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THE RELATION OF THE ENDOCRINE GLANDS TO HEREDITY AND DEVELOPMENT[1]

SINCE the object of the Eugenics Research Association is the advancement of knowledge that will contribute to the improvement of the human race by inheritance, its members can scarcely fail to be interested in the discussions that are now going on regarding the glands of internal secretion and their relations to heredity. As a medical man, deeply interested in the problems of constitution and of condition and profoundly impressed with the recognizable influences of internal secretions upon form and function in both normal and pathological states, I welcomed the suggestion of Dr. Davenport that I deal in my presidential address with the topic announced. The progress of research in endocrine domains and in heredity has of late been so rapid that no single person can keep pace with its strides. My remarks, therefore, will make no pretence to completeness of discussion of the reciprocal relations of heredity and endocrinology. They are intended rather to direct the attention of the members of the association to some of the more important facts that have been established and to stimulate interest in some of the newer problems that are emerging and clamoring for solution.

THE ENDOCRINE ORGANS AND THEIR PRODUCTS

It is only comparatively recently that the significance of the so-called ductless glands and of the substances they manufacture has become recognized, but, in a very short time, a considerable body of knowledge concerning their structure, their functions and their inter-relations has been accumulated. At the moment, studies of the internal secretions, or, as many now call them, the "incretions," are, on ac-

[1] Presidential address at the tenth annual meeting of the Eugenics Research Association, held at Cold Spring Harbor, Long Island, June 10, 1922.

count of their astonishing and novel revelations, attracting the attention not only of scientific workers in biology and medicine but, and perhaps to too great an extent, also of the laity. Important as a knowledge of these incretions is for an understanding of bodily and mental states, there is some danger, I think, of over-emphasis and of disproportionate prominence. Popular articles and treatises on endocrine subjects too often assume what is mere conjecture, or wild speculation, to be established as fact and reveal a tendency to exploitation that must sooner or later be followed by disappointment and disillusionment. There is, I fear, some danger that even scientific endocrinology may, temporarily at least, be brought into undeserved discredit. It would seem especially desirable, therefore, that those who write or speak upon the subject should discriminate carefully between fact and fancy. Every effort should be made rigidly to control hypotheses by accurate observation and careful experiment, for only thus can an orderly advance in knowledge be assured.

Though an incretory function has been ascribed to many organs of the body, the principal incretory organs, those whose function is best understood, are seven in number: (1) the thyroid gland, (2) the parathyroid glands, (3) the hypophysis cerebri, or pituitary gland, (4) the epiphysis cerebri, or pineal gland, (5) the suprarenals (consisting of two parts of entirely different functions, (*a*) the medulla or chromaffine portion and (*b*) the cortex or interrenal portion), (6) the islands of Langerhans of the pancreas, and (7) the interstitial tissue of the gonads (ovaries and testicles) or so-called "puberty gland."

There is evidence that each of these organs yields an internal secretion that, distributed through the blood, exerts important chemical influences upon other, more or less distant, organs and tissues. Some of these influences have been definitely determined, but it will doubtless be a long time before all of them will be well understood. The knowledge that has been gained concerning the thyroid, the pituitary, and the suprarenals gives promise, however, that steady research will gradually enlarge our information regarding the influences exerted by each of the incretory glands.

The chemical substances contained in the incretions have been called "hormones" and the determination of the precise chemical constitution of these hormones sets fascinating tasks for the biochemist. That the chemical constitution of some endocrine products may be closely approached, if not definitely established, has been shown by researches upon epinephrin (from the medulla of the suprarenal gland) and upon iodothyrin and thyroxin (from the thyroid gland). Studies of concentrated functionally potent extracts from other glands may before long reveal the chemical nature of other hormones; I have in mind, especially, studies of so-called "pituitrin" (hypophyseal extract) and of so-called insulin (extract of the islands of Langerhans of the pancreas). Clues as to the chemical nature of the hormones of the parathyroids, the pineal body, the interrenals and the gonads will probably be more difficult to obtain. Biochemical researches to establish the precise nature of the single hormones are extraordinarily important and should be vigorously prosecuted in order that experimental studies of hormone influences may be more systematically, exactly and intelligently pursued.

THE BETTER-KNOWN ENDOCRINOPATHIES

Our knowledge of endocrine functions has been variously derived, partly through keen clinical-pathological observations, partly through experimental work upon animals (surgical removal of single organs; organ transplantations; injections of organ extracts or of isolated hormones). Before discussing the relations of the endocrine organs to heredity and development, it may be helpful briefly to refer to a few of the classical clinical syndromes that are now justifiably believed to be endocrinopathic in origin. Time will not permit me to refer to more than a few of these, but those chosen will serve as illustrative paradigms.

I may cite first two characteristic clinical syndromes met with in association with disease of the thyroid gland, namely, exophthalmic goitre and myxœdema.

In the former, known also as Graves' disease or Basedow's disease, we observe, in typical instances, a markedly enlarged pulsating thy-

roid gland (goitre) in the neck, a persistently accelerated pulse rate (say 150 or more to the minute instead of the normal rate of 72), marked nervous symptoms including fine tremor of the fingers, outspoken protrusion of the eyeballs (exophthalmos), a tendency to profuse sweats and to watery diarrhœa, sensitiveness to heat, a peculiar psychic over-alertness and apprehensiveness, and a tendency to rapid emaciation (despite an abundant food intake) associated with demonstrable acceleration of the rate of the basal metabolism. Since similar symptoms can be produced by feeding thyroid gland extract, it is believed that there is a hyperfunction of the thyroid gland (hyperthyroidism) in exophthalmic goitre.

In the idiopathic form of myxœdema (or Gull's disease) the clinical conditions are diametrically opposite to those in exophthalmic goitre. The thyroid gland is small, the pulse-rate is usually slow, the eyes look sunken (enophthalmos), the lid-slits are narrow, the bodily movements are slow and clumsy, the patient is mentally dull, forgetful and apathetic, there is sensitiveness to cold and a tendency to constipation, the hairs fall out, the skin is dry, thick and wrinkled and there is a tendency to obesity (despite a restricted food intake) associated with demonstrable retardation of the rate of the basal metabolism. Since patients with idiopathic myxœdema rapidly improve if they are fed the thyroid gland of the sheep, and since a condition precisely similar to it occurs if the thyroid gland be surgically removed (cachexia thyreopriva), it is believed that myxœdema is due to a hypofunction of the thyroid gland (hypothyroidism).

Two similarly contrasting clinical syndromes due to disorders of the hypophysis cerebri or pituitary gland may next be mentioned, namely, (1) gigantism and acromegaly, due to overfunction, and (2) Froehlich's syndrome of obesity with genital dystrophy, due to underfunction.

When there is overfunction of the pituitary gland in early life before the epiphyses of the long bones have united with the shafts of those bones there is over-stimulation of bony growth and the patient becomes excessively tall (gigantism). When the overfunction of the pituitary gland occurs in later life (after epiphyseal union), bony overgrowth is still stimulated but manifests itself in enlargement of certain parts of the skull and of the hands and feet (acromegaly). There is also enlargement of the tongue and of the internal organs (splanchnomegaly). The victim presents a very characteristic appearance. The face is hexagonal, the nose is broad, the chin is prominent and curved so as to bend sharply upward, the cheek bones are outstanding and the arches above the eyes are prominent. Looked at from the side, the face resembles that of Punch (nut-cracker profile). The hands are spade-like, the fingers are sausage-shaped, and the feet are huge.

On the other hand, when there is underfunction of the pituitary gland during development a condition (Froehlich's syndrome) in marked contrast to gigantism and acromegaly results. The skeletal development is defective, the growth of bone being less than normal. The patient is short in stature, the face remains child-like and the hands and feet are small (acromikria). The subcutaneous fat is markedly increased (obesity), and is distributed in an uneven way over the body, being most abundant on the abdomen, over the buttocks, and in the proximal portions of the extremities. The secondary sex characters either fail to develop or develop in a faulty way. The pubic and axillary hairs do not appear or are scanty. The external genitals remain in an infantile state. In young men the voice is high pitched and there is a lack of normal virility. In young women, the menstrual flow is scanty or absent.

Next, let us contrast two clinical pictures believed to depend upon disorders of the suprarenal capsules, (1) Addison's disease, met with in destruction of the suprarenals (hyposuprarenalism), and (2) pseudo-hermaphrodism, premature puberty, and hirsutism, met with in association with hyperplasias of the suprarenals (hypersuprarenalism).

In Addison's disease there is great weakness and prostration, associated with low blood pressure, diarrhœa and other digestive disturbances, chronic anæmia and often a peculiar bronzing of the skin (melanoderma).

On the other hand, in cases in which there is

believed to be overfunction of the suprarenals, the clinical picture is markedly different though it varies somewhat with the time of onset of the assumed hyperfunction. Should this occur during fœtal life, a pseudo-hermaphrodite appears, the person presenting the external genital appearances of one sex while possessing the internal sex organs of the other sex. When the overactivity exists soon after birth rather than before birth, puberty appears prematurely, a little girl of three or four menstruating regularly and exhibiting the bodily and mental attributes (sexually) of an adolescent, or a boy of seven presenting the external genitals and the secondary sex characters of an adult. Should the overactivity of the suprarenals not occur until adult life, it may reveal itself in a woman of middle age by the rapid development of hairiness over the body (hirsutism) and by the exhibition of masculine characteristics (virilism).

Other examples of clinical pictures might be mentioned but these few will suffice to illustrate the extraordinary mental and physical changes that may become manifest when there are disturbances of function of the endocrine organs.

CONSTITUTION AND THE ENDOCRINE ORGANS

Biologically considered, a developed human being, like all developed higher organisms, must be looked upon as the resultant of a long series of reactions between the zygote (fertilized ovum) and its environment. The germinal type or genotype, reacting with the surroundings, becomes the developed type or phenotype, in the case of human beings, the "realized person." The germ plasm provides the determining factors, the environment the realizing factors. Everything in the phenotype attributable to inheritance may be spoken of as "constitution," everything attributable to environment as "condition." Medical men as well as biologists must, then, when studying a person or a single organism, be interested in differentiating, when they can, what is "constitutional" from what is "conditional" in origin. In experiments upon animals and plants such a differentiation may be relatively easy; in studies of human beings it is always extremely difficult and, as regards many features, as yet wholly impossible.

The importance of constitution will need no emphasis among biologists who are predominantly students of heredity. Among medical men, too, throughout the centuries, especially among practitioners, there have always been those who have been fully aware of the significance of constitution and of its relation to disease-disposition. During the past fifty years, however, under the spell of bacterial and protozoan etiology, medical men have been so absorbed by studies of influences arising in the environment that they have, too often, forgotten to continue their investigation of influences of endogenous origin. For a time, it was almost taboo to speak of "constitution," or of "disposition," owing to a justifiable reaction, perhaps, against the earlier prevalent tendency to use these words as a mask for ignorance. Recently, however, there has been a welcome revival of studies of constitution. Now that facts that supply a scientific basis for a general pathology of constitution have been accumulated, we may look forward to a greatly increased interest among physicians in the part played by inheritance in disease. Indeed, during the past five years, several treatises upon this and allied subjects have been published; and we may expect, I think, during the period just ahead of us, many attempts to present, more systematically than hitherto, the rôle played by constitutional disposition in the pathogenesis of a whole series of diseases.

The chemical consideration of endocrine disorders, has in my opinion, given a strong impetus to this movement toward a revival of studies of the physiology and the pathology of constitution. For though the endocrine organs are, in some instances, accessible to trauma and to poisons and parasites that reach them through the blood-stream, diseases of these organs, especially those "idiopathic" chronic diseases that develop insidiously and give rise to the classical endocrine syndromes, appear to be, usually, of endogenous rather than of exogenous origin, that is to say, they develop as the results of special anomalies of constitution. This accounts for the fact that endocrinopathies tend to run in families, and the

interrelationships that exist among the different endocrine organs may explain why a disease of the thyroid (exophthalmic goitre) may appear in one member of a family, a disease of the pancreas (diabetes mellitus) in another, a disease of the hypophysis (dystrophia adiposogenitalis) in a third, or a pluriglandular disorder in a fourth member of the same family. The experienced clinician can now often recognize phenotypes in which there are anomalies of constitution that predispose to endocrine disorders; and as a result of this recognition he may, sometimes, be able to institute a rational prophylaxis. The thyreotoxic constitution, the hypothyreotic constitution, the hypoparathyreotic constitution, the hyperpituitary constitution, the hypopituitary constitution, the hypergenital constitution and the hypogenital constitution are instances in point. Unfortunately we have not learned as yet how effectually to intervene in a prophylactic way in all of these anomalies of constitution, but rewarding experiences with the hypothyreotic and with the hypoparathyreotic constitution give us hope that, with widening knowledge, suitable preventive measures will be discovered.

Studies of the symptoms of endocrine disorders and studies of partial anomalies of constitution affecting the endocrine organs are thus throwing much light not only upon (1) the mode of action of the incretions, but also upon (2) inheritance as a determining cause of endocrinopathic phenotypes. The incretions may affect distant parts directly, being carried to them by the blood; or they may affect those parts indirectly through the intermediation of the autonomic nervous system, which they sensitize. When they act directly, they may influence the substances and processes in the localities that they reach (chemical correlation; regulation of metabolism) or they may supply materials for incorporation by the cells (nutritive and formative influences). When they act indirectly through the vegetative nervous system they may exert profound effects through the secretory activity of glands, through the contraction of smooth muscle, or through modifications of those neural mechanisms that have to do with the emotions and the will. During the developmental period, it is clear that the incretions are in part responsible for the dimensions and proportions of the skeletal apparatus and the soft parts. A normal functioning of the incretory organs is essential for the shaping of parts and for the maturing of functions in the right place and at the right time. Through correlative differentiation (due in part at least to the action of the incretions), the developing organism gradually comes to exhibit the characteristics of its species, its age and its sex. Even the anthropologists now maintain that the solution of the problem of how mankind has been demarcated into types so diverse as the Negro, the Mongol and the Caucasian will involve the study of hormonic mechanisms!

CAN HORMONES MODIFY UNFERTILIZED GERM-CELLS SO AS TO INFLUENCE INHERITANCE

Thus far in our discussion of the relation of the endocrine glands to heredity and development we have confined our attention to (1) the genotypic determination of endocrine functions in developing organisms, (2) the rôle played by the incretions in normal and pathological ontogeny, and (3) the fact that there exist heredo-familial anomalies of body make-up that predispose to endocrine disorders. But we must, for a few moments at least, consider the possibility that hormones, reaching unfertilized germ-cells, may modify the germ plasm in such a way as to give rise to new inheritance factors that will be transmitted from generation to generation.

Experiments upon the influence of incretory substances upon the development of cold-blooded animals have yielded such striking results upon cells of the soma that many have wondered whether incretions circulating in the blood might not also permanently alter the germ-cells so as to account in animals for the origin of mutations and new biotypes. You will recall the experiments to which I refer (1) the acceleration of tadpole metamorphosis by feeding thyroid substance and (2) the retardation of the same process by feeding thymus substance.

In endocrine diseases of either endogenous or exogenous origin, the cells of the soma are also markedly altered; and the question has naturally been asked, May not the germ-cells be simultaneously profoundly changed?

Since 1895, a number of investigators have suggested that the influence of specific internal secretions might easily be used for the explanation of the inheritance of acquired characters. Last year, an English evolutionist published a volume on "Hormones and Heredity" and suggested that environmental influences influencing an organ, or part, of the mother may set free chemical substances (hormones) that, carried through the blood to the ovaries, may affect the ova in such a way as to lead to similar changes in the same organ, or part, of the offspring. By such a mechanism he would attempt to account for a progressive evolution in the animal series. His theory would seem practically to be a modfiication of the pangenesis theory of Darwin with the substitution of "hormones" for Darwin's "gemmules."

Many physicians, too, have leaned toward Lamarckian or neo-Lamarckian theories that assume the inheritance of acquired characters and some of these have suggested that in such inheritance the incretions must be concerned. Those who have been trained in the methods of modern biology, however, usually reject Lamarckism, and attempt to explain the apparent inheritance of "acquired characters" for a generation or two by assuming either a "germinal injury" (in the sense of Forel's "blastophthoria") or a "parallel induction."

The consensus of biological opinion in this country is strongly opposed to the inheritance of acquired characters. Mendelian studies lend no support to the view that conditional influences can affect inheritance factors. Mendelism is, however, difficult if not impossible to apply to man. As some one has put it, "the propagation of man consists of a continual crossing of polyhybrid heterozygote bastards," not susceptible to analysis by Mendelian methods such as can be applied to the study of the propagation of plants and experimental animals. But if inheritance of acquired characters really occurred, why should there not be, as Conklin emphasizes, an abundance of positive evidence to prove it? When one plant or animal is grafted on another, there is no evidence that the influence of the stock changes the constitution of the graft. When an ovary is transplanted, the foster mother does not affect the hereditary potencies of the ova. Until more proof has been brought than has hitherto been advanced, we shall not be justified, so far as I can see, in accepting the theory that conditional influences change hereditary factors. There are, moreover, aside from the problem of the inheritance of acquired characters, enough relationships of the endocrine organs to heredity and development to long keep us rewardingly occupied.

CONCLUSION

Let me summarize in a few words the situation as I see it. The endocrine organs are of the greatest importance in normal development, their incretions exerting profound formative and correlative influences. In pathological development, the abnormal plenotypes that appear often point decisively to partial anomalies of constitution involving especially the ductless glands and their functions. Whether or not under normal or pathological conditions, hormones arising in the soma can so change the germ plasm of ova or sperm-cells as to account for certain mutations or for germ-cell injury is a question that deserves consideration and merits experimental test. Finally, the conjecture that conditional influences upon the soma can through hormonal production and transportation to parental gametes so modify the germ-plasm as to result in the inheritance of the conditioned modification seems, as yet, to have but little, if any, evidence to support it.

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AN ANALYSIS OF STUDENT GRADES AT WASHINGTON UNIVERSITY SCHOOL OF MEDICINE

THIS work was undertaken with the idea of obtaining some definite data upon which to base opinions of students' grades during their medical course. As the data obtained were of great interest to the staff of this school it was thought advisable to publish them in order that they might be used for comparison with those of other schools.

The records of those students in the classes of 1914, '15, '17, '19, '20 and '21 who spent all