroid is removed from tadpoles, feeding pituitary causes the beginning of metamorphosis. (Hoskins and Hoskins). Feeding pituitary to normal larvae causes precocious metamorphosis, due, perhaps, to the effect on the thyroid. Another example of the pituitary-thyroid relationship is the case of bull and green frogs. In these animals, metamorphosis does not naturally take place for one or two years. The thyroid is underdeveloped and comparatively inactive. Transplanting anterior pituitary from adults into immature larvae, however, causes

the development of the thyroid, and hence metamorphosis. The prolonged larval period is, then, apparently due to the lack of stimulation of the thyroid by the pituitary. This evidence and various other experiments would indicate, in amphibia, at least, a well-marked correlation of thyroid and pituitary.

With other animals there is less definiteness of relationship. In mammals, Houssay and Hug hypophysectomized eleven lots of puppies. The result in the thyroid was diminution to a very thin epithelium. In removing the pituitary from higher animals, Cushing and others found the thyroid at first hypertrophied. But afterwards there was functional regression of the gland, - more colloid and greater size, but less secretion. While, however, pituitary, particularly anterior lobe, seems to compensate for thyroid, the two glands do not act vicariously. Simpson and Hunter show that the pituitary does not have iodin after thyroidectomy. And pituitary preparation does not take the place of thyroid in cachexia, nor can it be used to treat goiter and myxoedema.

b. Relation of anterior lobe to gonads.

This relationship is perhaps the most secure of any. Experimentally and clinically, the intimacy of anterior pituitary and gonads seems to hold true.

Aschner, removing the pituitary of young animals, found marked interference with genital development. Either the sex apparatus did not develop, or regressed in formation. The sex glands of both male and female were affected, no further

spermatogenesis in the male, and cessation of ovulation in the female. Cushing reports that in partial hypophysectomy the animal suffers atrophy of the reproductive gland, with sterility, impotence, etc., and modification of most of the other ductless glands. In the puppy there is diminution of the interstitial cells, fatty degeneration setting in. Female dogs, after hypophysectomy, never come to heat. Puppies of both sexes, with the whole gland removed, never develop sexually. Bell gives similar results of the disappearance of interstitial cells and the degeneration of ova in pituitary removal. These results come only with the loss of the anterior lobe, - posterior extirpation has no effect on the development of the ovary, though it is thought, from limited experiment, that pregnancy is not then possible.

Hyperpituitarism, or early tumors, has the opposite effect of hypophysectomy, as one might suppose. There is sexual precocity, the interstitial cells developing in greater proportion than the germinal part. (Davis). Pituitary administration or excitation likewise increases sex activity. Evans and Long ('23) injecting intraperitoneally fresh anterior hypophysis in rats, caused the ovaries to develop to twice their normal size, and to have an increased number of corpora lutea. The uterus, however, was but half the normal weight, and oestrus occurred very infrequently. Posterior pituitary similarly injected has no such effects. Goetsch fed his rats with whole gland, with the result that the genital tract developed more rapidly. The sex glands also indicated greater

activity, the germinal portion showing earlier ovulation, and the interstitial portion increase in volume. Similar results were obtained in the male, - earlier genital tract development, and earlier gland maturity. With continued feeding, not only the physical organism, but the sex instinct ripened early. Adult rats fed with anterior substance increased the frequency of breeding and number of offspring, - the longer the feeding the greater the effect. Pituitary feeding was supposed to increase the egg-laying of hens; but Simpson ('20 and also '23) reported negative results on his experiments.

Clinically, the anterior pituitary has a striking effect on the gonads. Changes in the pituitary are concomitant with changes in the gonadal system. It is observed that the pituitary, like the sex organs, atrophies in old age. In the female the pituitary enlarges at menstruation, and during pregnancy. In the latter condition, there appear in the anterior lobe large cells, uniformly distributed. There is also underfunction of the pituitary in some common cases of gonad disorders.

One or two monstrosities in the clinical field are of the pituitary-gonad type. The defect of dystrophia adiposogenitalia, is a primary pituitary disorder, with secondary effects on the gonads. It brings about in the male a skeleton built on feminine lines, feminine hair distribution, and superfluity of fat. There is distinct underdevelopment

of the gonads, in both male and female. The cause may be traced to the hypo-function of the anterior pituitary, by tumor or disease, etc. Treatment by administration of the gland has done a great deal in restoring sex functions, and curing accompanying deficiencies, as blindness.

The opposite of dystrophia adiposogenitilia, in cause, and some of its symptoms, is acromegaly. It is caused by overgrowth of the pituitary, and hypersecretion of the anterior lobe particularly. The beginning is sometimes in pregnancy, when the hypophysis is naturally hypertrophied. The increased anterior secretion has an apparent effect on the interstitial cells, which multiply and cause an exaggeration of male characteristics. The female takes on the male type of hair, breasts, and pelvis. In the first stages of acromegaly, there is an increased sex activity; but before long the male becomes impotent, the female sterile. Acromegaly, then, indicates a close connection between anterior pituitary and gonad activity.

c. Posterior pituitary to gonads.

In male dogs, after partial posterior extirpation there is persistent sex excitement; feeding posterior lobe extracts, on the other hand, retards the activity of the testes. (Davis). For the most part, however, the posterior pituitary is connected with female sex functions. It causes uterine contraction, hence aids in parturition. Hofstaetter found that after administration of long duration, the mammary glands were

developed. This is questionable in the light of Bell's work, which indicated no mammary enlargement in virgin animals. The increased milk secretion which is sometimes claimed as a result of posterior pituitary extract was reported by Gains to be only the constriction of the smooth muscle of the glands, and not at all an increased flow of milk.

d. Relation to adrenals.

The effect of pituitary on the adrenals is not clearly known. In hypophysectomized tadpoles, the adrenal cortex is greatly decreased. The deficiency does not appear in thyroidectomized larvae; hence lowered metabolism, or other effect of thyroid decrease, is not the cause. (Smith and Smith). Albino rats injected with anterior ox pituitary gave a pronounced response of the adrenals. The adrenal cortex, before small in quantity, became normal in amount. (P.E.Smith). This mutual effect is further shown by Gottleib. But Bell, feeding anterior lobe pituitary to guinea-pigs, found the suprarenal cortex vacoulated. Removing the pituitary gave the same results. Hence no conclusion on the nature of the relationship can be drawn.

The clinical findings add little of value. Cushing reports that in hyperplasia of the pituitary, in giants, the adrenals are particularly small and underfunctioning, - the outer indications being low blood pressure, low blood sugar, and excess pigment. Delille reports in one case of acromegaly the cortex of the adrenal was small, but the medulla enlarged.

PITUITARY

e. Relation to pancreas.

In hypopituitarism (posterior lobe) there is an increased tolerance for sugar. Cushing, for instance, finds the secretion of the pancreas is increased after partial or total hypophysectomy, - hence sugar assimilates more readily. Goetsch, in animals, removed all but a small part of the pancreas. After the temporary glycosuria had subsided, he performed partial hypophysectomy, including the posterior lobe. The animal had a temporary lowering, then an increase of the sugar assimilation limit, due apparently to loss of antagonism of the pancreas by the pituitary. Injecting infundibulum, according to Pemberton and Sweet, caused inhibition of pancreatic action. We may say, then, that pituitary represses the action of insulin.

f. Relation to the liver, and other organs.

In partial hypophysectomy on animals, there are fatty changes in the liver and many ductless glands. (Cushing).

3. ADRENALS.

These glands are biologically of two distinct origins, modified nephridia becoming the cortex, and chromaffin cells the medulla of the adrenals. The cortical portion arises embryologically from the mesonephric tubules. (Swale Vincent). The medullary tissue contains multipolar ganglionic cells, explaining perhaps the close connection with the sympathetic nervous system.

a. Relation to thyroid.

Faught and Ryan say that thyroid feeding or thyroid-

ectomy each produces hypertrophy of the adrenals. Hence the problem is much obscured. It is reported by Marine and Baumann that adrenal-cortex insufficiency caused rapid loss of iodin from the thyroid. Removal of the adrenals in cats causes depression of metabolism, perhaps due to the thyroid. (Aub).

b. Relation to gonads.

The evidence of this relationship is largely clinical. Embryologically, the suprarenal cortex and gonads are closely related, both arising from the urogenital fold, and both modified mesonephric tubules. When the cortex is hypertrophied, due to tumors or other diseases or disturbances, there is change in the ovaries or testes, particularly the interstitial portion. This modified part then exerts pronounced effects on the secondary sex characters. In young females, there is marked sex precocity in menstruation, development of mammae, and other phenomena, and also some addition of male characteristics. In the young male, the sex characters develop very early, a case being on record when a child of five had attained full sexual development. The cause was a gigantic tumor of the adrenal cortex. In adult females, cortex hypertrophy leads to alteration of the female to the male secondary sex characteristics. Such women acquire the male growth of hair, coarser voice, and their gonads undergo atrophy, menstruation ceases, and their mammary glands degenerate. Tumors of the medulla cause no such symptoms. The clinical evidence is sufficiently striking to mark a strong relationship of the adrenal cortex and gonads; although without experimental proof it may not be accepted by

some as final.

b. Relation to pancreas.

Adrenalin is rather generally believed to antagonize pancreatic action. A great many experiments have seemed to bear out that conclusion. Pemberton and Sweet, for instance, found that extirpation of the adrenals, removing the antagonism, brought about a large internal secretion of the pancreas. Applying adrenal solution directly to the pancreas, however, stopped the secretion. Frouin found pancreatic diabetes in a dog to diminish after the removal of one adrenal and two-thirds of another. Hédon has secured more recent results ('23). In two experiments dogs were depancreatized, producing typical diabetes. When adrenalin was injected, it caused an increased amount of sugar, higher than the average amount in experimental pancreatic diabetes. Allen, however, gives an interpretation other than the antagonism theory. He, too, finds that injections of adrenalin in depancreatized dogs cause much more sugar than in the controls. But that need not indicate antagonism of insulin by adrenalin. In the first place, diabetic victims show none of the symptoms of adrenal excess: there is no rise in blood pressure (in fact the blood pressure falls with the advance of the disease [Foster]), hair is normal, etc. Furthermore, different amounts of epinephrin act differently on the blood sugar, and the method of administrating it produces different results. Hence adrenalin has, according to Allen, no effect on the pancreas, nor on diabetes. Further experiments by him tend to the same conclusion. Dogs without the pancreas, hence with latent

diabetes, were injected with epinephrin for several consecutive days. No active diabetes was discerned. There was slightly more sugar than in normal controls with the same epinephrin injections. As a final conclusion from his experiments, Allen believes that the increase of sugar by adrenalin injections in depancreatized dogs is not due to the degeneration of islet cells, for such effect is not demonstrable; nor is it due to increased mobilization of sugar; but it is probably the effect of the glycogen breakdown of the injured cells, or the decomposition of epinephrin. That epinephrin is not at all essential to the production of diabetes is demonstrated by the experiments of Stewart and Rogoff. On a variety of animals, the adrenals were removed, as is possible in rabbits, monkeys, etc.; in others, one adrenal was removed, and the other denervated, so that epinephrin was not secreted. Hyperglycemia was in these cases caused by puncture of the medulla. That there is some relation between the pancreatic secretion and adrenalin, though it may play no part in diabetes, is demonstrated by the fact that adrenalin placed in the eye of a depancreatized animal will cause contraction of the radiating iris muscles, where in normal animals no such reaction can be shown. (Geikie Cobb). So the adrenals, to all appearances, inhibit the action of the pancreas.

4. GONADS.

The gonads consist of at least two distinct parts, the interstitial portion, arising, like the adrenals, from epithelial cells of the mesoderm; and the germinal part, differentiating later, and consisting of larger and modified epithelial

cells.

a. Relation of one part to another.

In the female, there are several distinct portions of the ovary having supposed internal secretion, - the interstitial part, the Graafian follicle, the corpus luteum of menstruation, and the corpus luteum of pregnancy. (Bandler). One may exert its influence on other parts of the ovary. Corpus luteal substance is, for instance, antagonistic to ovulation, demonstrated by Pearl and Surface, when extract of corpus luteum in fowl prevented ovulation. Similarly, corpus luteum is necessary in mammals for fixing the ovule in the uterus. This fact was shown by Fraenkel. In rabbits, removal of the ovary after the egg is fertilized, prevents its successful stay in the uterus. Cauterizing the corpora lutea of the ovary in mammals has the same effect as the removal of the entire gland, indicating the part which exerts the influence. The same results on dogs are found in the work of Marshall and Jolly. After the removal of the ovaries, the embryos were aborted. In only one case was the pup born, and here autopsy proved one or two corpora lutea to have been left behind in the operation. Work on rats gives the same results. Here, controls having part of the ovary remaining, bore the offspring as usual.

b. Relation to thyroid.

Experimentally, little has been done. In cows, the iodin content of the thyroid was found to be .073 percent, while in pregnant animals it was .088 percent. The thyroid was

hypertrophied, but there was no proof of hyperfunction. (Decio). Castration in animals causes first hypersecretion, but later diminished secretion of the thyroid. The connective tissue is augmented. (Schenk, '22).

In the clinical field, it is a fact of common observation that the thyroid enlarges in pregnancy and during menstruation, and at other times of marked action of the gonads. There is lowered action of the thyroid at the menopause. Castration in man gives symptoms (obesity, etc.) of lowered speed of his metabolism, due, perhaps, to the lack of stimulation of the thyroid by the gonads. Insufficiency of the gonads has, too, a part in exophthalmic goiter. (Barker).

c. Relation to pituitary.

The effect of the gonads on the pituitary is more easily demonstrated than on the thyroid. Castration of animals results in enlargement of the pituitary, particularly in the additional number of large oxyphil cells in the pars anterior. (Schafer). Izumi, working on rats ('23) found similar results, growth of the anterior portion, with "castration" cells derived from the eosinophils. The enlargement is not so great, however, as in thyroidectomy. (Bell). Livingston discovered that the changes of the pituitary in rabbits were more marked in the female than in the male. That such changes are directly due to the interstitial cells of the gonads has been demonstrated by Steinach and Scheidt. After castration, implanting in the person part of the ovary, only the interstitial portion of which survives intact, prevents the changes in the pituitary. Fichera

found hypertrophy of the anterior pituitary after castration in various animals, but there have been some negative results since then. Bell reports a triangular series of interactions in the thyroid, gonads and pituitary of the female. After thyroidectomy, the changes in the pituitary were greater in pregnant than in non-pregnant animals, the increased activity of the pituitary varying with the amount of thyroid left behind.

It is clinically known that the pituitary enlarges during pregnancy and at menstruation. In pregnancy the gland is about three times its normal weight. Bell suggests that enlargement of hands and lips during pregnancy may be the effect of hyperpituitarism. Furthermore, the menopause is accompanied with underfunctioning of the pituitary.

To sum up, the fact that both pregnancy and castration produce hypertrophy of the pituitary might indicate that the pituitary aids and compensates for gonadal secretion. (Bell).

d. Relation to adrenals.

There is a close embryological relation between the adrenal cortex and the gonads, as already noted. The gonad-adrenal cortex relationship is substantiated by many animal experiments. Gottschau found distinct cortex enlargement with birds and amphibians during the breeding season. It was shown by Watson that the cortex increased in moles during March, when the testes contained active spermatozoa; a second hypertrophy of the cortex occurred in October, apparently preparatory to the second litter. It was supposed by him that the cortex stores lipoids necessary to the production of sperm. Other experimenters

claim a medulla connection with the gonads. Riddle performed very careful experiments with birds, pigeons and doves. The females were killed a ranging, but known, number of hours before ovulation; and the weight of the cortex and medulla, as well as the other organs, was taken. Diseased birds were not included, as tuberculosis and other diseases cause enlargement of the adrenals. It was discovered from the data of the experiments that growth of the ova and adrenals is simultaneous. The most marked correlation was in the common pigeon, where the two increased and otherwise changed almost together. It was found, too, that both medulla and cortex enlarge, each part increasing functionally as well, it is supposed. The epinephrin outpouring portions (according to Hartman, both cortex and medulla) are supposed to oversecrete as there is excess blood sugar at that time. Stilling ('98) found enlargement of the adrenals during the breeding season of both male and female frogs and rabbits. Stoerk and v. Haberer ('04) described hypertrophy of both medulla and cortex, but chiefly the latter, in many species during the breeding season. Herring ('20) discovered that albino rats showed enlargement of the adrenals during pregnancy, but believed it might be simply an adjustment to the increased body size of the rat.

Clinically the relationship is also evident. During pregnancy, the whole gland undergoes enlargement, the cortex the most. In lactation, similar enlargement is found. (Barker). It would appear from available data, then, that the gonads exert an influence on the adrenals, perhaps for the

purpose of added bodily stimulation.

e. Relation of ovaries to mammae.

Steinach, experimenting on young male guinea-pigs transplanted ovaries in them. The mammary glands developed and went so far as to secrete milk. This experiment indicated that some internal secretion of the ovary activated the mammary glands. A similar substance must be contained in fetus, for that ground up and injected, caused mammary development in virgin animals, and milk secretion in other rabbits. The mammary gland itself is supposed to exert an inhibitory effect on the ovary, for ovulation does not take place during the period of lactation.

5. PANCREAS.

a. Relation to adrenals.

It has been demonstrated that application of adrenalin to the pancreas causes glycosuria. Brushing with other endocrines produces nothing comparable to the effect of adrenalin. Lorand and Zuelzer found, moreover, that pancreatic secretion, or even pancreatic juice, prevents the sugar increase caused by adrenalin.

Although the effect of antagonism is apparently illustrated, Allen denies the adrenal factor in diabetes. There is he asserts, no proof that epinephrin can cause glycosuria. The effect of hypersecretion of the pancreas, and hence less blood sugar, brought about by adrenalectomy, is interpreted by Mann and Drips as due to the changed blood pressure.

PANCREAS

b. Relation to thyroid and parathyroids.

Removal of the pancreas in cats causes the thyroid first to grow larger, then smaller. (Faught and Ryan). Lorand noticed increased colloid in the thyroid of depancreatized animals; his report is not substantiated, although Sweet and Ellis noted some changes. Diabetic (depancreatized) dogs in which part of the thyroid and parathyroids is removed, are afterwards more liable to tetany than non-diabetics. Removing the entire thyroid from such diabetic dogs diminishes the excess sugar. Removing the parathyroids, however, causes excess sugar over the normal amount for depancreatized dogs. (Schafer). These effects might be the modification of metabolism by thyroid removal, or some such general effect.

c. Relation to pituitary.

Depancreatized animals have a changed posterior lobe, though normal anterior. (Cushing). In cases of human diabetes Kraus ('20) found in about half of the twenty-three victims examined, atrophy of the anterior pituitary, with loss of, and changes in, the eosinophil cells.

d. Relation to gonads.

In 1911, Carlson and Drennan found that pregnant animals, depancreatized, did not show symptoms of diabetes until after the delivery of the fetus. This is due perhaps to pancreatic extract of the fetus circulating in the blood of the mother, or perhaps, to the use of the surplus sugar by the fetus.

6. PINEAL.

Relation to sex.

Experiments indicate that the pineal gland has an inhibitory effect on the sex development of animals. Extirpation of the pineal in young rabbits and puppies (Sarteschi) brought about precocity of body growth and of sexual development, the testes becoming enlarged, both interstitial and germinal portions; and the secondary sex characters being definitely established. Foa's work, extirpation of the pineal in chicks, indicated, in the males, a premature development of combs and testes, the latter being of normal, though early, formation in both Leydig and sperm cells. On male rats similar results were obtained. But in the females no appreciable difference of genitals was discerned. Horrax, with careful and extended experiments on guinea pigs, found in the pinealectomized males a greater weight in the testes, and larger seminal vesicles. Histologically, the cells were active, spermatogenesis being found prematurely. Again in the females there was no demonstrable difference, except that the offspring were born at an earlier time than normal. These discoveries are not substantiated by Dandy ('15), who noted no changes in the sex apparatus of pinealectomized dogs. From most of the experiments in removing the pineal, however, the sex glands are allowed freedom to develop at an earlier age, indicating a usual inhibitory action of the pineal on the gonads.

Contrary to what one would expect, feeding pineal

to animals has no inhibitory effect on the gonads, according to the experiments so far carried out. If anything, feeding, like extirpation, causes premature development. Dana and Berkeley, working on guinea pigs, kittens, and rabbits, found slight gain in the weight of the gonads. McCord ('14) said that female guinea pigs, pineal-fed, gave birth to young, on the average, before the controls. The males were somewhat premature in the development of tubules, but not of Leydig cells. Pineal feeding also increases the milk secretion of animals; but, then, practically any endocrine extract except thyroid, adrenalin, and secretin, will give similar results. The whole question of pineal feeding may not be evidence at all for pineal action, as the internal secretion, if there is one, may not be effective by mouth.

Clinical evidence adds little to the problem. In reported cases of pineal tumors, the genitals are over-developed. The tumor is interpreted as hypofunction of the organ. The effects of this disorder on the premature development of gonads and secondary sex characteristics, are as striking as in cases of adrenal cortex tumors (hypertrophy). The pineal, then, retards sexual development, and in human beings, as well as other animals, regresses at puberty.

7. PARATHYROIDS.

a. Relation to thyroid.

Hammett ('23) discovered that lack of parathyroid secretion retarded the growth of the thyroid and other glands in both sexes of albino rats. The effect seems, however, to be a general one of upset equilibrium of metabolic processes, due to loss of the acid-base regulating organs. In the light of our imperfect knowledge, we may assume the two to be independent.

b. Relation to pituitary.

Parathyroidectomy in rats and cats diminishes the chromophobe cells of the anterior lobe pituitary, causing hyposecretion. (Izumi, '23). Added to this fact is that of the effects of tetany being possibly associated with disease of the pituitary. Here again, insufficient evidence makes one doubt any relationship whatsoever.

c. Relation to gonads.

The greater occurrence of tetany during menstruation, pregnancy, or lactation, might indicate a connection of parathyroids and gonads, of the female at least. During maternity, partial parathyroidectomy, otherwise harmless, causes maternity tetany. The explanation, however, may be the greater demands on the organ, and hence the dire effects of losing even a small part of its secretion.

d. Relation to thymus.

Experimentally, the relation seems clear, though backed by very limited work. Ulenhuth ('18) fed larval salamanders with thymus. Before metamorphosis, the animals devel-

oped tetany. After metamorphosis, however, there were no spasms of tetany. The explanation is that the parathyroids are undeveloped until metamorphosis, at which time its growth combats the effect of thymus feeding. Thymus and parathyroids appear to be antagonistic.

Clinically, the relation is shown by maternity tetany. The thymus of the fetus is actively secreting, and may in some cases overbalance the work of the maternal parathyroids. Tetany is the result.

e. Relation to pancreas.

Allen has contributed much of our knowledge on the mutual effect of parathyroid on pancreas. Total parathyroidectomy in animals, with its effect of tetany, caused besides, a lowered tolerance for sugar. Injections of parathyroid extract in these animals made no change in the excess blood sugar. Injecting a super-dose of insulin, to render the blood sugar less than normal, and then giving parathyroid injections, caused the immediate death of the animals. Usually, decreased sugar, with its attendant convulsions, does not prove fatal. Parathyroid, then, seems to act with insulin to reduce the blood sugar. This effect is further exemplified in experiments on rabbits. (Allen). The animals, when injected with not less than 30-40 mg. of insulin, took convulsions. When, however, parathyroid extract was first administered, only 10 mg. of insulin was required to cause convulsion. On a normal rabbit without parathyroid injections, 10 mg. would have a negligible effect on the blood sugar. Winter

and Smith ('24) have confirmed the evidence.

10. SUMMARY.

The endocrine system is normally in a state of balance, one secretion harmonizing in amount and activity with the others. When something disrupts the equilibrium,- over- or under-secretion of a gland, the interactions of the endocrines are much more apparent than normally. A few of these interrelationships are on a sound experimental and clinical basis. Most others are not yet fully known, but await the proof which is still being sought.

Of the definite and apparently final relationships, the link between thyroid and gonads is one. Experimental and clinical findings tend to the fact that thyroid secretion in right amounts is essential in the proper functioning of the gonads, and that the sex glands exert an influence in causing hypertrophy and other changes in the thyroid. The connection is more marked in females. The influence of the pituitary on the gonads is also beyond dispute. Regression of the gonads after removal of the pituitary, and stimulation in hyperpituitarism, with, however, gonad atrophy when the overfunctioning passes a certain limt, - all these, common in occurrence, support the relationship. The reverse interaction, - changes in the pituitary brought about by the gonads, is also fairly sound. Another connection, that between the adrenal cortex and gonads, is a secure one. That the cortex enlarges with marked gonad action, and that hypertrophy of the cortex exerts

SUMMARY

its influence on the gonadal system, is well borne out, either experimentally or clinically. The effects of pineal in preventing premature development of the gonads may be accepted as definite, being known in both experiment and medical practice.

There are other relationships, fairly secure, yet debated by various radicals who may yet prove to be in the right. The pituitary-thyroid relation, one compensating for the other, is on firm experimental ground, especially with amphibians. Yet these animals may, as some believe, have a peculiar type of pitiutary or thyroid; so that their apparatus would not indicate the relations in higher animals. So some clinicians give the connection no credence. That adrenalin is antagonistic to pancreas is still believed, although its effect in diabetes is a debatable one. Parathyroid aid to insulin appears to be sound insofar as it has been tested.

Some other relationships, as the thyroid-thymus, or the pitiutary-adrenal, or others, may be as sure as the ones enumerated. But either their relative importance in the welfare or development of the animal is not so great, or the effect is a general one which has had little experimental attention; for the literature discloses only limited proof in their support. The remainder of the interrelations have both negative and positive evidence in their behalf, or none at all to speak of; so no conclusion as to their worth can at this time be made.

=INTERRELATIONS OF THE ENDOCRINE ORGANS=

BIBLIOGRAPHY

- -

Allen, Frederick M. - Relation of the Adrenals to Diabetes.
Journal of Metabolic Research,
April, 1923.

Aub, J.C. - Metabolism
Journal of the American Medical Association, '22.

Bandler, Samuel W. - The Endocrines
Saunders Co.
1920

Barker, L.F. - Endocrinology
Journal of the A.M.A., 1922.

Barker, L.F., Ed. Endocrinology and Metabolism
Appleton and Co., 1922.

Barker, L.F., - Parathyroids: Clinical Syndromes, especially Tetany.

Bassoe, P.,- Hypophysis: Acromegaly.

Beck, N.G., - Hypophysis: Adiposogenitilia.

Cowdry, E.V., - Thyroid: Anatomy, Histology, and Embryology.
Parathyroids: Anatomy, Histology, and Embryology.

Hammett, F.S., - Hypophysis: Physiology, Chemistry, and Experimental Pathology.
Mammary Glands an Their Endocrine Relationships.
The Placenta as an Endocrine Organ.

Hartman, F.A., - Suprarenal Glands: General Physiology and Experimental Pathology.

Hoskins, R.G., - Thymus: Physiology, Physiological Chemistry, and Experimental Pathology.
Interrelation of the Endocrine Organs.

Howard, C.P., - Thyroid: Hyperthyroidism, and Dysthyroidism.

Jump, H.D., - Suprarenal Glands: Virilismus and Hirsutismus.

Lespinasse, V.D., - Male Gonads: Testes as a Gland of Internal Secretion.

Lewis, D.D., - Hypophysis: Physiology, Physiological Chemistry, and Experimental Pathology.

Simonds, J.P., - Hypophysis: Pathological Anatomy and Histology.

Timme, W., - Multiglandular Syndromes.

Vincent, Swale, - Thyroid: Physiology and Experimental Pathology.

Warthin, A.S., - The Pancreas as an Endocrine Organ.

BIBLIOGRAPHY (cont.)

Bell, Blair - The Pituitary
Wm. Wood and Co., N.Y.

Brown, W.L., - Biology of the Endocrine System.
N.Y. Medical Journal. April 5, '22.

Cannon, W.B., - Conditions Controlling Internal Secretions.
Journal of the A.M.A. 1922.

Cobb, I. Geikie, - Organs of Internal Secretion.
Bailliere Tyndall Co., London.

Cushing, H., - The Pituitary Body and Its Disorders.
Lippincott, 1912.

Faught and Ryan, - Functions and Interrelations of the Endocrine Glands.
American Journal of Medical Sciences, '22.

Foster, N.B., - Diabetes Mellitus.
J.B.Lippincott Co., 1915.

Fulton, J.E., - Controlling Factors in Amphibian Metamorphosis.
Endocrinology, Jan., '21.

Funk, - Disorders of Nutrition and Metabolism.
Progressive Medicine, June, '21.

Hoskins and Hoskins - Interrelation of the Thyroid and Hypophysis in the Growth and Development of Frog Larvae.
Endocrinology, Jan., '20.

Howell - Text Book of Physiology.

Jones, W. A., - Relation of the diseased Thyroid to the Other Ductless Glands.
Journal-Lancet, April, '23.

Kaplan - Endocrine Interactions
N.Y. Medical Journal, March 15, '22.

Marine and Baumann, Journal of Metabolic Research, '22.

Ott, Isaac - Internal Secretions.

Riddle, O., - Suprarenal Hypertrophy Coincident with Ovulation in Birds.
American Journal of Physiology, Oct., '23.

Sajous - Internal Secretion and Principles of Medicine.
Davis Co., Vol. I, 1903.
Vol. II. 1907.

Schafer, Sir Edw. A. - The Endocrine Organs
Longman Green Co. 1916.

Smith, P. E. - Pigment Changes in Frog Larvae Deprived of Epithelial Hypophysis.
Proceedings of the Society for Experimental Biology and Medicine, 1919.

Smith, P.E. and Smith, I.P. -
Function of the Lobes of the Hypophysis as Indicated by Replacement Therapy with Different Parts of OX Gland.
Endocrinology, July, '23.
Repair and Activation of Thyroid.
Journal of Metabolic Research, 1922.

Stewart - Adrenal Insufficiency
Endocrinology, May, '21.

Winter and Smith - Possible Relation of Pancreas and Parathyroids
Journal of Physiology, Oct., '23.

PHYSIOLOGICAL ABSTRACTS.

Decio, Nov. '23.

Evans and Long, July, '23.

Hammett, Nov. '23.

Izumi, July '23.

Winter and Smith, Jan. '24.

ENDOCRINOLOGY (Abstracts).

Hammett, Jam. '24.

Hēdon, Sept. - Nov. '23.

Houssay and Hug, VII, 5.

Hogden, VII, 5.

Note: The articles and books in this bibliography have all been read completely in so far as they relate specifically to the subject of the interrelations of the ductless glands. Other portions of them have been perused cursorily or not at all.