The Biology *of the* Internal Secretions

THE ENDOCRINE FACTOR IN DEVELOPMENT, IN SUBNORMALITIES, IN NEOPLASMS AND MALIGNANCY, IN NERVOUS AND MENTAL DISEASES AND IN HEREDITY

By

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FOREWORD

In the within essay the problem of the internal secretions has been approached from a general biological point of view. For a long time past it has seemed to the writer that this method of approach is not only necessitated by the nature of the subject, but is the only one which promises a comprehensive and a logical interpretation. The writer ventures to point out that viewed in this light, the basic facts which underlie our knowledge of the internal secretions arrange themselves in a natural and orderly sequence. From a mass of details, often vague and obscure, the essential and important facts rise into outstanding prominence, while their significance and their relation to each other are either clearly indicated or become matters of logical inference.

The phenomena presented by the internal secretions are in their ultimate analysis problems of metabolism. It seems logical, therefore, to begin with a consideration of the elemental facts of metabolism in unicellular forms and to follow this by a consideration of the elemental facts of metabolism in the individual cells of cell-aggregates. Ferments, enzymes, catalysts next claim our attention. Very soon the picture of the developing metazoan presents itself. The layers of the embryo, their problems of physical and chemical interpretation, and the rôles which these layers play in the evolution of the organism in turn come before us.

A pause and a brief consideration reveal the fact that it was the clinic, that most marvelous of all laboratories, which gave us our first knowledge of the internal secretions. A discussion of the facts presented leads naturally to a discussion of subnormalities. A relation of the latter to the development of the embryonic layers now becomes apparent. This relation proves to be close and inherent. It is true of all of the layers, but the story is told with almost dramatic force by the history of the mesenchyme and the rôle which the mesenchyme plays in lymphatic persistence, lymphatic hyperplasia, and in the all-important functions of the thymus. Indeed, it would appear that disturbances—arrests—of this layer, together with the concomitant involvement of the lymphatic system and the thymus, are basic to most if not to all of the great endocrine pictures met with in the clinic. Arrests are always expressive of a diminished vigor—a lessened intensiveness—of the physical and chemical processes of the developing organism, and this reveals itself—to state the fact very conservatively—with especial frequency in the mesenchyme and its intimately related structures, the lymphatic system and the thymus.

The relations of the thymus to the other endocrine organs leads naturally to a discussion of these organs and of the various metabolic, trophic, and nutritive disturbances which their abnormalities entail. Synergic and antagonistic relations now reveal themselves. Without anticipating the facts pointed out in the text, it may be here stated that the glands of internal secretion arrange themselves spontaneously into groups more or less well defined. The great rôle of the sympathetic and autonomic nervous systems now also becomes apparent.

However, it is in the field of the glandular "imbalances" that the most important facts are brought to light. Glandular imbalances result in "under-" and "overcompensations." Atrophies, hypertrophies, neoplasms, malignancies, follow. Indeed, the facts indicate that herein lies the explanation of malignancy in general, and the writer earnestly bespeaks the careful consideration of the views of malignancy advanced in this essay.

Again, a consideration of inadequate and subnormal development of the endocrine apparatus leads to an interpretation, alike fruitful and convincing, of the rôle which these structures play in functional nervous and mental diseases. Much becomes clear, both in the arrested and autodegenerative conditions and in the more purely functional affections, such as the manic-depressive disorders. Incidentally it may be mentioned that the interplay of the hormones, the sympathetic, the thalamus, and the cortex points —as shown in the within pages—to an explanation both of the mental states and of the nature of the delusions commonly present. The writer believes that in attempting to blaze the path into this hitherto unknown field he has not gone farther than the facts justify.

Finally, a biological consideration of the internal secretions and of the rôle which they play in the metabolism of the organism as a whole, leads to certain conclusions regarding heredity; more especially as to the inheritance of acquired characters. For the views herein advanced, the writer bespeaks the thoughtful, if not indulgent, criticism of biologists into whose hands this essay may fall.

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I

INTRODUCTION

The subject of the internal secretions has today assumed an importance second to none other in medicine. In the midst of details and of new discoveries, we are apt to lose sight of certain basic facts which I believe have not only a theoretical but also, as I hope to show, a practical value. To me it has for a long time seemed that general biological considerations have a special bearing upon the subject.

The first fact to be recognized is that the problem of the internal secretions is but a part of the general problem of metabolism. Metabolism, in turn, clearly consists of changes which are both chemical and physical in their nature. What the chemical changes are which take place in such a relatively simple form as a protozoan must remain largely a matter of speculation. However, certain facts must be definitely admitted: first, changes which result from oxidation and which are analogous to the changes resulting from respiration in the higher animals; second, changes which are analogous to those of digestion and assimilation in the higher animals. When a food particle is taken into the interior of an ameba it gradually disappears, and finally becomes part of the substance of the ameba. That this constitutes a process of digestion and assimilation and that it is expressive of chemical change is an unavoidable inference. It would appear that, as in the higher animals, the protoplasm of the ameba has the power of fragmenting—*i. e.*, of reducing chemically and physically—proteins, fats, and carbohydrates. In the higher animals these changes are known definitely to be the result of the action of "ferments," and it is doing no violence to facts to assume that ferments of similar import are present in the ameba. Can we not rightly regard such ferments as "internal secretions" of the ameba?

It is interesting to note that in the reduction of highly complex organic bodies, such as proteins, carbohydrates, and fats, into simpler compounds, energy is released. Protein is reduced successively into peptones, amino-acids, and a series of intermediate products until the final stage of urea, uric acid, and kindred substances is reached. Carbohydrates are by a long series of intermediate stages converted into carbon dioxid and water. Fats, also, by decomposition into glycerin and fatty acids and by further reduction into simpler bodies, contribute their share in the production of energy until end-products are likewise reached. The rôle of oxidation in complementing and completing the reduction initiated by the ferments of digestion is alike interesting and obvious and need not detain us.

There is no inherent improbability in the inference that changes like or analogous to these take place in the ameba. Certain it is that the various food particles are so metamorphosed that they disappear into the general substance of the organism, and can after a time no longer be distinguished. It would also seem to be a legitimate inference that as a result of the action both of ferments and of oxidation, the process of reduction is progressive and continuous, so that finally the older particles of the protoplasmic mass become so far reduced that they are no longer sources of energy, and then disappear by solution into the surrounding medium.

The rôle that special enzymes, catalysts, play in the metabolism of the ameba, their origin, and details of action are, of course, unknown, but as to the existence of such bodies there can, I think, be no reasonable doubt. The question arises, Does the ameba discharge into the surrounding medium any other than inert and waste materials? or, Are perhaps special substances also excreted which have to do with the apparent "choice" or "selection" of food by the animal, or which exercise some hitherto undiscovered function? No answer can be given to this question, but the possibility should not be lost sight of. The "selective" action of the ameba, at all events, demands a moment's consideration. When the pseudopod of an ameba comes in contact with a foreign body, one of two things occurs: either the protoplasm of the pseudopod flows around the foreign body, and thus takes the latter into the interior of its own substance, or the pseudopod is withdrawn. If the foreign substance is capable of serving as food, it is appropriated; if not, it is rejected. Should the foreign body be made up both of material capable of serving as food and of material incapable of serving such a purpose, the two are separated; after a time the first disappears, apparently becomes a part of the substance of the ameba; the second is ejected. These phenomena which at first sight seem so mysterious—indeed, suggestive of volition—are doubtless merely the result of the physical or chemical reaction of the protoplasm of the ameba with the material of the foreign body; but, no matter how explained, this "selective" action is one of the most important of the elementary facts of cell life, as we shall presently see.

When we turn our attention to the metazoa, we find that the individual cells of multicellular forms possess two functions: first, they have the special functions of the tissues of which they are component parts, *e. g.*, of muscle cell, of nerve cell, of gland cell; second, they retain, in addition, the primordial property of selecting, digesting, and assimilating their own food. Each cell possesses not only the special structure which enables it to fulfil the functions of the tissue of which it is a part but also special ferments by means of which it builds itself up, adds to its own substance out of the general material of the blood-plasma. Each cell possesses the power of "selecting" foreign materials, of fragmenting them, and of utilizing them for purposes of reconstruction or as sources of energy.

In return, each cell gives up to the blood-stream such substances as are of no further value to it. These substances, the products of its continued chemical changes, may consist in part of materials which are no longer sources of energy and are ready for discharge from the organism as waste materials, such as urea; or they may consist of substances which have, first, still a food or, second, a catalytic value for the cells of other tissues. As an instance of the first may be mentioned the glycogen of the liver; as an instance of the second, the epinephrin of the adrenals.

Let us now turn our attention for a moment to what is meant by the terms "ferment," "enzyme," and "catalyst." The term "ferment" is derived from the Latin word *fermentum*, itself derived from *ferveo* or *fervo*, to boil up or foam, and is to be regarded as a contraction of *fervimentum*, the intrinsic meaning of which is something that produces agitation or commotion. A ferment may be defined as something which when in contact with another substance is capable of setting up or greatly facilitating changes in the latter without itself undergoing any change, at most, very little change. Substances having this property are not by any means limited to those derived from the organic world. Thus, dilute sulphuric acid added to starch will convert the latter into glucose; the acid itself neither qualitatively nor quantitatively undergoes any change. Again, hydrogen peroxid is decomposed by soluble alkalies and also by many insoluble substances, such as metallic silver and platinum; as before, the substances inducing the chemical change themselves undergo no change whatever. A similar statement applies to the action of platinum in bringing about the oxidation of alcoholic vapor, and to the action of spongy platinum in bringing about the union of hydrogen and oxygen. Similar truths apply to both gold and silver, though neither are as active as platinum. Such action is termed "catalytic." The word "catalysis," derived from the Greek καταλύειν, to dissolve, has been employed to designate the phenomenon. It implies more especially the setting in motion or the precipitating of possible or impending chemical changes; it was first employed by Berzelius. The process is one in which given substances by their presence alone set into activity chemical processes otherwise dormant without themselves suffering any chemical change. A discussion of the rôle of adsorption and other possible physical causes of catalysis would take us too far afield. For our present purpose the frank recognition of the fact of catalytic action and of its nature is sufficient.

The most common instance of a fermentative process is that of alcoholic fermentation in which sugar is converted into carbonic acid and alcohol. Ordinarily this change is due to a ferment derived from the yeast cell. Other substances, however, such as animal fibrin, coagulated plant albumin, and cheese,[1] will also induce the change, though they are less

[1] Bayliss, General Principles of Physiology, 1920, p. 302.

active. In alcoholic fermentation we have an instance in which substances organic in their origin act as catalysts. Such catalysts are termed "ferments" or "enzymes." The latter word is derived from ἐν ζύμῃ (in yeast).

The statement that the ferment itself undergoes no change needs a slight modification. The inorganic catalysts appear never to suffer any change chemically or physically. The organic catalysts, the enzymes, however, while they never suffer any chemical change, appear to undergo a slight reduction in quantity. In the organism they are being constantly renewed, apparently to provide a continuous supply. It is only reasonable to infer, therefore, that in the exercise of their function they are being used up. It is significant, perhaps, that the amount of the renewal is relatively very small. However, in the fermentation which we so often observe outside the body, namely, alcoholic fermentation, the supply of ferment is kept up by the continued growth of the yeast cells. Further, the torula does not schematically and at once decompose the grape-sugar into alcohol and carbonic acid, but this is accomplished by a series of intermediate reactions. This fact appears to be true of other fermentative processes as well. In other words, the chemical changes induced by a ferment appear to take place in progressive gradations.

One of the remarkable facts in regard to the ferments or enzymes is that under their influence chemical changes take place in the living organism which can only be brought about in the laboratory by powerful reagents and high temperatures. For example, the change of protein to amino-acids can only be effected in the laboratory by boiling in concentrated hydrochloric acid. In the organism it takes place at an equal rate at ordinary temperatures and in a medium which is only just faintly alkaline or neutral.[1]

When we turn our attention to the individual cell we are at once impressed by the peculiarities of its structure. We are confronted not only by the nucleus but also by the problems of the cytoplasm with its centrosome, mitochondria, Golgi network, canalicular apparatus, and other possible constituents. The Golgi apparatus especially has been the subject of recent study.[2] This network, appar-

[1] Bayliss, loc. cit., p. 301.

[2] E. V. Cowdry, Science, N. S., vol. lvii, No. 1488, July 6, 1923, p. 1.

ently fluid in its nature, is found in all of the cells of the metazoa and also in isolated masses in the protozoa. It is wanting only in cells that are dead or dying. Gland cells especially have a large Golgi apparatus. It is apparently well developed in stages of cytometamorphosis; it becomes gradually smaller as the cell ages; it disappears with senility and death. Certainly it seems justifiable to regard it as actively concerned in cell metabolism, just as the centrosome is actively concerned in cell division. That the other cell contents also play important rôles is, to say the least, exceedingly probable. Notwithstanding our increasing knowledge, very much remains in the domain of speculation; but of one thing we are certain, and that is that the cell is a teeming chemical laboratory. Not many years ago the atom was the unit of the chemist and physicist. Today, with its nucleus and revolving electrons, it is known to be of great complexity and to be a marvelous storehouse of energy. Similarly is it with the biological unit, the cell. It also has revealed itself to be of great complexity. It is able to accomplish quietly and without disturbance chemical transformations which, as we have just seen, can only be accomplished in the laboratory with the aid of powerful reagents and high temperatures. The living cell is not only a chemical laboratory, but is one of great dynamic power.

Let us now turn our attention to those associations of cells we call the metazoa. Here the difficulties of interpretation appear at first almost insurmountable; and yet, I believe, the facts presented permit of generalizations and conclusions of great value. Why in the course of organic evolution a stage was reached when the daughter-cells resulting from cell division no longer became separate and distinct individuals, but became associated, so that by a continuation of the process of cell division large cell aggregations were finally formed, cannot now be answered save in a speculative manner. Perhaps these aggregations resulted from an agglutination, an adherence of cell to cell, due to the formation of a special secretion; perhaps other physical causes were at work. But whatever the causes, the fact remains that the problem that now confronts us is that of multicellular activities.

Let us see how these multicellular activities at first manifest themselves. Evidently they find their simplest expression in the early stages of embryonic development. Here we are not concerned with two-parent or germ cells, the gametes, but only with the cell resulting from their union, the zygote. By the continued cell division of the latter a spherical aggregate is formed, the blastosphere, called also by the older embryologists the mulberry mass. Soon an infolding takes place which results in a sac-like structure, the gastrula, with a central opening, the blastopore. Two layers of cells are formed, one called the ectoderm or epiblast, and the other the entoderm or hypoblast. Next a third layer, the mesoderm or mesoblast, is developed. It lies between the other two and itself consists of two portions, one the somatopleure, the other the splanchnopleure. The ectoderm gives rise to the general epithelial covering of the body, but, most important of all, by an infolding of a longitudinal area it forms a tubal structure which develops into the central nervous system. Similarly the entoderm by a process of infolding forms the digestive tube. In general terms, the splanchnopleure is the visceral layer of the mesoderm covering the digestive tube; the somatopleure is the layer which lies beneath the ectoderm and from which the structures subjacent to the latter are developed. The space between the two layers of the mesoderm is known as the celom or body cavity. In the vertebrates it is represented by such structures as the cavity of the peritoneum and the cavity of the pleura.

How are the above sequences which constitute the elementary facts of embryology to be explained? Are we to apply a principle of inheritance of cell growth and of cell arrangement? or are we perhaps to content ourselves with the view that the embryo rehearses, other things equal, the various steps traversed by its ancestors, a view which appears to be abundantly justified when the details of the evolution of the organism are considered? Unfortunately, neither the view of inheritance nor of repetition explains; neither can be considered, at most, more than a mere statement of fact. Clearly, the explanation is to be sought in an application of physical and chemical principles, although this forces us more or less into the field of speculation. It is not difficult to understand how the continued reproduction of cells by division—the daughter-cells being coherent—should result mechanically in an agglutinated spherical mass. However, the formation of the gastrula and the differentiation into a series of layers at once introduces problems that can only be referred to differences in rate of growth, to differences in the rate of chemical activity, and finally, to differences in the kind of chemical changes taking place. Such differences may have their origin in slight but potential differences in propinquity to food and to slight differences in the degree of regional oxidation. Naturally, differences in rate of growth would result in changes of form. Differences in the degree and rate of oxidation would inevitably lead to differences in chemical changes, both in degree and in kind. This result would be further favored by differences alike in the amount of the food and in the character of the food, both of which factors would result from the relative propinquity to food and the possibilities of selection (see p. 21). That the materials discharged by the cells as a result of their metabolism would under these circumstances differ decidedly is a legitimate inference. As already pointed out, such materials may consist of waste materials, of materials which still have a food value or of materials which influence the chemical changes in other cells (see p. 22). Have we not here the beginning of the "internal secretions"?

The thought also suggests itself that the reason the embryos of a given form always pursue the same course in their development—in the process of their "unfolding"—is merely because like causes produce like results. Have we not here also the keynote of the explanation of inheritance? However, this is beside our present subject.

Let us now turn our attention again to the three layers of the embryo. The outer layer, as we have seen, gives rise to the epithelial covering together with a portion especially modified by its reactions to the environment; namely, the nervous system. The inner layer, as a result of its position, has its functions limited to the metabolism of food particles. Naturally, the structure of the cœlenterates suggests itself in this connection, but the comparison ceases here, as in these animals the external layer develops no special nervous area.

It is, however, the mesoderm—absent in the cœlenterates—which now especially invites our attention. The mesoderm, or mesenchyme, a name which in some respects is to be preferred, is a layer the cells of which, doubtless because of their independence both of external relations and of the intake of food, retain, more than the cells of either of the other layers, the generalized properties of the simple, primordial, undifferentiated cell, and, in consequence, reveal the most marvelous polymorphic possibilities. Lymph and blood, heart and vessels, muscle and bone, connective tissue, the major portion of the sympathetic nervous system, various glandular structures, all have their origin in this layer. A discussion of how these structures are differentiated would take us too far afield. It is not the object of this essay to trace the details of organic evolution as revealed by embryology, but merely to consider such facts as have a bearing upon the internal secretions.

II

THE CLINIC; EXPERIMENTS MADE BY NATURE

It will now serve our purpose best to approach the subject from another point of view. One of the first and most important facts to bear in mind is that our earliest knowledge of the subject of the internal secretions—its very beginnings—was derived not from experiments made in the laboratory, but from experiments made by nature, experiments which came under the observation of physicians in the ordinary course of medical and hospital practice. To realize how strikingly true this is we need but recall the observations of Basedow and Graves in exophthalmic goiter, of Sir William Gull and William Ord in myxedema, and of Charcot in his "cachexie pachydermique," of Addison in the disease that so justly bears his name, and of the remarkable observations of Pierre Marie in acromegaly. To these may be added the observations made in adiposis dolorosa, in dystrophia adiposogenitalis, in disease of the cortex of the adrenals, in disease of the pineal gland, in disease of the thymus and of the lymphatic system. Not one of the original observations which led to our subsequent knowledge of the subject was made in the laboratory. All were clinical. The laboratory, it is true, later and in given instances, added to and expanded our knowledge; but in not a single instance did the laboratory originate it. This remarkable fact cannot be too strongly impressed upon our minds in virtue of what is to follow. It is interesting further to reflect that but a few generations ago the glands of internal secretion were the subject merely of anatomical study and of curious speculations in which theories of vestigial survival played a prominent rôle. All this clinical observation has swept aside.

In what did the experiments which nature performed for us and which she still performs for us in that most remarkable of all laboratories, the clinic, consist? Evidently they were in part due to disturbances of development, to morphological arrests and overgrowths, and in part to disease processes superimposed upon structures otherwise normally developed.

Clearly, the morphological disturbances are the first to present themselves for our consideration.

To begin with, a metazoan, though made up of many cells, is a unit. Its various parts are, beyond all question, interrelated. This has already been indicated in the considerations advanced in the preceding pages. Further, this unit is "in balance"—*i. e.*, its various parts are in such relation with each other physically and chemically as to constitute a harmonious whole. Lastly, in order that it should constitute in the individual instance a "normal" individual, its various parts must be developed in given relative proportions and to the degree which constitutes the "normal" level. To make it possible that the organism should attain this "normal" level—should in the course of the cycle of its existence attain that stage which we speak of as the "normal adult form"—it is necessary that the germ plasm of the parents and, in consequence, the resulting zygote and the daughter-cells of the countless generations that follow, should be the seat of those active physical and chemical changes which, as we have seen, are inherent in cell life, and further, that these changes should be present in a degree of such intensiveness as to lead to the production of an average or "normal" individual. In the gametes these chemical processes are, of course, largely potential, are largely quiescent; in the zygote they become active and intensive; and this continues in the cells resulting from each cell division.[1] Should these physical and chemical processes not possess the necessary degree of intensiveness, the organism as a whole is reduced, and defects and deficiencies, deviations and malformations are the inevitable result.

The word "normal," of course, expresses only an average of qualities which allows of some though not a large degree of variation. Wide departures, especially in the human organism, are so striking as to permit of no misinterpretation. Again, these departures are of two kinds: first, those which are general and clearly involve the organism as a whole, and others

[1] It is interesting to reflect upon the enormous amount of energy present in the larger metazoa. With each cell division there is an addition of a new laboratory. Each new cell laboratory means a fresh accretion of energy; and this process continues at a rapidly increasing ratio until with the truly infinite number of cells a result of such magnitude is reached as to baffle the imagination and to be incapable of mathematical expression.

which appear to be local and relatively unimportant, such as the anomalies not infrequently found in the dissecting room; yet even these are not without a general significance.

Among the evidences of abnormality and subnormality in the human subject—among the evidences of aberrant, incomplete, or imperfect development—many present themselves to direct observation. Thus, inspection may reveal a trunk which does not present the normal contour of the adult or youth, but which is distinctly infantile in type; it is cylindroid in shape; the normal expansion in breadth at the shoulders and pelvis may be absent; even the lumbar flexure may be absent or very slightly marked. The scapulæ may be unusually winged; or perhaps the spine of the first thoracic vertebra is unusually prominent. At times also a distinct projection suggesting a rudimentary tail may be observed at the end of the spine.[1] Again, the extremities may show an excessive length or the normal proportion of length between the upper and lower extremities may be departed from, so that the arms

[1] Such a case was observed some years ago in the nervous wards of the Philadelphia General Hospital.

are relatively too long and the legs too short. There may also be abnormalities in the relative lengths of the digits, of the phalanges, and of the shapes of the hands or feet; this may be noted in the middle and ring fingers, or in the thumb; or the little finger may be disproportionately small; or the little finger when the hand and digits are extended may be slightly overextended in the proximal phalanx and flexed in the middle and distal phalanges (the "main nevropathique" of French writers). Sometimes there is—and this is much more common—a tendency to flat-foot. The presence of supernumerary digits also may be observed.

When we turn our attention to the head, we may note on opening the mouth a high, a narrow, or perhaps an irregular hard palate, due apparently to the failure of the fronto-nasal process of the embryo to descend to its usual level. We may note also an irregular conformation and abnormal position of the teeth; the latter may be unusually small, suggesting the teeth of childhood, and are often widely separated. They may also reveal striking morphological peculiarities, *e. g.*, rather large canines, canine interspaces, or crowns that are much and prematurely worn.

When we look at the ears we not infrequently observe that the lobe is small or imperfectly formed or that it is confluent with the cheek; that the concha is flaring and projecting from the side of the head; perhaps we note also that the concha is pointed or that the Darwinian tubercle is unusually pronounced; perhaps other irregularities are observed, for instance, that the external meatus is unduly narrow.

When we examine the skull we may find that it is unusually small or unusually large; that the forehead is unusually prominent and high or that it is unduly receding. We may note again that the vault of the skull is unusually pronounced or even pointed (oxycephalic), or that it is too low or even saddle shaped (clinocephalic), or that the occipital region is flattened, or that the parietal regions partake of this peculiarity. Perhaps we will observe that the face is too small in comparison with the size of the cranium; or, on the other hand, that the face is disproportionately large and the cranium too small; perhaps the lower jaw is too short and the chin receding, or too large and projecting, so that prognathism results.

It may be that in looking at the eyes we find that the space between them is unusually small, the globes seem to be too close to each other; or, on the other hand, they may seem too far apart. In examining the pupils, also, we may observe that they are somewhat unequal and that this inequality is morphological; or that they are not well rounded, perhaps plainly elliptical; or it may be that they are not exactly in the middle of the iris, but are eccentrically placed. Occasionally, too, we may note the presence of a fold of membrane over the inner angle of the eye, an epicanthus, calling to our mind the nictitating membrane of birds.

In looking at the body as a whole we may observe that the musculature is poorly or, it may be, unduly developed; or perhaps that the deposit of fat beneath the integument is excessive or unusual in its distribution, or, perhaps, that it is strikingly deficient. Unusual pigmentations, nevi, angiomata may be noted; or, the skin may be unusually dry, may seem thickened and coarse, perhaps scaly; on the other hand, it may be unduly moist or changed in hue; perhaps livid, especially in the distal portions of the extremities. At times the surface of the body generally is darkened, especially under the flexures of the limbs and in the groins and axillæ. At times, again, the surface of the body is unduly hirsute; hair, often coarse and dense in quality, is noted upon the limbs, the chest, the back, and even over the abdomen.

Interesting observations may also be made as to the genital development and the secondary sexual characters. We may note, for instance, in men, that the genitalia are small, perhaps decidedly undeveloped; that the hair of the pubis is very sparse or that it is abnormally distributed, *i. e.*, is of the feminine type, and instead of being prolonged in triangular extension upward, ceases abruptly and transversely. Together with this there is usually an absence or feeble development of hair upon the trunk or extremities; the skin is unduly smooth and resembles that of the female; the beard and moustache are likewise either feebly developed or absent; the larynx and voice are feminine in character; the voice smooth, soft, and rather high in pitch. In keeping with these findings there is commonly a fulness of the breasts, buttocks, and extremities suggesting the feminine contour. The pelvis also is likely to be broad and of the feminine type. Sometimes such features are associated with knock-knee and with retroflexion at the elbow.

In women the pubic hair may have the distribution typical of the male, and together with this there is frequently a tendency—at times marked—to the growth of a moustache and beard. The pelvis is narrow and the shoulders broad, suggesting those of the male. The musculature, too, is masculine in type; this is especially noticeable in the development of the upper extremities. The mammæ are small and commonly flattened; the nipples are poorly developed; at times supernumerary nipples are noted. The external genitalia are frequently small, sometimes infantile in appearance. A cleft vagina may be present.

Should anatomical studies be made in such cases, anomalies may also be found in the deeper lying structures. For instance, the vascular apparatus may present the evidences of an incomplete development; thus, the heart may be unusually small, and this may also be true of the aorta and of the blood-vessels generally; a persistent foramen ovale may also be noted. Occasionally other viscera show unusual features; thus, the kidneys may be lobulated, or joined together in such a way as to form the "horseshoe-kidney"; at other times the renal substance may be so distributed as to be truly amorphous. The liver, too, may show an unusual arrangement of its lobes; the lungs may show a persistence of the lobular formation present in the early fetus and in monkeys. The intestinal tract may reveal an excessive length, unusual diverticulation, departures and irregularities of lumen, and other anomalies. If the brain be examined, abnormal fissures may be noted in the cerebral cortex. Sometimes these, because of their anatomical relations and resemblance to fissures found in the brains of anthropoid apes, are spoken of as "ape-like" fissures; they are always the expression of a failure of the cortex at the special point or area involved to grow up to the general cortical level.

Should our anatomical studies be carried still farther, we may find a supernumerary rib, *e. g.*, a seventh cervical; or, it may be, that besides the eleventh and twelfth being floating ribs, the tenth also partakes of this peculiarity; perhaps, too, that the spinous processes of some of the vertebræ—*e. g.*, of the lower dorsal or lumbar regions—are divided or forked. Studies of the muscular apparatus also yield interesting details, but they hardly add to the significance of the facts already enumerated. Many more interesting details, also, could be cited based upon the morphological findings in idiots and feeble-minded children, but these would take us too far afield and are not necessary to our purpose.

The mass of clinical and anatomical findings expressive of deficient and aberrant development are spoken of collectively in the clinic as "stigmata of arrest." Some of them are quite common, others infrequent, and others still quite rare. All, however, have the same significance, namely, that the physical and chemical processes inherent in the germ plasm of the parents lacked the necessary intensiveness to lead to a full and normal maturity (see p. 37). The lessening or flagging of this intensiveness leads to a reduction of the organism as a whole as manifested by the presence to a varying degree of these stigmata. Sometimes the number of the stigmata is small; sometimes, too, the surface stigmata are slight or even wanting, and yet the fact of a reduction of the organism may be revealed by other features no less significant. Among these, "left-handedness" should especially be mentioned. Not infrequently left-handedness is associated with other unmistakable evidences of abnormal morphology and endocrine anomalies.

III

RELATION OF THE EMBRYONIC LAYERS TO DEVELOPMENTAL FAILURE

Let us now turn our attention once more to the three layers of the embryo, and more especially to the marvelous protean mesenchyme. The cells of this layer are, of course, at first undifferentiated. Soon some of them become joined together and constitute a network in the interspaces of which other cells, which have remained separate from each other, are freely floating. Clearly, these cells suggest lymph-cells, and together with the network suggest a "lymphoid tissue." Soon other and more elaborate changes take place which result in the differentiation of heart, vessels, blood, muscle, nerve-cell, gland, bone, etc., but some of this primitive and comparatively undifferentiated tissue—this lymphoid tissue—always remains. Some of it persists in the interspaces between the tissues; here and there channels are formed; here and there well-differentiated vessels. Here and there loose aggregations occur forming the lymph-glands. Everywhere does it communicate with the body spaces, large or small, and everywhere do these body spaces form part of its system. The very capillaries lie in such spaces; every capillary is surrounded by a lymph space, nowhere does the blood come directly in contact with the tissue which it supplies, but always and only through the intervening capillary lymph space. No matter how complex the chemical interchange between the blood and a tissue, this interchange can only take place through the lymph, this simple saline fluid, with its simple,[1] loosely floating, undifferentiated[1] corpuscle.[2]

Clearly, we have in the lymphoid tissue of the body a tissue that is very primitive, one that differs but little from the tissue of the mesenchyme in which it has its birth. Certainly it differs from the mesenchyme very much less than do the muscle-cells, nerve-cells, gland-cells, blood-cells, and the other highly differentiated structures that have their origin

[1] Question marks might be placed after these adjectives.

[2] The mechanism of our nutrition does not differ so widely after all from the water vascular apparatus of our remote aquatic ancestors.

in the same layer. Is it not fair to assume that the physical and chemical processes necessary to its production are far less intensive, require the expenditure of far less energy, than in the case of the other greatly modified and highly differentiated structures to which the mesenchyme gives rise with their marvelously individualized metabolism? Is it not fair to assume—to state the fact in other words—that because lymphoid tissue is so simple and so primitive, it is produced at a greatly lessened expense to the organism? If this inference be justified, we should expect, when the organism undergoes a reduction as a result of a lowering of the intensiveness of its processes, an excess of lymphoid tissue to be formed. This is exactly what we find. Clinically this condition is termed the "lymphatic constitution," the "lymphatic diathesis," or, better still, "lymphatic hyperplasia." In its simplest expression it is frequently met with in children. The latter often present a superficial appearance of good nutrition, but also enlargements, overdevelopments of the lymphatic glands, and lymphatic structures generally; quite commonly such cases are featured by an excessive development of adenoid tissues in the nasopharynx. Quite commonly, too, they present an unusual feebleness of resistance to infections. We find, also, that the various stigmata of arrest and deviation which are so expressive of the reduction of the organism (see p. 38) are commonly associated with an overdevelopment of the lymphatic system. Indeed, the impression which one receives at times in such cases is that of a general feebleness of tissue development. In enumerating earlier in this essay the various evidences of reduction, the fact of the frequency of a lymphoid hyperplasia was purposely withheld in order that later it might, because of its importance, be placed in its proper perspective. That it is of great and fundamental significance cannot, I think, be questioned.

Another matter of great and equal importance now demands our attention, namely, the subject of the thymus gland. Quite commonly we find that the thymus gland is strikingly associated with lymphatic hyperplasia. In order that we may form some conception or even in a measure be able to picture to ourselves the position and the rôle of this gland, a brief consideration of its origin and structure is necessary.

The thymus makes its appearance in the embryo as an involution of the entodermal layer on either side of the pharynx. It soon separates from the latter and later makes its appearance as an independent structure considerably removed from its site of origin. It is remarkable, also, for the fact that it is constant in the vertebrate series, being found in fishes, amphibians, reptiles, birds, and mammals. The fact that the thymus arises from the entoderm and that it is primarily of epithelial origin is, in the judgment of the writer, of great significance and has an important bearing upon our interpretation of the organ.

When we examine the structure of the thymus we find that it is composed of *two* morphologically distinct parts, fundamentally different from each other. The first is of undoubted epithelial origin and consists of a reticulum with a series of nests of cells, the so-called concentric corpuscles of Hassall. This reticulum and the corpuscles of Hassall constitute the *fixed* structure of the thymus. The second part is made up of a large number of small movable cells which cannot in any way be distinguished from lymph-cells. That they are in reality lymph-cells was successfully shown by Hammar, Maximow, and Hart.[1] They are, therefore, of mesodermal origin, and having originated in the mesoderm, the mesenchyme, they can only be regarded, as far as the thymus is concerned, as immigrants or accretions. According to the modern interpretation, the special parenchyma of the thymus is represented by the epithelial elements; these constitute the specific part of the organ. The second component consists of lymphocytes which originally have no place in the organ, but simply wander into it from without. In keeping with this we find the gland consisting, roughly speaking, of a cortical and medullary portion. The cortex is composed of lymphoid tissue; the medulla, of nests of epithelial cells.

Speaking of both the epithelial and lymphoid portions together as one organ, it may be stated that the thymus continues to enlarge in size until the second year of life. It then

[1] See Joseph Wiesel, Lewandowsky's Handbuch der Neurologie, Vierter Band, Spezielle Neurologie, iii, p. 383.

becomes stationary and remains so until puberty, when it again rapidly diminishes; but it never entirely disappears, and it is very probable that it continues to exercise some function during the entire lifetime of the organism. The diminution in size appears to be due mainly to an emigration of the lymphocytes; at all events, the epithelial elements are the least affected and persist the longest. A senescence of these epithelial elements may, it is true, take place at puberty—analogous to that which takes place in the pineal gland—but the fact of their persistence in a greater or lesser degree lends support to the view that their function, whatever it may be, is never entirely abolished. To the consideration of this problem we will later return.

The fact which most concerns us at present is that in cases presenting lymphatic hyperplasia together with the other evidences of organic reduction, such as the stigmata of arrest and deviation, the thymus gland fails to undergo diminution at puberty, but persists unchanged and perhaps even enlarged. When we realize the rôle that lymphoid tissue plays in the size of the thymus and bear in mind that the diminution of the gland at puberty is due mainly if not altogether to the loss of this lymphoid tissue, to the emigration of the lymphocytes, it becomes clear that the persistence and enlargement of the structure is but a part of the picture presented by general lymphatic hyperplasia.

In times past, as well as in recent times, the thymus gland has been the subject of laboratory research. The method pursued has been that of removal of the gland and observing the results. Knowing as we do now the double structure of the organ, this method can only be looked upon with doubt and distrust. This attitude of mind is strengthened when we find that the results of the experiments have often differed widely. From the earliest experiments no satisfactory conclusions whatever could be drawn. However, the results of Basch, Klose, Vogt, and Matti seem to indicate that extirpation of the thymus in very young animals leads to bony changes similar to those found in rachitis, accompanied by a general cachexia, with retardation of growth, softness and fragility of the bones, and muscular weakness. These results were obtained in the majority of the animals operated upon provided the animals were sufficiently young. Other changes noted were increase in the size of the thyroid gland, the pancreas, and the medulla of the adrenals; increase of the interstitial tissue of the testicles was also reported by some observers. These observations have failed of confirmation in whole or in part by other observers.[1] Crass contradiction has been the result; on one side it has been maintained that the thymus gland is intimately concerned with the development of the skeleton and other structures in the fetus and young animal; on the other hand, that it has no function and should not be included among the organs of internal secretion. Upon the assumption that the organ is useless and has no significance we must unhesitatingly turn our backs. Such an assumption in the case of a structure which is present in all vertebrate forms—fishes, amphibians, reptiles, birds, and mammals alike—is manifestly a gross absurdity. It is merely a return to the attitude of mind that because we do not understand a

[1] See, among others, Park and McClure, Amer. Jour. Dis. of Children, vol. xviii, No. 5, p. 317, November, 1919.

structure therefore it has neither use nor meaning. It is not our task, moreover, to attempt to reconcile divergent views. Possibly differences of results are due in part to differences in the ages of the animals experimented upon; possibly the absence of positive findings are due to compensation of function by other structures; indeed, as far as the lymphoid part of the thymus is concerned, it must be conceded that compensation by other lymphoid structures could very readily result. Perhaps other causes are at work to account for the presence of positive findings at one time and not at another. However, the important fact looms up before us that extirpation establishes a condition which is the very reverse of that of persistence and enlargement of the organ, the condition which is actually met with in nature. Inferences based upon extirpation are, therefore, for this added reason extremely hazardous.

Happily, under the circumstances, we have one recourse; one, too, that is much more satisfactory. It is the clinic, that wonderful laboratory in which the experiments come to our hands ready made. Here we meet with the condition which we have been studying, lymphatic hyperplasia; which, associated with thymic persistence or enlargement, is spoken of as the status thymicolymphaticus. It can properly be regarded, as already indicated, as expressive of an inherent feebleness of tissue development. It must not be inferred, however, that all feebleness of tissue development expresses itself necessarily as a lymphatic hyperplasia; it may express itself as we shall see in other ways. Indeed, lymphatic hyperplasia may be but little marked or altogether wanting, and instead the feebleness of tissue development may express itself in local and special deficiencies, or it may be in overdevelopments suggestive of overcompensation. Clearly, lymphatic hyperplasia is to be looked upon as a generalized condition. In the form of the status thymicolymphaticus, in which it presents itself most often clinically, it is clearly the first condition to claim our attention.

Here we meet with the various deficiencies and anomalies—the stigmata of arrest and deviation—already sufficiently considered in the preceding pages, and which are so significant of a general failure or lowering of the intensiveness of the physical and chemical processes concerned in cell growth and, consequently, in tissue development. We note also, as has already been mentioned, a special vulnerability, a feebleness of resistance to infections and traumata of all kinds, especially in children, though this is also noted in adults. Comparatively simple and mild disturbances may be followed by grave exhaustion or even have a lethal termination. Operations, too, are frequently badly borne. In adults feeble resistance to fatigue is commonly noted; also asthenia, various forms of nervous exhaustion, nervous instability, slowness of thought, lack of mental energy, lack of initiative, lack of power of concentration, and absence of pertinacity of purpose. Again, simpleness or childlike character of thought, inadequacy and inferiority, or, it may be, symptoms embraced under such captions as psychasthenia, mental underdevelopment, psychic infantilism, and even graver forms of mental disease may be the accompaniments. Very frequently the symptoms of the nervous and mental disorders are so pronounced and dominant that they feature the clinical picture, and the underlying and inherent constitutional inferiority may be lost sight of.

In addition to the above facts of general significance, there are several special features presented by the status thymicolymphaticus which must be considered, and which, both because of their theoretical as well as their practical importance, demand especial emphasis. I refer more especially to so-called "thymic asthma" and "thymic death."

The occurrence in children of severe asthmatic attacks, with great difficulty of breathing and laryngeal spasm followed by sudden death, has been known to physicians for a long time. Autopsies have revealed a thymus that was abnormally large, and the explanation naturally presented itself that the symptoms were the result of an abnormal pressure exerted by an enlarged thymus on the trachea, nerves, and blood-vessels. However, the theory of pressure seemed to be inadequate and led for a time even to the denial of the existence of a specific thymic asthma or thymic death. However, the very frequent occurrence of an enlarged thymus in the autopsies finally forced the admission of the undoubted association of enlarged thymus with the symptoms. Attempts have at various times been made to revive the theory of pressure, but an increasing experience has proved it to be totally inadequate.

Setting aside for the moment the explanation as to the possible cause, it should—in the experience and judgment of the writer—be regarded as significant when asthmatic symptoms make their appearance in early childhood and persist throughout childhood and for a variable period throughout youth. Very suggestive is it, too, when in such cases the larynx, especially in males, remains somewhat undeveloped and the voice a little higher pitched than normally and rasping in quality. Such a clinical history is every now and then met with in persons who later on develop some nervous disorder presenting symptoms such as those above enumerated, *e. g.*, a psychasthenia. It is even met with, though infrequently, in the past histories and as a recurrent and persistent disorder in dementia præcox. Certainly "pressure" does not explain the symptoms.

Further, thymic asthma, which in its paroxysmal form in children so frequently leads to a fatal termination, is not a necessary precursor of thymic death. Sudden death every now and then occurs in adults under circumstances not preceded or attended by any illness of moment. Sometimes muscular effort or mental excitement—at times so slight a cause as, for instance, the trauma of a bath in the surf even when the latter is not rough—is the determining factor. A seemingly unaccountable and unexpected "heart failure" appears to be the cause; the autopsy not infrequently reveals a persistent or enlarged thymus, together with the absence of other lesions to which the death could be attributed. The death is unquestionably a heart death, and the question arises Can such a death be ascribed to a lymphatic hyperplasia? If so, why were not a long train of symptoms indicative of gradual and increasing cardiac weakness previously present? It is difficult to avoid the conclusion that thymic death is a toxic death and that the source of the poison must be sought elsewhere than in the lymphatic tissue. The explanation that suggests itself is that the toxic agent, whatever it may be, is secreted by the epithelial tissue of the thymus—the true thymic gland—and that this toxic agent is overwhelmingly vagotonic and thus brings about the cardiac arrest. Similarly, the vagotonic action of this toxin or hormone brings about the excessive contraction of the circular muscles of the bronchial tubes, and thus causes the thymic asthma. The laryngeal spasm, so often an accompaniment, has, of course, a similar explanation; and it is not going too far to assume that such an action also explains even that less serious affection, the laryngismus stridulus of children. That the experimental laboratory has failed thus far to isolate a thymic hormone is, of course, no argument against its existence; but more of this later.[1]

[1] It is, of course, not impossible that an enlarged thymus leads indirectly to lecithin decomposition with the formation of cholin and the oxydized products of the latter, neurin and muscarin. If so this would offer an explanation of the various thymic crises, for these substances, notably the muscarin, are powerful poisons and depressants. Proof, however, is lacking.

IV

THE ADRENALS; THEIR THYMIC RELATIONS

THE discussion of the thymus leads very naturally to the discussion of another gland. It has been noted—and Wiesel has directed especial attention to this fact—that in thymic excess and persistence, the medullary portion of the suprarenal capsule is inadequately developed or has perhaps suffered from a superimposed infection, as in the tuberculosis of the capsule in Addison's disease. Let us, therefore, at present turn our attention to the suprarenal or, better, the adrenal capsule.

One of the most interesting and important facts that first impresses us is that the medullary and cortical portions of the adrenals really constitute two entirely different organs which have no relation to each other save that of a tissue propinquity. The facts of morphology may be briefly stated as follows: Nothing corresponding to the adrenal glands of other vertebrates is found either in the amphioxus or in the dipnoic fishes. In the sharks and allied forms, however, structures are found in relation with the ganglia of the sympathetic nervous system which clearly correspond to the chromaffin structures of the higher vertebrates, while another structure lying between the kidneys and termed the "interrenal body" appears to represent the cortical substance of the adrenals of the higher forms. In any event, there can be no doubt as to the separateness—the morphological independence—of the two portions of the adrenal in mammals; the cortex and the medulla. This independence is further borne out, as we shall see, by an utter difference in the respective rôles played by these two structures in the organism.

It should be added here that the medullary portion, because it is stained yellow by the chromium salts of the hardening reagents, is spoken of as the chromaffin portion. Further, this tissue is not confined to the medulla of the adrenals, but is found distributed through the ganglia of the sympathetic nervous system, and is also met with elsewhere; for instance, in the carotid and coccygeal bodies. Clearly, this tissue, though so widely distributed, constitutes but one apparatus. It is conveniently spoken of as the chromaffin system.

Another exceedingly interesting fact that presents itself is that the cells of the adrenal medulla and of the chromaffin system generally —the cells which produce the remarkable hormone adrenalin—arise side by side in the same blast of the embryo as the sympathetic nerve-cells, with which they are closely associated. Apparently the cells which become glandular and the cells which become nervous are at first indistinguishable from each other, but in the course of development one cell throws off a catalyst which induces profound changes in the metabolism of the other, as a result of which the latter liberates energy; in other words, the catalyst, which has received the names of adrenalin or epinephrin, is sympathicotropic and its action is sympathicotonic. Now, the heart receives a sympathetic innervation through the accelerator nerves, but it also receives an innervation through the vagus. The heart is thus, as is well known, under the influence of two antagonistic nervous influences; and the facts justify the assumption that if the accelerators (the sympathetic supply) are acting under the influence of a special hormone furnished by the chromaffin system, a hormone that is sympathicotropic and sympathicotonic, the vagus, in its turn, is acting under the influence of a hormone that is vagotropic and vagotonic; although, as has just been stated, such a hormone has not yet been isolated. The facts justify the inference that in thymic enlargement and persistence this enlargement and persistence is the indirect result of a biologically feebly developed chromaffin system. It would appear that the hormone, adrenalin, which is so markedly sympathicotonic has an exactly opposite action on the vagus or on the structures supplied by the latter. It is deterrent, restraining, inhibitory. Its antagonistic action being lessened or withdrawn, the thymus would, other things equal, become abnormally large under the unrestrained stimulation of the vagus supply; and in order that vagal crises should occur, such as result in attacks of asthma or in arrest of the heart, it is only fair to assume the existence of a special vagotonic hormone. The thymus gland, it should be remembered, also, has both a vagus and a sympathetic nerve supply, though the supply is small. It is probable that the original feebleness of development of the chromaffin system in given cases is related to the general feebleness of development instanced by lymphatic hyperplasia. Just why this structure, the chromaffin system, should in given instances suffer rather than the thymus is a question which we will consider later. It is enough for the present to recognize the resulting physiological imbalance.

V

THE THYMUS; ITS THYROID AND OTHER RELATIONS

The question next arises, Are there other glands which have thymic relations? It is stated, for instance, that in cases of thymic enlargement and persistence the sex glands are feebly developed or are in a condition of arrest. The tendency has been on the part of many writers to attribute this result to the thymic enlargement and to infer a relation of antagonism between the thymus and the sex glands. Castration in animals, according to some observers, results in an enlarged thymus; other observers have denied this. The statement that extirpation of the thymus leads to enlargement of the sex glands is likewise interesting, but requires confirmation. When we turn our attention to autopsies of the human eunuch we find that, among other changes, the thymus may present an infantile persistence, but that this finding is not constant. It is, on the whole, probable that the sexual deficiencies and abnormalities observed in the status thymicolymphaticus are related to and are to be ascribed to the general biological feebleness of development instanced, as just stated, by the lymphatic hyperplasia itself.

As regards thymic relations to other glands still, we are impressed by the frequent finding of an enlarged thymus together with the lymphatic hyperplasia in exophthalmic goiter. According to Klose,[1] there is no Graves' disease without thymus enlargement. If so, the thymus is probably playing a rôle along with the thyroid in the production of the symptoms. It is interesting to add in this connection that in the opposite condition, that of marked deficiency or failure of development of the thyroid gland, Pineles found in very young individuals a marked deficiency of thymus development, the organ being almost free of lymphocytes and Hassall corpuscles, but rich in connective tissue. It would seem, therefore, that morphological overdevelopment and morphological underdevelopment of the thyroid and thymus go hand in hand. The inference that the two organs are in some way

[1] See Wiesel, loc. cit., p. 405.

interrelated in function seems, therefore, justified. However, the thymus persistence and enlargement is, as we have seen, in all probability, determined by other factors than enlargement of the thyroid gland; more especially, as already pointed out, by inadequacy of the chromaffin system. Further, thymic persistence and enlargement may occur without thyroid enlargement, as is well known, and, as the writer believes, with disastrous results to the organism. It must be admitted, on the other hand, that cases of hyperthyroidism are met with in which thymus enlargement appears to be absent; at least remains unrecognized. Commonly I believe this enlargement to be overlooked, and clinically it is very frequently difficult of demonstration; even studies with the *x*-ray are unsatisfactory and inconclusive, and yet there are fundamental reasons—as I hope to show—for believing in its existence. To the consideration of this problem we will presently recur.

The relations of the thymus to the lymphatic system, finally, demands our attention. These relations are so intimate that they must have a profound significance. Early in the development of the epithelial thymus it is invaded by the lymphocytes, and the period of its greatest functional activity seems to correspond with the maximal period of this invasion. It would seem as though it formed a special nidus for the maintenance and growth of the lymphocytes, and it is not going too far to assume that one of the functions of the epithelial thymus is to furnish a substance which is especially favorable to lymphocyte life. In such case the dynamic principles which govern cell nutrition—indicated earlier in this essay—would abundantly explain the invasion. It would appear, finally, that the thymus, like some of the other glands, possesses more than one function.

VI

THE THYROID

THE discussion of the possible relations of the thymus with other structures will be deferred for the present. Let us now turn our attention to the thyroid. Like the thymus, the thyroid has its origin in the entoderm. It is developed between the second and third branchial clefts. It at first is provided with a duct which, however, in the course of development becomes separated from the main body of the organ, but persists as the foramen cecum of the tongue. It is found in tunicates, in the amphioxus, and in all vertebrates. In the larval lamprey the connection with the pharynx is present, but in the adult, as in all vertebrates, the connection is lost.

Clinical studies have thrown much light upon the functions of the thyroid. Nature has presented to us two conditions, one expressive of thyroid inadequacy and the other expressive of thyroid excess. It is to thyroid inadequacy that we will first give attention.

Thyroid inadequacy presents itself under several forms: thus, it is met with as a congenital condition; it is met with in the form of endemic cretinism; again, as myxedema of the adult; as myxedema the result of thyroid extirpation; and finally, it presents itself in relatively mild forms of hypothyroidism. In congenital myxedema the gland may have failed in great part to develop; it may, indeed, be almost wholly wanting and be represented only by a very few thyroid acini. In such cases evidences of a destruction of a previously existing gland by some inflammatory or other pathological process are wanting; for instance, the parathyroids which have their nidus in the same anatomical region may be entirely normal. Quite commonly children so affected seem normal at birth and for several months after birth. Possibly during fetal life they receive an adequate supply of thyroid elements from the mother through the placenta and later from the mother's milk. At any rate, usually after this supply of nourishment is cut off, the symptoms of a myxedema set in rapidly and may become very pronounced. The child sleeps excessively, grows stouter, the skin becomes infiltrated, acquires folds and wrinkles, the nose becomes broad, the root of the nose depressed, the nostrils large and prominent, the mouth open, the tongue large and protruding, the lips large and swollen, and the tissues of the face distended, while the eyes seem small and deeply placed. In short, the appearances suggest those of the more commonly observed cretin. While cretinism is due apparently to a degeneration of a previously present and normal thyroid—a degeneration which occurs endemically and appears to have a relation to the drinking-water of given localities—the symptoms observed are in their essence the same. Similar is it with the myxedema of the adult and with the myxedema of extirpation. The clinical pictures differ, of course, greatly in their details according to the age at which the thyroid insufficiency becomes established, but our immediate interest centers in the changes fundamental to them all.

The most striking feature of the affection, namely, the swollen, distended skin, results from the formation of mucin or a mucin-like substance. In fact, it is this characteristic which suggested the name of the disease, mucin-edema, myxedema. It is an edema which does not pit on pressure. Pathological examination of the skin reveals the interspaces in the connective tissue of the corium filled with a viscid semifluid substance. The precise nature of this substance is not yet definitely known, though its identity with mucin was made exceedingly probable by the studies of Hun and Prudden and of Stevenson and Halliburton, who found the mucin content of the skin greatly increased. It does not appear to be limited to the skin, though it is by far most evident in the latter. It has been found in experimental myxedema in monkeys to be present also in the blood and in the parotid gland. It should be mentioned, also, that Ewald some years ago made the interesting suggestion that the physical appearances in myxedema are really due to a trophic change which results in the formation of a tissue which remains at an embryonal stage.

The objects of the present essay do not include a detailed discussion of symptomatology, but merely the presentation of such facts as have a bearing upon the profound nutritive disturbances present. Among the most striking of the latter are the well-known changes in the osseous system. If the affection be congenital or due to cretinism, or, in fact, occurs at any time previous to the cessation of skeletal development, growth, stature, is greatly inhibited; this in children results in dwarfism. Microscopic investigations show an arrest or greatly delayed ossification both in the periosteal and cartilaginous bony development. That other tissues are affected—if not in their structure at least in their nutrition—is revealed by various symptoms. Prominent among these are the mental symptoms. Should the condition be congenital or be established in infancy or childhood, failure or arrest of mental development is the invariable result. This failure is so marked as to place the patients definitely among the group of the idiots and feebleminded. If the myxedema be established in adult life, mental impairment more or less marked in degree again results. The patient is dull, apathetic, and indifferent. Thought is greatly retarded, the speech slow and monotonous. All spontaneity is absent; there is great lack of energy and of voluntary effort. The movements are slow; the patient becomes readily fatigued and often remains seated in one position for a long time; is heavy and somnolent; but the sleep is often restless and disturbed by dreams. If the condition persists—remains untreated—loss of memory, confusion, featured it may be by hallucinations and an increasing mental impairment, lead to dementia.

While other symptoms are not so striking, it may be stated in general terms that the digestive tract and the circulatory apparatus likewise show a reduction in activity. That which interests us most, however, are the changes in metabolism. As might be anticipated, these also are reduced. Both the consumption of oxygen and the elimination of carbon dioxid are diminished, and this is also true of urea and uric acid. In keeping with this is the finding of a subnormal temperature, which though slight—97° F. and a fraction—is quite constant. Clearly the effect upon the organism of a deficiency or deprivation of the thyroid secretion is the reduction in the intensiveness of the chemical and physical changes in the organism. If this reduction occurs early in the history of the organism, it results in retardation of growth, in failure of development, in arrest. If it occurs later, it results in a retardation of the functions of the organism as a whole, and even—if we are permitted to interpret the suggestion of Ewald—in a reduction of the subepithelial cutaneous structures to an embryonic level.

Let us now turn our attention to thyroid excess. Here the conditions met with range from comparatively mild forms of hyperthyroidism to those presenting the symptoms typical of exophthalmic goiter. The picture is in its essentials the exact opposite of that observed in thyroid deficiency. Setting aside for the moment the triad of symptoms which form the striking clinical features, namely, the thyroid enlargement, the rapid pulse, and the protruding eyeballs, we note that the skin instead of being thickened and distended, as in myxedema, is thin; this is due in part to a thinning both of the subepithelial structures of the skin and to a diminution of the subcutaneous fat. Further, the surface is warm, not cool, as in myxedema; and its color is frequently heightened, not pale, as in myxedema. Again, the behavior of the patient is in crass contrast with that in myxedema. Instead of being dull and apathetic, difficult to interest or arouse, the patient is alert, nervous, excitable, restless. His movements, too, lack altogether the slowness and sluggishness noted in myxedema, and often a tremor is present. It is suggestive, also, to note that when the affection has made its appearance in a young individual that the latter has attained a rather unusual height; not gigantism, but, speaking in averages, it may be correctly stated that the height of youthful persons suffering from exophthalmic goiter is above the average with suggestive frequency. In the thyroid deficiencies of the young, as we have noted, just the opposite, shortness of stature and dwarfism, obtain. As regards the circulation and digestive tract, equal contrasts are the rule. In myxedema the circulation is reduced, the pulse-rate slow; in hyperthyroidism it is raised, stimulated, and the pulse-rate greatly increased. In myxedema there is dryness, sluggishness of the intestinal tract, and often obstinate constipation; in hyperthyroidism there is frequently diarrhea, often difficult of control; often, too, the gastro-intestinal irritability is featured by attacks of distressing vomiting. Many more clinical contrasts might be adduced, but they are sufficiently well known and are not necessary to the purposes of this essay. What most concerns us is the metabolism of hyperthyroidism.

One of the most impressive facts that confronts us is that patients suffering from hyperthyroidism, especially in the pronounced form seen in exophthalmic goiter, are emaciated or sooner or later become so. This occurs in spite of the fact that the appetite—in contrast to that of myxedema—is good, and in spite of abundant nourishment and in the absence of digestive disturbances. Just as in myxedema the consumption of oxygen is diminished, it is in hyperthyroidism increased, often to a very marked degree, as shown by Magnus-Levy, together with an increased output of carbon dioxid. As a result of the increased protein disintegration the output of nitrogen is increased. The metamorphosis of the fats and carbohydrates is greater still than that of the proteins. Sometimes, too, the temperature is slightly but distinctly elevated. Clearly, in thyroid excess, the intensiveness of the chemical and physical changes is increased, just as in myxedema it is decreased. These observations, it need hardly be added, are confirmed by the results of thyroid administration both in myxedema and in obesity in which increased metabolism follows, the changes being slow or rapid in proportion to the amount of thyroid administered. Indeed, when the latter is given in excessive doses, a decided febrile reaction results, while the nervous phenomena may become exaggerated until an active delirium is established. Similar phenomena, it need hardly be recalled, occur in the course of thyroid auto-intoxication when at any time this intoxication is suddenly increased or becomes massive.

The conclusion is inevitable that in the thyroid gland we have a structure that is intimately related to the intensiveness of the chemical and physical processes going on in the body. Metabolism, tissue oxidation, seems to be immediately under its control. The question arises, How and why do variations in the degree of the exercise of its functions occur? The problem of thyroid insufficiency may, as we have seen, be the result of an aplasia or hypoplasia, may be the result of a deficient development, itself the outcome of and in keeping with a lowered level of development of the organism as a whole. Doubtless a given number of cases of hypothyroidism are to be explained on this basis, *i. e.*, they are morphological in origin. Among them are to be grouped, for instance, many of the milder forms such as are observed so frequently among our psychasthenics. A large number, perhaps the majority, as in the case of cretinism and many cases of adult myxedema, are to be regarded as the results of disease processes superimposed upon previously normal glands; yet even here the suspicion is justified that often there is present an innate feebleness of biological resistance.

How are we to explain, on the other hand, the excessive development of the thyroid? The clinical histories tell us that in the vast majority of cases the patient fails to give an account of any incident to which the affection could be attributed. We are commonly told that the trouble came on gradually. Very general symptoms first make their appearance; ready fatigue, nervousness, weakness, palpitations, disturbed sleep. Later only and by degrees do the other symptoms make their appearance and become pronounced. On the other hand, the statement has been repeatedly made that fright, great emotional shock, has been the cause of exophthalmic goiter, and that this has occurred in persons previously healthy. The rarity, however, of such a sequel is a sufficient answer. Surely the great World War should have been a prolific cause of hyperthyroidism, and the latter should have been a common accompaniment of "shell shock"; which was certainly not the case. When hyperthyroidism follows a fright, an escape from drowning, a hold-up, or what not, it is quite safe to assume that the hyperthyroidism has existed previously and that the nervousness following the occurrence has merely called attention to it; at most, fright or shock could in such cases only be considered exciting causes. Similar is it with physical traumata. It appears that direct injuries of the gland itself, more particularly of its capsule, or traumata of the gland that may occur inadvertently during surgical operations, are necessary to a production of thyroid intoxication. Such results do not follow traumata of other portions of the body.

To the writer the conclusion seems more than justified that the enlargement of the gland in exophthalmic goiter and hyperthyroidism generally is morphological. The question at once arises, What is the cause of this morphological excess? Is it the result of a morphological "imbalance"? Is it the result of an overcompensation? If so, is this overcompensation shared by other glands? Evidently if an answer to these questions is attempted, the relations of the thyroid to other structures first demand attention.

VII

THE THYROID; ITS RELATIONS

We have already in part considered the relations of the thyroid to the thymus. The facts, I believe, unquestionably justify the following interpretation: First, the thymus is vagotropic and vagotonic; the thyroid is sympathicotropic and sympathicotonic. In this fact lies the explanation of the parallelism observed in their under- and overdevelopments (see p. 69); an underdeveloped thymus, an underdeveloped thyroid; an overdeveloped thymus, an overdeveloped thyroid. The persistence and enlargement of the thymus associated with lymphatic hyperplasia is, as we have seen, expressive of a feebleness of development of the organism, *i. e.*, is expressive of the lowering of the intensiveness of the chemical and physical processes of the organism as a whole. The dangers to which such an organism is exposed—dangers which may culminate in a vagotonic death—have already been pointed out. If now the thyroid increases in proportion, the situation is saved. The function of the thyroid is, as we have seen, that of raising the level of the chemical and physical processes of the body; that of increasing tissue oxidation and metabolism generally. One can readily understand that thyroid development having once begun may not cease within normal limits when the time comes for the thymus to undergo diminution. The latter failing of diminution or failing to diminish to the normal degree, the thyroid continues to grow and the condition of hyperthyroidism is established. Thus, thyroid excess becomes thyroid overcompensation and is clearly morphological. In its essence the condition, having its origin indirectly in the lowered biological level of thymic persistence, is itself expressive of an impaired development. An imbalance having once been established, other consequences naturally follow. The first is, that if the thymus is in antagonism with the chromaffin system, and the thyroid is in antagonism with the thymus, the thyroid must, other things equal, be in synergic accord with the chromaffin system. In a way the thyroid and the chromaffin system reinforce each other; each is, so to speak, necessary to the other. Clinically, very suggestive facts are observed. Every now and then glycosuria is noted in hyperthyroidism. This is apparently the indirect outcome of adrenalin excess. It is an important clinical fact, also, that glycosuria rarely if ever occurs in hypothyroidism; it has only been observed in isolated instances and in slight degree in myxedema, and then is probably to be ascribed to special causes. Further, we are informed that in thyreodectomized animals injections of adrenalin fail to produce glycosuria. The above facts suggest that in order for glycosuria to occur there must be a diminution of pancreatic function, a diminution in the amount of the insulin, that remarkable catalyst upon which the metamorphosis of carbohydrates ultimately depends. Evidently the conclusion that presents itself is that hyperthyroidism and hyperadrenalism depress pancreatic function. No such depression occurs in hypothyroidism; indeed, it is fair to assume that in myxedema the pancreatic function is relatively exaggerated; possibly this is true also in some forms of obesity.

Finally, it may be added that the hyperadrenalism secondary to thyroid overcompensation is also manifested by other symptoms referable to sympathetic excitation, *e. g.*, flushing or pallor, sometimes local, sometimes fugitive; or more persistent erythemas often accompanied by sensations of heat, moisture, or sweating, local or general.

Let us now turn our attention once more to myxedema. Here we find, not infrequently as an accompaniment of an atrophied or degenerated thyroid, an enlargement of the anterior lobe of the pituitary body. This finding is in keeping with the results of the experimental extirpation of the thyroid gland in animals; in such animals the anterior lobe of the pituitary likewise enlarges. The facts suggest, of course, that the pituitary enlargement is an effort at compensation. The posterior lobe or the nervous portion of the pituitary remains unaffected. However, the enlargement which ensues spontaneously in myxedema is not attended by increase in height or other acromegalic features. Clearly, we have here an instance in which compensation fails. It is a compensation which continues to be overweighted by the relatively greater hypothyroidism, a hypothyroidism often profound in degree; and it remains as an undercompensation. In hyperthyroidism, in exophthalmic goiter, a different story obtains. Occasionally the anterior lobe of the pituitary enlarges in this affection. Here true acromegalic symptoms expressed by excessive height—even gigantism—accompanied by typical changes in the head and extremities may result. In the majority of cases of hyperthyroidism such profound changes do not, of course, occur, but in the previous pages the writer called attention to the fact that the stature in hyperthyroidism, particularly when the affection begins before the growing period ceases, is apt to be exaggerated. This was attributed in part to an action on bone metabolism the reverse of that which obtains in hypothyroidism—in cretinism, in myxedema. Here, however, another factor comes into play. It would appear that in hyperthyroidism—in exophthalmic goiter—the anterior lobe of the pituitary joins the thyroid in an effort to overcome the depressing influence of the persistent and enlarged thymus. In other words, as in the case of the thyroid, the enlargement of the anterior lobe is an effort at compensation, a compensation directed against the thymus. This compensation may express itself merely as an increase in stature or, if overcompensation results, in a true acromegalic symptom group.

VIII

THE PITUITARY BODY

LET us now turn our attention directly to the pituitary body. The pituitary body consists of two structures which, as in the case of the medulla and cortex of the adrenals, have no relation with each other save that of tissue propinquity. The anterior lobe arises in the roof of the oral cavity as an involution of the ectoderm; the posterior lobe has its origin in a downward protrusion from the base of the brain. Between the two and forming part of the posterior lobe is a thin layer to which the name pars intermedia has been given. It is the anterior lobe which first demands consideration. We have already called attention to the enlargement of this lobe in our discussion of hypothyroidism. The question arises, Is the enlargement of this lobe in acromegaly—not mere increase in stature, but acromegaly in its typical form—also to be regarded as compensatory? In other words, Is the enlargement of the anterior lobe and the resulting acromegaly the result of an overcompensation? A fact that has an important bearing upon this problem is that while extirpation of the thyroid is followed by enlargement of the anterior lobe of the pituitary, the reverse—extirpation of the pituitary—is not followed by enlargement of the thyroid. In other words, the relations of the anterior lobe are primarily not with the thyroid, but *with the thymus*, though this relation may be indirect and through the thyroid. The inference, therefore, that the enlargement of the anterior lobe in acromegaly is, like the enlargement of the thyroid in exophthalmic goiter, the result of an overcompensation possesses much inherent probability. The coincidence of both hyperthyroidism and acromegaly occasionally observed clinically, as has just been pointed out, is confirmatory of this interpretation. In both instances as a result of the persistent thymus and its attendant lymphatic hyperplasia—so expressive of biological retardation—the thyroid or the anterior lobe, or both become enlarged. Why in one instance one becomes enlarged in one case and not in the other, or why one becomes enlarged in excess of the other is doubtless determined by secondary factors which need not detain us and which, moreover, in the present state of our knowledge would lead us too far into the realms of speculation. The fact, however, that does concern us vitally is why these glands enlarge at all. Here, again, the answer must be sought in a biological explanation.

We must remember that a metazoan, while it consists of a multicellular aggregate, is, notwithstanding, a unit, a biological whole. Among its constituent cells there is a constant competition; in the simpler forms this competition is for the nourishment which is available for all of the cells. The cells, therefore, exercise a mutual restraining influence upon each other. In the more complex forms many instances might be cited of the competition of cells and tissues from the domain both of physiology and pathology. We recall, for example, the behavior of the phagocytes under given conditions, of the behavior of connective-tissue cells in the scleroses of various tissues. Usually it is the simpler and biologically lower tissue which wins out. Woe betide the nerve tissue in which the neuroglia gains the upper hand. Perhaps in this, also, resides the ultimate secret of malignancy.

What is true of the cells of the simpler metazoa is also true of the various organs into which these cells become differentiated in the more complex forms. The various organs—each a subcenter of activity—are in mutual competition; a competition modified and tempered by a mutual interdependence. The dejecta of one group of cells are the food or catalysts of other cells. The food which one group rejects from the blood-plasma other cells greedily seize upon. All of the structures strike a balance and exercise a mutually restraining influence upon each other. If, therefore, the bioplasm of the parents, the germ plasm which gives rise to the resulting composite cell, the zygote, does not possess in its chemical and physical processes the necessary intensiveness, *i. e.*, the necessary energy, the organism as a whole does not attain the normal level (see p. 37). If so, the cheaper tissues, as instanced by lymphatic hyperplasia, are formed in excess. Persistence of the lymphatic excess is associated sooner or later with persistence of the thymus, and imbalance having once been established, other imbalances, as we have seen, follow. A restraint or "inhibition" having been lessened or removed, this or that related structure enlarges.

The objection may be made that the enlargement is not always a mere hypertrophy of the pre-existing glandular tissue. In the thyroid it is frequently merely such a hypertrophy, though not always. In the case of the anterior lobe of the pituitary the enlargement frequently suggests a tumor formation classifiable under this or that well-known pathological form of neoplasm. At one time such neoplasms were commonly regarded as sarcomata; later the tendency has been to regard them as epitheliomata or as adeno-epitheliomata. In these structures the alveolar or serial arrangement of the anterior lobe is more or less preserved; the cells themselves, however, are increased in number and size. Further, and this is significant, the cells have lost their differentiation, their special characteristics; for instance, the cells, which were either eosinophil, basophil, or chromophobe in the normal pituitary, have lost these distinctions and all are alike, all chromophobe. Sometimes, again, the structure is so atypical that it is classified roughly either as an epithelioma or sarcoma. Finally, cases occur in which it is very difficult to distinguish between a simple hypertrophy and a pathological neoplasm. Perhaps this is what we might on *a priori* grounds anticipate.

The first effect of a beginning enlargement of compensation would be naturally to bring about a hypertrophy. However, it is conceivable that, the restraint being removed rapidly or in massive degree, time would not suffice for the proper development and multiplication of well-differentiated cells; it might also be that the blood-plasma would not contain all of the necessary materials either in the proper amount or of the precise character demanded. It can be readily understood that the cells forming the resulting tissue would be cells of a lower biological level and lacking the arrangement seen in the normal structure; or perhaps presenting no arrangement at all; or perhaps one that is anomalous. Clearly, the fact that the enlargement of a given compensation departs from a simple hypertrophy in no way invalidates the interpretation advanced in this essay.

It is very clear also that an enlargement which begins as a simple hypertrophy, but later departs more or less in structure from that of the normal gland, cannot continue to exercise its function unaltered or unimpaired; new or anomalous symptoms must make their appearance. It is to this condition that the term "*dys*-function" is especially applicable. For instance, in adiposis dolorosa there are found, among other changes, changes in the thyroid gland; here and there the acini are enlarged and distended; here atrophied and degenerated. Adiposis dolorosa is neither hypothyroidism nor hyperthyroidism; it is something else. Evidently there is present a dysthyroidism. Similarly, some of the symptoms of acromegaly—probably the later ones—are to be attributed to a dyspituitarism.

The essential and underlying nutritional changes which attend pituitary enlargement are those of an increased and persistent overgrowth of bone and a hypertrophy of the connective tissue of the skin and subcutaneous tissues. The overgrowth of bone is both periosteal and medullary. The marrow is red and the cavities containing it increase in size as the bone grows. The hypertrophy of the connective tissue is not limited to the skin and subjacent tissues, but involves the sheaths and connective tissue which accompany the vessels, lymphatic structures and nerves, or in which these structures lie; also the attachments of the skin to the deeper tissues, the aponeuroses, tendons, etc.

It is interesting to note that in a large number of cases the thyroid is enlarged, often markedly so. According to the interpretation here presented, it is not hazarding too much to suggest that this thyroid enlargement probably preceded that of the pituitary. Further, in many cases, again, a persistent and enlarged thymus has been noted. Here again the facts suggest that the primal cause lies in the thymus. The adrenals have at times also been found enlarged, and to this point we will refer again. The testes are small and in keeping with this; there is a feeble or absent sexual function. Analogous changes are noted in women, amenorrhea, frigidity, and sterility being the accompaniments.

One of the most interesting and important facts is that in from one-third to one-half of the cases, according to Marie, glycosuria is present. The glycosuria may be comparatively slight or, on the other hand, very pronounced, polyuria and increased thirst may accompany the condition. The thought suggests itself that the pituitary, like the thyroid, depresses the function of the pancreas, and again, like the thyroid, is in synergic relation with the chromaffin system.

Just as Marie in 1886 described hyperpituitarism under the name of acromegaly, so Frölich in 1901 described hypopituitarism under the name of dystrophia adiposogenitalis. It is to hypopituitarism that we will now give our attention. Setting aside the symptoms that are merely the mechanical results of the location and pressure exerted by the tumor formation present, the essential features consist of adiposity usually very marked, of genital atrophy, of abnormalities in the development of the skeleton, of changes in the skin, polyuria, and increased sugar tolerance. The obesity is often so great as to be the most striking feature. If the disease begins before puberty has been established, the genitals are infantile in appearance, the secondary sexual characters fail of development, the contour of body and limbs is in men feminine in type, the breasts notably developed, the pelvis broad, the voice high pitched, very little or no hair upon the face, very little or no hair upon the pubis, or, if present, feminine in distribution. In women the sexual organs likewise remain infantile, or the secondary sexual characters, if present at all, are masculine in type; male contour, tendency to beard, male pubis, low-pitched voice, etc. If the disease develops after puberty the testes become small, the secondary sexual characters recede, pubic and axillary hair fall out; obesity becomes steadily more pronounced.

Beginning early, the disease may be attended by a persistent general infantile appearance. In individual cases the growth of the skeleton is found to have been retarded; in others again dwarfism results. The skin is much stretched over the masses of fat, and every now and then whitish areas, suggesting lineæ albicantes, are observed. The skin is smooth and soft; sometimes in its feel it suggests myxedema and at other times the infiltrated stage of scleroderma. Its color is sallow and pale; at times over the face dusky and edematous. Doubtless the surface symptoms of the skin are purely secondary; it is the adiposis which is the important and outstanding feature. Further in contrast with the relatively frequent glycosuria of hyperpituitarism there is here an increased sugar tolerance. As is well known, relatively enormous quantities of sugar can be given such patients without sugar appearing in the urine.

The clinical findings in the hypopituitarism of Fröhlich's disease have received a most remarkable confirmation in experimental extirpation of the pituitary in animals. Briefly stated, these are as follows: It was at first believed that if the anterior lobe were removed *in toto*, the animal invariably died; but it was later found that if injuries to the infundibulum and third ventricle were avoided, this result did not ensue. It was further found that in adult animals no very definite symptoms resulted; if, however, extirpation is practised in very young animals, dogs from four to six weeks old, very decided changes make their appearance. The dogs grow fat; their growth is much retarded; they retain the soft and wooly hair of their puppyhood, and the first dentition persists during the lifetime of the individual. The epiphyseal separations persist. The thymus becomes persistent. The adrenal medulla (the chromaffin system) becomes small, while the cortex shows thickening. In many cases the thyroid becomes enlarged and seems to undergo colloid degeneration. The testicles fail to grow, while the penis, scrotum, and prostate remain small and undeveloped; analogous changes are noted in the female. These results, it should be emphasized, follow extirpation of the anterior lobe; extirpation of the posterior lobe is not followed by such results.

The metabolism reveals a lessened protein reduction. The Carbohydrate metabolism is increased; as in hypothyroidism, adrenalin-glycosuria is diminished. It would appear, therefore, that the function of the pancreas is exaggerated, as though a restraint, an inhibition, had been removed. In other words, as has already been pointed out in the preceding pages, the normal pituitary reinforces the chromaffin system. It is synergic with the thyroid and, like the thyroid, it favors also protein metabolism.

The posterior or nervous lobe of the pituitary may be disposed of very briefly. It contains a hyaline substance which apparently constitutes a secretion. According to some observers, this secretion finds its way into the cerebrospinal fluid of the third ventricle. However, the evidence is, I believe, strongly in favor of its entering the blood-current. Removal of the posterior lobe, as just stated, is followed by no noticeable disturbances of function. The extract of the posterior lobe has, however, a most remarkable effect upon smooth muscle-fibers; thus it stimulates the muscular fibers of the blood-vessels, uterus, and bladder to contract. It promotes diuresis and increases blood-pressure. In other words, its action is synergic with adrenalin.

Returning once more to the hypopituitarism of the anterior lobe, let us see whether some of the other glands are not also involved. Often enlargement of the thyroid is noted, though Cushing has noted the opposite, and Patrick, even entire absence of the thyroid. Sometimes a neoplasm has been found in the thyroid. That the thyroid should show vagaries in its condition is hardly surprising when we recall that extirpation of the thyroid is followed by enlargement of the anterior lobe of the pituitary, but that extirpation of the pituitary does not bring about enlargement of the thyroid. We have already pointed out (see p. 92) that the relations of the pituitary were rather with the thymus than with the thyroid. It is interesting, therefore, to learn that the thymus has been found enlarged in Fröhlich's disease, together with numerous evidences pointing to the status thymicolymphaticus. The reader will at once recall that many of the symptoms recounted above have already been recounted in connection with lymphatic hyperplasia and persistent thymus. Further, we are told by Wiesel that tumors of the pituitary and the status thymicolymphaticus are not seldom associated. Clearly, it would seem that the fundamental cause in hypopituitarism, as in hyperpituitarism, is a lowering of the developmental energy inherent in the organism (see p. 49), a lowering which in its simplest and generalized form expresses itself, as we have seen, as the status thymicolymphaticus, and which leads to various imbalances, some of them exceedingly special in character.

Interesting facts are also revealed by the tumors of the hypopituitarism of Fröhlich's disease. It would appear that we have to do mainly with adenomata made up of a stroma of chromophobe tissue and which is often cystic and softened. Not infrequently, too, these adenomata assume a malignant character, a fact perhaps not without significance. Sometimes the growths have their origin in the epithelial cells of the gland, and such growths also may become malignant. Further, tumors of the pituitary in Fröhlich's disease have at various times been classified, as sarcomata, gliomata, lipomata, fibromata; even, though very rarely, teratomata have been described. All of the changes are characterized by one fact, namely, the destruction of the gland proper. Finally, we should not be surprised, I think, that in a structure in which all restraining influences have been removed, the cells should fail to grow in conformity with a given plan or, in fact, with any plan. What really occurs is that cells proliferate and proliferate irregularly. These cells may have their origin in some of the original components of the gland or they may be cells relatively simple and undifferentiated—cells of a lower biological level, the tissue being unable to reproduce the higher forms. Is it surprising that such cells—living biologically cheaply—should proliferate without restraint and assume what we call a malignant character?

IX

THE PANCREAS

Let us again turn our attention briefly to the pancreas. Like the thyroid and the thymus, it has its origin in the entoderm. It is interesting as being the only one of these three glands which continues to be connected by a duct with the cavity of the entoderm. It is constant in fishes, amphibians, reptiles, birds, and mammals. Its morphological importance cannot, therefore, be questioned, and is, indeed, in keeping with the great rôle it plays in the organism. It possesses a double function: first, it pours into the intestine a secretion which digests the starches and fats of the ingested food; second, it secretes in its "islands of Langerhans" a hormone to which the name "insulin" has been given, and which has been only recently and brilliantly isolated. The physiological rôle and importance of the pancreas has been for many years known as a result of clinical observations, disease of the gland resulting in diabetes mellitus. Experiment also long ago confirmed these observations. Extirpation of the gland results in glycosuria, and this obtains even when in the animal experimented upon all carbohydrate food is withheld. As in diabetes in the human subject, there is execssive thirst and hunger, and in spite of full feeding the animals die of exhaustion.

We have already considered the relations of the pancreas to other glands, how in hyperpituitarism and hyperthyroidism its function is depressed so as to permit of glycosuria, and how this result also follows an overfunctioning of the chromaffin system. On the other hand, the adiposity seen in hypopituitarism indicates an overfunctioning of the pancreas; very probably, too, hyperpancreatism also explains some of the other forms of adiposity, more especially those which yield so readily to thyroid administration. It is said also that among the results which follow experimental extirpation of the thyroid is pancreatic enlargement. Whether, on the other hand, the thymus is in synergic relation with the pancreas is the next interesting question which presents itself. Some facts, such as the adiposity—the exceedingly "well-nourished" condition—of children suffering from lymphatic hyperplasia, would indicate an affirmative answer; but more of this later.

X

THE ADRENAL CORTEX

LET us now turn our attention once more to the adrenals; but this time to the cortex. We have already pointed out (see p. 64) the general biological facts—how in the sharks and allied fishes the two entirely independent bodies—the "interrenal bodies"—are found which are the homologues of the adrenal cortex of other vertebrate forms. This fact demonstrates conclusively that the cortex and medulla of the suprarenal bodies are entirely separate structures. It would appear, too, that while the cortex has its origin in the epithelial cells of the mesoderm of the body cavity, the medulla arises in close connection with, if not in common with, the cells of the sympathetic nervous system (see p. 65). The cortex consists of cells irregularly polygonal in shape separated by connective-tissue stroma and septæ into groups; three layers can be distinguished. It arises from the anterior portion of the wolffian body and is, therefore, derived from the same blast in the embryo as the sex organs. This fact probably possesses much significance.

Such knowledge as we possess concerning the function of the cortex of the adrenals is derived from ready-made experiments presented by the clinic. Here the symptoms and autopsies have revealed a remarkable relation between these organs and the sexual apparatus. For instance, female children have been observed in whom the external genitalia reveal appearances approaching more or less closely the male type, such as a clitoris of abnormal size or even a penis with a male urethra, labia suggesting a scrotum, or labia perhaps partially united. Subsequent examination has, however, revealed female internal organs, but, in addition—and this is the important point—great enlargement of the cortex of the adrenals. Other children, again, who present no peculiarities at birth or for months or several years thereafter, begin after a time to develop a decided amount of fatty tissue. The deposit is especially marked in the hips, buttocks, abdomen, and mons Veneris; is less noticeable over the extremities. Very frequently, too, but not always the child begins to grow abnormally. A change in disposition and demeanor is also noted. The child becomes very active and reveals a remarkable degree of muscular strength, so much so that French writers have used the term "enfants hercules" in describing such children. Precocious sexual development now manifests itself. Copious growth of hair makes its appearance on the pubis and in the axillæ, and, in boys, moustache and beard also begin to make their appearance. The external genitalia—as in a case studied by the writer—assume the adult male appearance. The occurrence also of erections and emissions may be noted. The voice, too, approaches the adult character. In girls the external genitalia likewise assume the adult appearance; the clitoris may become very large; indeed, as already stated, it may assume the character of a small penis. The mammary glands and nipples grow and menstruation may also make its appearance. The obesity is, in some cases, especially in older children, at times very pronounced, but there is never any pituitary enlargement such as is met with in Fröhlich's disease. On the contrary, if the cases come to autopsy, an adrenal tumor is invariably found. It may be added here that after a shorter or longer period of time the children lose their fatty tissue, become rapidly thin and emaciated, and die of exhaustion; it may be with a cachexia suggesting malignancy or it may be that some intercurrent disorder attended by vomiting and diarrhea brings about the fatal termination.

In older individuals, in young women and less frequently in older women, but never after the menopause, similar facts obtain. A woman previously apparently well begins to suffer from menstrual disturbances, irregularities, and finally cessation of the periods. Sometimes nausea and vomiting suggest a beginning pregnancy. However, very early there ensues an excessive adiposity, and at the same time a remarkable increase in muscular strength and endurance. Hand in hand with these symptoms a change in disposition is noted akin to that in the younger patients. The woman, formerly quiet and perhaps retiring, is now active, self-assertive, overbearing, excitable, and, it may be, easily angered. Sexually, too, the patient may be unduly or strongly excitable. In due course, growth of hair, pronounced and masculine in character and distribution, makes its appearance; moustache, beard, whiskers are developed in a noticeable degree, while the hair upon the pubis assumes the pyramidal distribution seen in the male extending, it may be, up to the navel, or even above the latter over the chest. Back and shoulders may also be covered—and the extremities as well—with hair, coarse and thick. As might be expected in adult women, the external genitalia remain unaffected; only seldom is an enlargement of the clitoris observed. As in the case of the younger patients, after a variable period the obesity begins to lessen and soon rapidly disappears, and the former exaggeration of the muscular strength is now replaced by weakness which may be extreme. The aggressiveness, the sexual excitability, are replaced by depression and sexual indifference. The emaciation often makes possible the discovery of a retroperitoneal tumor. Death is preceded by an increasing asthenia, gastric and intestinal disturbances, epileptiform or tetanoid convulsions.

According to Wiesel,[1] upon whose admirable

[1] Lewandowsky's Handbuch der Neurologie, vol. iv, Spezielle Neurologie, iii, p. 376.

description the above account is largely based, the cases in which the affection is congenital, *i. e.*, the cases featured by the stigmata of pseudohermaphroditism at birth, usually live much longer than the cases in which the affection makes its appearance later. It is probable that the reason lies in the fact that in such cases the lesion is always a simple hypertrophy of the cortex, while in the later cases the cortex is the seat of an enlargement in which a neoplasm, malignant in its nature, is the outcome. The final emaciation and asthenia are to be looked upon as a result of this malignancy, a malignancy which sooner or later invades the contiguous medulla, rather than as due to an insufficiency, a hypofunction of the cortex. In this malignancy we have again an instance in which an overgrowth, itself the result of the diminution or absence of the normal restraining influence, leads to the production and proliferation of cells biologically simpler and less differentiated than that of the original tissue. Just what the restraining influence in the present instance is may be questioned, though probably it is in women the hormone, the internal secretion, of the ovary; the symptoms are always ushered in by ovarian failure. The condition is precisely analogous to what we have seen exists in the case of the pituitary, and the explanation there advanced applies, I believe, equally here.

It should be added that in some cases associated with enlargement of the adrenal cortex enlargement of the parovarium has been found. This fact is exceedingly interesting, as the parovarium, like the adrenal cortex, arises in the wolffian body. The query also suggests itself, What is the meaning of the hydatids of Morgagni? Is it possible that these are in some way connected with the maintenance of sexual equilibrium?

XI

THE SEX GLANDS

Let us now turn our attention to the sex glands, the testicle and ovary, or, to use the term applicable to both, "the gonads." Beginning with the testicle, the first fact of importance to recognize is that the testicle is made up of two portions, one of which produces the germ cells, while the other produces an internal secretion. The former is an epithelial tissue, the latter an interstitial tissue. The latter is made up of cells termed the "cells of Leydig," is of mesodermal origin, and is not unlike the adrenal cortical tissue. It is intimately related to and concerned in the development of the secondary sexual characters. It is well known, for instance, that diseases which destroy the germ-producing portion may leave the interstitial portion intact, in which case the secondary characters remain unchanged; such facts are observed now and then in cancer and in tuberculosis of the testicle. Again, when the vas deferens is obstructed or resected, the germ-producing portion atrophies, but the interstitial portion persists, and with it the secondary characters; similar results are said to follow sterilization by the *x*-ray.

Before taking up the subject of testicular deficiency, male hypogonadism, let us consider briefly the effects of the entire absence of the glands, *i. e.*, of castration. Here we have before us, of course, the results of the removal of both of the secretory structures of the testicles; and the facts, as we shall see, are most instructive and significant.

Our knowledge of the subject of human castration is owing largely to the studies of Tandler and Gross[1] made upon the Skoptzi of Roumania. These observers noted two groups of cases. In the first, the individuals had been the subject of early castration; they had grown to excessive height, and examination revealed the persistence of the epiphyseal separations. The second group presented no excess of height, but were very fat. The hips were broad, the breasts large, the buttocks and thighs fat. The first group, it should be added, likewise presented fatty deposits over the buttocks, lower

[1] Cited by Wiesel, loc. cit.

abdomen, and pubis. In this group, also, disproportionate length of the extremities is noted; the head small, with occipital flattening and enlargement of the sella turcica; pelvis broad, slight lumbar flexure, bow-legs not uncommon. In both groups the skin of the face is sallow, pale, wrinkled, and—what is especially significant—hairless. The hair of the scalp may be dense, but there is no beard; only on the upper lip may there be seen a slight development of lanugo-like hair. Sometimes in the older eunuchs there is seen a slight growth of hair upon the face such as is occasionally seen in old women. The trunk and extremities are smooth; there is but little hair in the axillæ and the same is true of the pubis; here there is but little hair, and this is feminine in type. The larynx is small and infantile, the voice high pitched. The thyroid gland also is small, but the thymus may be found persistent, corresponding to the infantile period of life. The penis is very small, and this is true of the prostate and seminal vesicles. We know much less of the results of early castration in women, but the latter also are said to be taller, while the secondary sexual characters are wanting, as in the male. Castration after maturity leads, as is well known, merely to atrophy of the uterus and breasts and to an increase of fat and body weight.

When we turn our attention to those experiments observed in the clinic which are featured by failure of sexual development, we meet with a picture more or less resembling that presented by eunuchs, and such cases have been termed by Griffith and Duckworth "eunuchoids." Here we again distinguish two forms, the tall and the fat forms. The first represent the early cases; here there is again, besides the increase in stature, the same disproportionate length of the extremities, and the same persistence of the epiphyseal separations. The sella is not reported as increased in size; this does not, of course, exclude pituitary involvement. In the second group we find similar excessive deposits of fat, as in the corresponding group among the eunuchs, and the same absence of secondary sexual characters is revealed, especially in the early cases. In later cases the hair upon the face, in the axillæ, and on the pubis is thin or falls out; the hair of the scalp may be well preserved, but it becomes dull, dry and brittle, and early turns gray. The penis and testicles are small; in women the uterus and ovaries are small. As in eunuchs, the thyroid is small; the thymus, on the other hand, shows an increase in its parenchymatous—its epithelial—elements.

When we compare the findings in the eunuchs and eunuchoids, we learn that these findings are due entirely to the loss of the internal secretion of the testicle; the loss of the germinal portion of the gland seems to be without any effect on the organism; perhaps this is what might be expected, for the product of this germinal portion is an excretion, something to be thrown off. Again, the excessive adiposity suggests the findings in dystrophia adiposogenitalis (Fröhlich's disease, see p. 99), and this, together with the small thyroid and enlarged thymus, points to a multiglandular involvement featured by the special factor of failure of sex gland development. Clearly, also, many of the symptoms suggest the findings in the status thymicolymphaticus. Little by little the fact of the glandular interrelations is impressed more strongly upon us, but most of all the relations which failures of development of all kinds bear to that generalized form presented by lymphatic hyperplasia and its attendant persistence of the thymus.

XII

THE PINEAL GLAND

THE pineal gland next claims our attention. This structure makes its appearance in the embryo during the second month, and is developed from the posterior portion of the roof of the diencephalon or "between brain." It is absent in the acrania, but is present in all other vertebrates. Very curiously, in certain lizards it is developed as an eye. It has relations through its peduncles with the thalamus. Its constancy in all vertebrate forms justifies the assumption that it has both significance and importance. Extirpation of the gland in animals has failed of results, and we are again referred to the clinic. Here tumors of the gland are met with in which, in addition to the general symptoms of brain tumor and special localizing symptoms, very definite in character, there are present others which can only be interpreted as the disturbances of an internal secretion. One of these disturbances consists of a high-grade adiposity or, in a minority of cases, of a grave cachexia. A second symptom which has been observed in tumors of the pineal gland is premature sexual development. This is manifested by the general physical development, by the development of the sexual organs, and by the appearance of more or less marked secondary sexual characters. A decided sexual excitability may accompany this condition. A third symptom which makes its appearance at the same time is a remarkable precocious development of the intellectual and emotional faculties. The number of cases thus far reported is comparatively small, but the facts are extremely interesting. Marburg regards the adiposity as the result of a hyperpinealism, and the opposite condition as due to a hypopinealism. In the case described by himself, as in that of others, an examination proved the pituitary to be intact, as were also the other glands. Of course, inasmuch as the aqueduct of Sylvius is usually obstructed in pineal tumors, and as distention of the third ventricle and pressure on the pituitary may take place, disturbance of pituitary function cannot be absolutely excluded. However, evidence from other sources is wanting to show that pressure upon the pituitary results in adiposity and, to the writer, the evidence points to the pineal as the cause of the condition. The sexual phenomena, also, are exceedingly remarkable. Our review of the subject of the internal secretions has brought to light a number of instances in which aberrancies of sexual development accompany disease of the glands, but we will recall that in almost every instance the anomalies observed were those of failure or partial reversal of development; only in the instance of the cortex of the adrenals was a sthenic, a reinforcing influence noted; but here again accompanied, in the female, by phenomena of reversal. In pineal disease a reinforcing influence is likewise at work, but it is unaccompanied by phenomena of reversal.

One of the most remarkable facts about the pineal gland is the involution which it undergoes at puberty. The gland consists of glia cells and of others epithelial in character. The latter appear to be the source of the internal secretion. At the time of the involution of the gland they do not entirely disappear, but some of them persist throughout life. The pathological changes to which the organ is subject consist almost entirely of cyst formations. Sometimes these cysts prove to be teratomata; they may contain cylindrical or pavement epithelium, hair, cartilage, fat, or it may be, smooth muscle-fibers. Marburg has, in addition, described tumors made up of layers of pineal, epipendymal, and glia-cells, and he includes in this group the sarcomata, carcinomata, and gliomata of other writers.

Clearly, if the pineal undergoes involution at the time of puberty, it seems reasonable to look upon the precocious establishment of puberty, and the attendant phenomena as an accompaniment of premature pineal involution. The condition is, therefore, to be regarded as a hypopinealism; as due to a premature failure of pineal function. The occurrence of cysts, teratomata, and malignant neoplasms again suggests the explanation advanced in the case of the pituitary and the cortex of the adrenals (see pp. 95, 115). What, however, is the restraining influence which has given way in the case of the pineal? Here speculation may carry us too far afield. However, the facts suggest the following thoughts: We have seen that sexual hypoplasia—failure of sex development —accompanies lymphatic hyperplasia, thymic persistence, and lowering of the pituitary; all of these states—as we have seen—are expressive of a general failure of development; and when sexual hypoplasia is met with as the most prominent feature, it is always accompanied by changes in other glands and structures which mean the same thing. In other words, failure of sex development occurs when the organism as a whole fails to reach the normal level; when the intensiveness of the chemical and physical processes inherent in the germ plasm has not been sufficient to lead to the development of a complete, a normal organism. This seems to the writer to be a more philosophical explanation than to attribute the failure of sex development to one or more special glands, themselves concomitantly abnormal. This does not, however, impair the fact of glandular interrelations demonstrated by such facts as the atrophy of the sex glands which follows experimental pituitary extirpation; for, the organism once having evolved to a normal level, certain interglandular relations become definite and fixed, and it is just such an interglandular relation which, it seems to the writer, explains the normal involution of the pineal gland at puberty as well as its premature and pathological downfall.

The pineal gland makes its appearance early in embryonic life, and is present, as we have seen, in all vertebrate forms save the amphioxus. These facts alone guarantee to it a very great importance. Developing early and being so constant, it seems probable that it is in relation with nutritive and developmental processes in general and that the action of its hormone or catalyst is such as to balance—to hold in restraint—these processes, especially during the early formative period. It is quite conceivable, too, that after a time it should be overbalanced by the increasing mass and vigor of these very processes themselves, and then give way in the struggle and enter upon a period of involution such as we observe at puberty. The facts might be expressed by saying that at puberty the gland enters upon a period of physiological hypopinealism. Should the organism because of a lowering of the intensiveness of its processes—an inherent deficiency of energy—be impaired, it is quite possible that due to special causes, such as disease of the germ plasm, the vigor and resistance of the pineal gland may be lessened so as to bring about its early involution, and thus the very symptom group we have been considering.

To the neoplasms of the pineal, malignant and otherwise, the same explanation applies which has been advanced in the case of the pituitary, of the adrenal cortex, and other structures. The teratomata, however, deserve a special word. Practically teratomata occur in only one instance elsewhere, namely, in the sex glands; certainly with such rarity in other structures as to be almost unknown. In the pineal gland, on the other hand, they occur with relative frequency. Is it not significant that various forms of epithelial tissue, cartilage, adipose tissue, sebaceous structure, and muscle should make their appearance in the pineal gland? Is it not in keeping with the thought that the relations of this gland, whatever they may be, are general in character and have to do with fundamental processes taking place in the organism?

XIII

THE PARATHYROID BODIES

Various other organs present themselves for our consideration, *e. g.*, the parathyroid bodies and the carotid and coccygeal bodies. The parathyroids are glands of a highly special character, and with definite and special relationships. They will next receive attention. The carotid and coccygeal bodies merit, as we shall see, a brief notice in connection with the sympathetic nervous system.

The parathyroid bodies have their origin from the entoderm of the third and fourth branchial clefts. They have been found in reptiles (serpents and tortoises), in birds, and in mammals. As is well known, they are present in two pairs. During the embryonic period they migrate downward, and in such a manner that the pair originating from the third branchial cleft come to occupy a lower position than those arising from the fourth. In animals the number has been observed to vary so that at times accessory parathyroids are present, and this has also been observed in the human being. These accessory glands are always lower down and often near and about the thymus, just as the two upper pairs commonly present are close to or even embedded in the thyroid. Unlike in the cases of the thyroid and thymus, there is never any trace of duct formation in the embryo. Further, in spite of the close anatomical contiguity which exists between the upper two pairs and the thyroid, there is no structural relation with the thyroid, and this is also true of the accessory glands, when present, as far as the thymus is concerned.

The glands are very vascular and have an epithelial make-up. They contain, besides epithelial cells, other tissue resembling the tissue of the thymus gland, such as the Hassall concentric corpuscles.

It has been found that in extirpation of the parathyroids in animals symptoms are produced which are practically identical with those of tetany. They consist, first, of muscle spasms which may become clonic or even epileptiform; second, of greatly increased mechanical excitability of the motor nerves (Chvostek's sign); third, of greatly increased electrical excitability of the motor nerves (Erb's sign), and lastly, of Trousseau's sign, the induction of tonic spasm in a limb by its constriction. Tetany, it need hardly be added, is now regarded as a disease the result of parathyroid deprivation, *i. e.*, a hypoparathyroidism.

The relations of the parathyroid to other glands and to metabolism are very interesting and suggestive. In extirpation, sugar metabolism is lowered; for instance, adrenalin injections induce a greater output of sugar in parathyroidectomized animals than in normal animals. The inference is that an intact parathyroid apparatus exercises an inhibitory influence on the elmination of sugar; in other words, it reinforces or acts synergically with the pancreas. It naturally follows, also, that the parathyroids are in antagonistic relation with the chromaffin system, just as the pancreas is in antagonistic relation with the chromaffin system. A similar antagonism persists between the parathyroids and the thyroid, a fact which might also have been predicted, as the thyroid is in synergic relation with the chromaffin system. It has been found that thyroid extirpation is followed by parathyroid hypertrophy; and the reverse also obtains, namely, hypertrophy of the thyroid after enucleation of the parathyroids. It would seem that the benefit derived in hyperthyroidism from the serum or milk of thyroidectomized animals is due to a relative excess of parathyroid elements. One of the important observations made, also, in parathyroid enucleation is an increased elimination of calcium. It would appear, therefore, that the function of the intact parathyroid is to restrain such elimination. Finally, the fact that the parathyroid gland contains thymus elements in its structure would place it in synergic relation with the thymus gland, a fact in harmony again with the antagonism of the thymus to the thyroid.

Investigations have shown that the parathyroids are subject to the same pathological processes as are other structures, such as hemorrhages, cysts, tuberculosis, metastases, tumor formations, etc., but these are rarely accompanied by tetanoid phenomena, due probably to the multiple nature of the parathyroid apparatus. The occurrence of tetany in epidemic and endemic forms suggests, of course, an invasion from without; the superposition of disease upon a previously normal structure. Regarding purely biological or morphological departures the facts as yet do not permit of an inference.

XIV

THE SYMPATHETIC NERVOUS SYSTEM

A discussion of the biological factors concerned in the internal secretions demands, also, a consideration of the sympathetic nervous system; and to the latter we will at this point direct our attention. The fact that the various glands of internal secretion—indeed, all of the structures of the body—stand in chemical relation with each other, in chemical balance, must, I think, be freely admitted. In addition, another factor comes into play, and that is the nervous communication which exists between the various organs and which is featured by an action on gland cells, on smooth muscle cells, and by a control of vascular supply. It was Sajous, who has done so much for endocrinology, who was among the first if not the very first to point out the importance of the sympathetic nervous system in the interglandular relations.

The sympathetic nerve-cells have their origin, as we have seen, in the same blast of the embryo as the cells of the chromaffin system (see p. 65). It is primarily the function of the latter to furnish the hormone—catalyst or food—for the latter. While the sympathetic nervous system is connected with the cerebrospinal axis, its own intrinsic cells and fibers are of mesodermal origin. They differ widely both in their structure and in their function from the cells and fibers of the cerebrospinal system. The cells of the latter are differentiated largely for the reception and transmission of impacts received from the external world; accuracy, definiteness, and precision, differentiations, limitations, and specialization of transmission are the results of its evolution.[1] In the sympathetic system, on the other hand, wide diffusion and dispersion of impulses, often over great areas, take place, but this diffusion is not at random, but is well co-ordinated, limited and controlled, and, in its own way, specialized. Further, as just referred to, the sympathetic nervous system is connected with the cerebrospinal nervous system, and this fact still further modifies its action; and, in its turn, the sympathetic nervous system modifies the

[1] See Dercum, Physiology of Mind, 1922.

action of the cerebrospinal. The physiologist Langley, it will be remembered, renamed the sympathetic nervous system the autonomic nervous system, largely on the basis that the structures supplied by the sympathetic nerves are independent of the will. The cerebrospinal nerves which execute the mandates of the will, that is, carry out voluntary movements, terminate only in striated muscular fiber. The sympathetic nerves, on the other hand, terminate in smooth muscular fiber and in glandular tissue; in other words, the sympathetic fibers include all efferent nerve-fibers except those which go to the voluntary muscles. In accepting the term "autonomic" as a substitute for the term "sympathetic" nervous system we should bear in mind, however, that the first or proximal neuron of this apparatus is always situated in the gray matter of the cerebrospinal axis; that is, in the cord or in the brain stem. Further, this proximal neuron gives off an axone which, passing out by way of the rami communicantes, terminates in an arborization about the distal neuron situated in the sympathetic ganglion. Thence fibers pass to smooth muscle or gland. The sympathetic nervous system is, therefore, not an independent system and is only in a measure autonomic.

In recent years the sympathetic or autonomic nervous system has come to be divided into the so-called autonomic nervous system proper and the so-called sympathetic nervous system proper. The word "autonomic" is applied to that portion above the second dorsal segment of the cord and to that portion below the second lumbar segment, while that portion included between these levels is spoken of as the sympathetic proper. This division, which has no biological basis, is made rather arbitrarily on the differences in function which obtain in some measure between the two. For instance, fibers of the sympathetic proper pass from the upper dorsal cord through the superior cervical sympathetic ganglion to the dilator muscle of the iris, to the constrictor fibers of the vessels supplying the ear, the oral and nasal cavities, the eyeball, and the salivary glands. On the other hand, autonomic fibers, so-called, orginate in proximal neurons in the midbrain, accompany the oculomotor nerve, and terminate in arborizations about cells in the ophthalmic ganglion, from which fibers, in turn, originate which supply the ciliary muscle and the constrictor fibers of the iris; at the same time other autonomic fibers supply the dilator fibers of the vessels of the mucous membrane of the mouth, throat, nose and nasal sinuses, and also the salivary glands. A similar duplex arrangement exists in the innervation of the heart; for example, a sympathetic innervation through the accelerator nerves and an autonomic innervation through the vagus (see p. 65). Likewise duplex innervations can be traced in the glands of the mucous membrane of the trachea and bronchi, the muscles of the trachea and bronchi, and the glands and muscles of the intestinal tract from the esophagus to the anus, and likewise, in the case of the urinary bladder, genital organs and the vessels of these structures. To a degree these two systems are physiologically antagonistic to each other, and are each capable of separate stimulation. For instance, adrenalin induces contraction of the blood-vessels of the abdominal viscera and thus leaves a larger supply of blood for the brain and muscles; the heart's action is accelerated and fortified; the respirations are increased; the pupils are dilated so as to permit of the entrance of a larger amount of light. On the other hand, there is drying of the mucous membranes, inhibition of the salivary glands, and inhibition of the motility and secretion of the stomach and of the intestines. The skin, however, shows increased activity by free perspiration and sweating. At the same time an increased amount of sugar is thrown into the blood; the importance of this fact for increased muscular effort is obvious. Again, when the excess of adrenalin ceases to be formed, the abdominal viscera once more receive a larger amount of blood, and digestion and assimilation go on as before.

The synergic relation between the chromaffin system and the sympathetic nervous system requires no further emphasis. However, the play of the glands which are in synergic relation with the chromaffin system must also be considered. Clearly the thyroid and the pituitary form with the chromaffin system a synergic group. All of these glands promote tissue activity; all of them increase metabolism; all of them promote the release of energy.

On the other hand, the pancreas and, in

fact, all of the glands of the alimentary tract together with its adnexa are under autonomic influence. They are all concerned in the processes of digestion and assimilation; in other words, in storing up energy. The thymus and the parathyroid are both in synergic relation with the pancreas and must, therefore, be added to this group. All are opposed to the disintegration, to the downward change of the body constituents; in other words, to catabolism. We have already pointed out the vagotonic, *i. e.*, the autonomic, rôle of the thymus, and as regards the parathyroids enough is known to show that they too are conservators, more especially perhaps of muscle tissue, but probably also of other tissues as well.[1]

Hormones are apparently consistent in their action upon the sympathetic nervous system; that is, they apparently act exclusively upon either one or the other of the two divisions of

[1] In considering the constructive or anabolic organs from a broad point of view, emphasis must, of course, also be placed upon the liver. Like the pancreas, it is one of the adnexa of the intestinal tract, and, like the pancreas, it is of entodermal origin. Further, in its production of glycogen, it is a great storehouse of energy. In addition, in a still wider sense, the spleen and other blood-making organs should also be included in the constructive group. However, these considerations are not necessary to the purpose of our present discussion.

the sympathetic. However, in considering the action of substances other than hormones, such as the alkaloids and other poisons, we soon learn that few if any have an action limited solely to one of the divisions; that is, exclusively to the sympathetic proper or exclusively to the autonomic. Often, too, the symptoms of the stimulation of one portion are complicated by paralyzing effects on another portion of the same division; possibly this is what might have been expected of poisons beforehand. Thus, just as adrenalin stimulates the sympathetic fibers proper, and may, therefore, be said to be sympathicotropic and sympathicotonic, so does pilocarpin stimulate the autonomic system. Pilocarpin is a vasodilator, and in full doses slows the heart's action. At the same time the perspiration and saliva are greatly increased. The pupil also is contracted, and gastric and intestinal movements, as has been shown in experiments on animals, are increased. Pilocarpin can, therefore, be spoken of as autonomic-tropic, or, to employ the terms actually in use, vagotropic and vagotonic. The stimulation of the sympathetic by adrenalin brings about, as we have seen, sweating. Is the opposite action by pilocarpin due to a paralyzing effect on the autonomic system? or does the pilocarpin stimulate the autonomic supply of the pupils, heart, and digestive tract, and also stimulate the sympathetic supply of the sweat glands?

Again, atropin acts as a paralyzer of the autonomic apparatus. There is here, because of the paralysis of the autonomic apparatus, dilatation of the pupils and arrest of the secretions. In full doses the heart-beats become exceedingly rapid, the pulse ranging from 120 to 160. Atropin is, therefore, vagotropic, but is paralyzing in its action instead of being vagotonic.

Less is known about substances or poisons which being sympathicotropic, also paralyze the sympathetic. In paralysis of the sympathetic there would be vascular dilatation, contraction of the pupils, slowing of the heart's action, and increased glandular activity; but when we come to look for poisons having such an action we cannot find one which will fill all the requirements. Morphin, which contracts the pupils, and slows the heart's action, is an indifferent vasodilator; and, instead of increasing the secretions, inhibits them, unless it be that of the skin. Similarly, when we turn back to stimulating drugs of the autonomic apparatus, among which, in addition to pilocarpin, may be mentioned physostigmin, cholin, and digitalis, we find that there are many variations in the details of their action which do not admit of an explanation limited to an exclusive and stimulant action on the autonomic apparatus. This, it may be added, is also true of the paralyzing drugs and toxins.

The fact that the synergic relations of various glands to each other enables us to arrange them into groups does not imply that each glandular structure has not its own general sympathetic nerve supply, for this is assuredly the case; although it must be admitted that this has not in every instance been satisfactorily worked out. However, it exists typically in a sufficiently large number of instances to justify the conclusion that the duplex innervation, sympathetic proper and autonomic, is universal.

A word remains to be said concerning the carotid and coccygeal bodies. Both of these structures contain chromaffin tissue. They are, therefore, in all likelihood parts of the chromaffin system. The first, also, contains epithelial cells suggesting a parathyroid make-up; possibly they in part share the functions of the parathyroid apparatus. The coccygeal, on the other hand, contains also structures suggesting thymus gland. Possibly the epithelial and the thymic elements in these glands bespeak for them in addition to a sympathetic also an autonomic function. It is interesting, also, to add here that both the solar and suprarenal plexuses are rich in chromaffin material.

XV

THE CONNECTIVE-TISSUE GROUP

Let us now turn our attention to the connective-tissue group. The cells of the mesoderm early give rise to lymphoid tissue, to reticular tissue, to areolar tissue, to fibrous tissue, to elastic tissue, or, it may be, to adipose tissue, to cartilage, or to bone. For us it is the less specialized forms that are significant; lymphoid tissue and fatty tissue we have met with repeatedly in our discussion. What can we say as to simple connective tissue? We have seen in lymphatic hyperplasia the persistence of a tissue which is relatively primitive, much less differentiated from the mesoderm than the other structures to which this layer gives rise. Such persistence can only take place at the expense of other structures. What is true of lymphoid tissue is unquestionably true of simple connective tissue. Indeed, the latter seems to be even "cheaper" biologically than lymphoid tissue. Its function is purely static, and unless disturbed by pathological incidence it merely binds and supports. Its metabolism is practically nil; at most its anabolic and catabolic changes are at a very low level. Very different is it with the specific cells of the glands of internal secretion. Here we deal with structures which are highly differentiated; often the size of the gland itself is exceedingly small and the amount of hormone supplied to the organism exceedingly minute—almost inconceivably so—and yet of such a nature as to accomplish the most marvelous results. The cells of such glands are the seat of intensive and highly specialized processes. Now, every gland is made up of such cells together with a supporting structure consisting of connective-tissue elements. Evidently the gland cells as compared with the connective tissue are very expensive to the organism; and, should the latter—to repeat an oft-told story—fail in its developmental power, the cheaper tissue is formed in relatively large amount and the more expensive secreting cells in relatively small amount. In this, I believe, lies the explanation of what the French have called "pluriglandular insufficiency." Evidently such a condition may be general in character, or perhaps unevenly accentuated, or localized here and there. It may, as just indicated, be biological in origin and therefore in its essence be congenital. Sometimes, indeed, there seems to be a general tendency in the organism to connective-tissue hyperplasia, and, in such cases, the involvement of the glands of internal secretion may be associated with general sclerotic changes or with sclerotic changes in other organs, *e. g.*, in the liver.

While the tendency to connective-tissue hyperplasia is in its essence doubtless congenital, there can be no doubt that local and special connective-tissue changes may be acquired. It is, however, in patients with the tendency to connective-tissue formation—a tendency expressive of a lower biological level—that damage to the glands of internal secretion may more readily result from various injurious causes; for instance, alcohol unquestionably damages the secreting epithelial cells and promotes the growth of the cheaper connective tissue. This is true also of other poisons and of the various infections. When marked endocrine symptoms make their appearance after an ordinary infection, such as influenza, scarlet fever, diphtheria, it is safe to infer that there was a previous organic weakness of endocrine development. Sometimes the picture is emphasized in a special gland such as the thyroid, but in such cases associated symptoms due to the disturbances of other glands are usually also observed. Sometimes mixed clinical pictures are met with, such as combinations of thyroid and pituitary disturbance; or dysfunctions are observed in which a classification is impossible; for instance, as to whether a hyper- or a hypothyroidism is present.

XVI

THE VITAMINS

A SUBJECT that at first sight appears foreign to the purpose of this essay is that of the vitamins. However, in the judgment of the writer, these remarkable substances demand at least a brief mention. It is known, for instance, that certain diseases, such as beriberi and scurvy, are the result of a diet from which uncooked and raw foods are excluded. For instance, beriberi is caused by a diet limited to boiled polished rice. In the polishing not only are the protein elements of the grain removed with the hull, but something is also dissipated by the cooking. A grave disorder of nutrition results which is especially featured by a multiple neuritis. Similarly, scurvy results from a diet from which fresh meats and fresh vegetables are excluded. It is not improbable, also, that other disorders, such as pellagra and rickets, have a similar origin. The vitamins are clearly substances which are introduced into the organism from without. Animals are entirely unable to produce them. It appears that they are manufactured exclusively by plants. Flesh-eating animals derive their vitamins, therefore, indirectly from the plant-eating herbivora by whose flesh they are transmitted. Our interest in them here lies in the fact that when they are rigidly excluded from the diet of young animals, the latter cease to develop, and finally die in spite of an abundance of non-vitamin-containing foods. This can readily be demonstrated by segregating a given number of animals from a litter and restricting them to a non-vitamin diet, the other members of the litter being allowed an ordinary diet. The first fail to grow, the latter develop normally. The arrest of growth and development, therefore, occurs *in spite of the glands of internal secretion*, and it is proper to infer that the latter along with the other tissues have their function inhibited by vitamin starvation. This is a point of practical importance. Some of the symptoms observed in children suffering from various forms of malnutrition and from rachitis are in harmony with this view.

XVII

IMPORTANT SEX GLAND INTERRELATIONS

In the preceding pages attention has been directed to various glandular associations that appear to be fundamental in character. Several others of very great importance, however, now present themselves. We have repeatedly called attention to the sexual factors—hyposexualism, anomalies, and aberrancies—associated with disease of various glands and which we have interpreted as due, on the whole, to a general failure of the developmental power of the organism. There is, however, one functional relationship which should be stressed and which is observed in the female. It is the relation between the function of the ovary and the thyroid gland. The thyroid enlarges in the female at puberty; it enlarges also upon marriage and again upon pregnancy. Further, the involution of the ovary at the time of the menopause has a depressing effect upon the thyroid and possibly upon the pituitary; many women grow stout at this period. Finally, it is not unusual for myxedema also to have its incidence in middle life.

There are, in addition, two other relations of the sex glands that are of great importance. The first is the relation of the ovary to the mammary gland, and the second, the relation of the ovary to the uterus; as well as the analogous relation of the testicle to the prostate.

The close relation of the ovary to the mammary gland is so well established that it hardly requires emphasis. The mammary gland develops hand in hand with the ovary at the time of puberty; again, the glandular structure of the mammary gland atrophies at the time of the menopause; further, it is significant that this atrophy also follows oöphorectomy. These facts point to a dominance on the part of the ovary over the mammary gland. This dominance is analogous—though apparently much more intensive—to that exercised by the thyroid over the anterior lobe of the pituitary (see p. 88) and akin to that which we have reason to believe exists also both in the case of the adrenal cortex and in the case of the pineal body. We have seen how the pituitary, both in hyper-and in hypopituitarism, when the restraint imposed by the interglandular balance is destroyed, enlarges in an effort at compensation, a compensation, however, that does not remain as a simple hypertrophy, but terminates in neoplasms and malignancy. It is not only conceivable, but to the writer extremely probable, that the impairment of the balance between the ovary and the mammary gland—the lessening of the restraint exercised by the former over the latter—should lead to changes analogous to those which we have seen take place in the pituitary. The lessening of restraint leads to the multiplication and proliferation of cells no longer well differentiated, cells of a lower level biologically, lacking the normal arrangement; perhaps having an anomalous arrangement or no arrangement at all. It is hardly surprising that such changes should result in neoplasms and malignancy.

The question at once presents itself, If removal of the ovary leads to atrophy of the mammary gland, what is the change that leads to overgrowths, overgrowths always pathological?

The endocrine function of the ovary is much more complex than that of the male gland. In the latter the endocrine function is definitely known to be discharged by the interstitial tissue containing the cells of Leydig. In the ovary there appears to be, in addition to a function discharged by the interstitial tissue, also another function discharged by the corpus luteum. The corpus luteum, which in the absence of pregnancy undergoes a relatively rapid involution and disappearance, persists to a remarkable degree during pregnancy. Its persistence is doubtless related to the latter function, and it may for that reason be dismissed from our immediate consideration. Regarding the interstitial tissue, it may, I think, be safely predicated to be in relation with the secondary sexual characters and, among the latter, especially with the mammary gland. Can it be that in given pathological conditions of the ovary this interstitial tissue is in neoplasms and malignancy of the breast so changed as not only to suffer a lessening of its restraining power over tissue growth, but actually to favor the latter? Such a relation obtains beyond question between the ovary and fibroid disease of the uterus, and, to pursue the analogy, between the testicle and disease of the prostate. Surely, it seems admissable to extend the same interpretation to disease of the mammary gland. A kindred interpretation naturally applies to malignant disease of the uterus.

Can it be that after all the cause of malignancy is biological and that the mystery lies in the internal secretions? If so, this abundantly explains the failure of the search for special cancer causes. Further, the explanation of malignancy advanced in this essay applies not only to the pituitary, the adrenal cortex, the mammary gland, the uterus and the prostate, but, it would appear, to malignancy in general. Relationships between glandular structures may not always be so clearly indicated as in the organs we have considered, and yet many suggestive facts present themselves. For instance, as repeatedly pointed out, the autonomic group of glands comprise those of the digestive tract and its adnexa—including, of course, the pancreas—together with the thymus and the parathyroids. All of these glands constitute together a synergic group (see p. 140). Evidently, we must look for the counterbalancing or "mutually dominating" influence among the antagonistic group of glands, the glands of the sympathetic proper; these consist, as we have seen, of the chromaffin system, the thyroid, and the pituitary. It would appear that morphological weakness of these structures predisposes to overdevelopment, to overcompensation of their antagonists. Such an overcompensation is the enlargement of the thymus and the lymphatic hyperplasia which occurs in underdevelopment—in hypoplasia—of the chromaffin system and in Addison's disease. It is readily conceivable that such an unstable equilibrium involves not one gland of the autonomic group, but all of these structures alike. There is established a tendency to hyperplasia, to overcompensation, of all the glands, indeed, of all of the tissues, of the autonomic group.

Now, the explanation of malignancy is often sought in some special cause, such as a local irritation, in something which causes a local lesion, a break in the tissues. When we reflect upon the fact that in countless instances such local lesions fail utterly to result in malignancy, it is evident that they can only have an incidental value. What happens when malignancy does result is probably this: The effort to heal the abrasion, the fissure, the simple ulcer, or whatever the break may be which subsequently leads to cancer—it may be of the tongue, stomach, rectum, or other organ—*fails;* it fails because of the loss of control over the growth and proliferation of the cells of the structure involved. There is an unrestrained "overeffort" at healing, and during which both the cells of the biologically inferior tissue, the supporting tissue, and the cells of the organ proper—the highly differentiated cells, the epithelial or epithelioid cells upon which the special function of the given organ depends—alike fall in biological level. Cells are reproduced, but they are simpler, relatively undifferentiated and rapidly proliferating. The attempt at healing, no longer or inadequately controlled by the "sympathetic group," now results in an "overcompensation," an overeffort at healing, a mad building up of tissue, in which biologically primitive cells and cells of the supporting and of the epithelioid tissues play varying rôles. Sajous has long maintained that adrenalin has an action opposed to malignancy, and I believe that the facts necessitate our attributing such an action to the entire "sympathetic group."[1]

This explanation applies not only to malignancy of the structures which have their origin in the entoderm and splanchnopleure, but equally to malignancy of the structures which have their origin in the ectoderm and somatopleure. In the case of the latter, however, it is especially the persistence and enlargement of the thymus and of the lymphatic system which play the principal rôle in the imbalance. The sympathetic group being morphologically deficient or impaired, there is, as before, a hyperplasia of the autonomic group. As before, special causes—lesions of the surface, traumata of the deeper structures—lead to efforts at repair which end disastrously. Here again overcompensation and the consequent biological reduction result in the production of primitive and relatively undifferentiated cells growing without restraint. In malignancy of all kinds, no matter of what

[1] It is interesting in this connection to recall that *primary* malignancy of the chromaffin system is practically unknown and that this is true also of the thyroid. Further, it appears that imbalance resulting in malignancy having once been established, it cannot be corrected by the administration of adrenalin or of thyroid. Have we, however, here a hint as to possible prophylaxis in given cases?

structures or how arising, these primitive cells, living more cheaply, requiring less and growing more rapidly, present a competition for survival which is hopeless for the more highly differentiated tissues, and the invasion and destruction of the latter naturally follows.

As regards the so-called "benign" tumors, a similar explanation of "imbalance" or "loss of restraint" must equally apply; at least to those that make their appearance spontaneously in the tissues, and in which special factors—in themselves doubtful—such as the possible persistence of "displaced embryonal rests" or coarse factors, such as direct trauma, seem to play no rôles. Further, it is not necessary to point out that the transition from non-malignancy to malignancy is of frequent occurrence. Finally, it must be frankly acknowledged that in many instances the line drawn between malignancy and non-malignancy is extremely shadowy.

As is well known the statement is frequently made that malignant disease is increasingly prevalent. If this be true, the cause is clearly not to be sought in some dietary or other fault, as has at various times been suggested, but in a general reduction in the biological level. That such a reduction should ensue as a result of the unprecedented strains of modern civilization is not surprising; never before, in the history of the world, have these strains been greater or more incessant. If the organism be inadequate to meet them, glandular failure, glandular exhaustion, glandular imbalance result. The breakdown may occur primarily in the autonomic or sympathetic groups, but in women it appears to occur with especial frequency in the reproductive group. It would seem that in the great drafts made upon the organic resistance of the individual, this group is in women prone to sacrifice.

XVIII

THE ENDOCRINE FACTOR IN NERVOUS AND MENTAL DISEASES

LET us now turn our attention to the endocrine factors in mental and nervous diseases. As above pointed out, the sympathetic nervous system and the cerebrospinal nervous system are closely interrelated (see p. 137). Certain interesting phenomena growing out of this relationship now present themselves for our consideration. They are of great practical importance, but in order that we should observe them in their proper perspective, one or more general facts first require attention. To begin, a comprehensive view of the subject of the glands of internal secretion reveals the fact that there is no uniglandular endocrine disease. A number of glands is always concerned, possibly the entire chain; certainly never one gland alone. Again, when we consider the mass of clinical material that comes under our observation, we realize that the number of cases presenting the very gross and striking results of endocrine disease, such as gigantism, dwarfism, gross acromegaly, enormous obesity —in other words, the "freaks" of the museum and of the side show of the circus—is relatively small. However, in a larger and not inconsiderable number of cases the symptoms are less marked, less striking, but still such as to lead to a ready diagnosis and classification. Again, in a still larger, a very large number of cases, symptoms of endocrine disturbance are present without striking or gross abnormalities of structure. In such patients careful examination, however, frequently reveals the presence of the stigmata of arrest and deviation which we have considered in the preceding pages; sometimes these are present in very marked degree and sometimes in very slight degree, but all have the same significance. Sometimes notable departures in the secondary sexual characters are observed, sometimes slight departures; sometimes peculiarities of the circulatory apparatus, of the digestive apparatus, of the skin, of the secretions, of the sexual life, and, last but not least, of the nervous and mental functions. Indeed, it is the disturbance of the latter that usually brings the patient to the attention of the physician. Sometimes the patient betrays in outward appearance little that is wrong, and yet presents quite an array of nervous symptoms often associated with visceral disturbances. It may be that he presents the symptom of fatigue, a fatigue marked and persistent, induced or made worse with the greatest ease. Slight effort, physical or mental, exhausts him. Food and rest, which cause the disappearance of ordinary or normal fatigue, fail to restore him. He tells us that he is tired, always tired. Fatigue sensations, diffuse and general, may be pronounced, or he may tell us of localized fatigue sensations, headache, backache, or limbache. If we examine his circulation, we find that the action of the heart is impaired; it lacks its customary force and its rhythm may be disturbed; the pulse is small, soft, compressible, and its rate is increased. The extremities are cold; the hands and feet are damp, they may be wet; sometimes they are livid; sometimes the features are dusky. If we turn our attention to the gastro-intestinal tract, we find that digestion is delayed and difficult and that the bowels are constipated; in other words, there is present an atony of the digestive tract, a marked deficiency of innervation, a deficiency, which as we have just seen, is paralleled by the deficiency of innervation of the circulatory apparatus.

The condition here outlined is that of a neurasthenia, a so-called nervous exhaustion. The cardinal fact is the lowered output of energy by the organism. It is possible that in overfatigue this diminished output of energy is in part due to change in the nerve substance itself; indeed, the experiments of Hodge and others—now many years old—appeared to show that nerve-cells undergo an actual diminution of substance as a result of the excessive exercise of their function. However, in overfatigue, as it presents itself clinically, the symptoms leave no doubt as to the involvement of the internal secretions. The disturbance, which is, of course, purely functional, involves in a striking manner the chromaffin system and the thyroid, and in all probability, also, the pituitary. It is a functional reduction, but one which is not limited to the distribution of the sympathetic proper, but involves also the autonomic innervation. The last mentioned fact is shown conclusively by the condition of the digestive tract and of the circulatory apparatus. Indeed, the involvement of the autonomic group is probably primary. The chromaffin system, the thyroid, and the pituitary are all concerned with effort, with the output of energy. On the other hand, the glands of the digestive tract, the pancreas, and the synergically related thymus and parathyroids are all concerned with the storing and the conservation of energy (see p. 140). Necessarily the weakness of the autonomic group leads to a weakness of the sympathetic group.

Let us pause for a moment to consider an important clinical fact, and that is, that neurasthenia, the neurosis of chronic fatigue, is not induced—at least not readily induced—in the ordinary or normal individual. Overfatigue and tire are common enough as the result of the stress and strain of our lives, but this is a very different thing from neurasthenia. All the evidence at our command points to the fact that the "neurasthenic" is innately a "neuropathic" individual; and "neuropathic" means nothing less than that the individual is organically, that is, morphologically, defective. The lower biological level upon which he stands is revealed among other things by his lowered resistance to fatigue, by the lowered efficiency of his glands of internal secretion.

When we turn our attention to other "functional neuroses," kindred facts present themselves. Every now and then nervous exhaustion is featured by special symptoms. Thus, the non-aggressiveness, the timidity, the fear of the neurasthenic—a fear which sometimes manifests itself in the severer forms by spontaneous and seemingly causeless paroxysms—may assume a special character. Thus, the patient develops a fear of special places, of special surroundings; sometimes it is the fear of being alone or of being in crowds; or it may be that he develops a phobia associated with some past occurrence; some occurrence perhaps the memory of which is unpleasant or of which he is ashamed, and which he wishes to forget and tries to suppress, but which notwithstanding crops up possibly in some distorted form and manifests itself as a special fear or perhaps as an obscure phobia or some strange obsession. Fear and weakness go hand in hand.

Again, it may be that the special feature of a given case is that of a chronic indecision. The person who is normally tired may be unable to decide an important matter with his usual confidence and promptness; the neurasthenic habitually defers, postpones, avoids decisions which require effort, and this attitude of mind in some patients becomes habitual, so that it is revealed in the most trivial affairs of life and conduct. Again, the patient being weak, may lose the well co-ordinated control of his person. The tired man grows angry more readily, strikes more quickly, weeps more easily. Normally the outflow of nervous impulses passes through well co-ordinated channels, channels that are in harmony with and inhibited by the other nervous processes. Normally the channels are those of well-directed and purposive movements; at times, too, they are movements expressive of the pleasurable discharge or overflow of energy, as in children or animals at play. In the neurasthenic, however, weakness leads to loss of balance, loss of inhibition, and to the discharge of impulses that are purposeless. At times the movements resulting are associated with some past occurrence, some fear or phobia.

It is thus that involuntary automatic movements, the "tics"—tics convulsifs—are established; often so annoying and distressing to the patients.

Finally, the man who is tired suffers a diminution of his energy, of his personal force, of his ability to do. In the neurasthenic this symptom is more pronounced and may in given cases lead to a marked weakness of will. Sometimes this weakness prevents the patient from performing, save with stress and difficulty, if at all, many of the ordinary acts of life. Sometimes, too, as may be anticipated, this weakness of will, which has received the name of "abulia," is associated with some special fear or obsession, and is thus related to the performance of some special act.

As may be inferred, all of the special symptoms, the fear, the indecision, the abnormal movements, the tics, and the lessening of will power are all interrelated, are all expressions of the same thing. Janet has applied to the forms of nervous exhaustion especially featured by these symptoms the term "psychasthenia." Like the ordinary neurasthenics to whom they are so closely related, the psychasthenics betray the earmarks of an imperfect development, not always crass and striking, to be sure, but no less evident and no less significant. The same is true of the endocrine factors; these may betray themselves not only by symptoms such as are presented by the ordinary neurasthenic, but even at times upon gross inspection. In some a slightly enlarged thyroid may be discovered; on the other hand, in others, again, an unmistakable infiltration of the skin suggesting a partial or incomplete myxedema may be made out. Occasionally such a patient, in whom indecision is usually a prominent symptom, is, like the typical case of myxedema, extraordinarily slow; one of my patients between indecision and slowness, would require many hours to dress himself. In short, all that has been said in this essay in regard to the biological and morphological position of the neurasthenic may be repeated here in regard to the psychasthenic, and with even greater emphasis.

When we turn our attention to the more pronounced forms of mental disease the great rôle played by biological and morphological factors is again very apparent. Beginning with the idiot and feeble-minded children, we find that these separate themselves naturally into several groups. The first consist of those in which the idiocy is symptomatic of an arrest of development pronounced in degree. The evidences of arrest are so marked in such cases as to form very striking features. That they should vary greatly in individual cases and be irregular in their distribution is, of course, what might be expected. Together with the anatomical deficiencies and aberrancies, there are also frequently present the signs of decided anomalies of the glands of internal secretion, such as deficient development of the thyroid, the presence, it may be, of lymphatic hyperplasia, or, it may be, of persistence of the thymus. In a second group, we have patients who, though normal at birth, have suffered from a disease imposed on the thyroid gland and who present the symptoms of cretinism. In a third group, we have children in whom the brain has suffered from grave traumata, such as occasionally occur during birth, and also children who have been the victims of grave infections or other destructive pathological processes. Clearly it is morphological idiocy which is especially pertinent to our subject.

When we turn our attention to the imbecile, another interesting picture is unfolded. The imbecile is one in whom the mental deficiency is not apparent at birth or shortly after birth, as in idiocy, but only after several years have elapsed; sometimes it is not until the child begins to go to school or has entered the period of puberty or adolescence that the deficiency attracts attention. Often such a child is spoken of as retarded or delinquent. The law expresses the underlying fact of imbecility by defining an imbecile as an adult with the mind of a child; a definition, however, which is inaccurate, inasmuch as the deficiency becomes apparent long before adult life is reached. On the other hand, it covers the cases that survive up to or live through the adult period, and which are often spoken of as cases of constitutional inferiority. That various stigmata of arrest and deviation are present in imbeciles—stigmata general in character, together with frequent peculiarities in size and shape of skull—need hardly be pointed out. Evidence of endocrine deficiencies may also be present; in the older patients the secondary sexual characters are worthy of note. In short, imbeciles are merely cases of morphological arrest in which the incidence of the arrest, instead of being marked very early as in idiocy, is delayed for a variable period.

XIX

THE MENTAL DETERIORATIONS

We now come to a group of mental affections featured not only by various evidences of an imperfect morphology but also by the onset of a deterioration after a certain level of development has been reached. This deterioration may have its incidence at puberty or a little after puberty, more frequently during the period of adolescence; sometimes the incidence is delayed until adult life is reached. The younger cases have been grouped under the head of the early dementias or the insanities of adolescence; the technical term commonly employed is that of "dementia præcox." The older cases have been grouped under the head of the paranoid dementias and paranoias. The group as a whole forms the larger mass of the patients in the asylums for the insane or hospitals for nervous and mental diseases, as we now prefer to call these institutions.

As may be inferred from what has been said, this group of cases of deterioration falls naturally into two subgroups—the adolescent and the adult forms. At the outset it is important to bear in mind that in neither subgroup are we dealing with a specific, a sharply delimited clinical entity, such as epilepsy or manic-depressive mental disease, but merely with a mass of mental cases that possess the one common factor of endogenous or, better still, of autogenous degeneration. That this mass of cases, however, pursuing a common pathway of degeneration, should present some symptoms in common is not surprising; this makes possible some classification, but such classification has its limits and besides is proximate only. Further, it does not here concern us.

To begin, when we turn our attention to the adolescent group, we find a number of very significant facts presented by the family histories of the patients. Such histories frequently present not only instances of frank nervous and mental disease in the ancestry but also of eccentric and unusual personalities, of criminals, prostitutes, tramps, vagabonds, and other degenerates. The wide range of the hereditary findings is also a fact of some significance. If the inquiry be limited to the direct transmission of dementia præcox, we find that such transmission is relatively infrequent, as a large number of cases, especially the hebephrenics and catatonics, never reach parenthood. It is otherwise, however, if we include the older, the paranoid cases. Ruedin, from studies made of Kraepelin's material, comes to the conclusion that dementia præcox is probably transmitted in accordance with the Mendelian law of heredity and appears as a recessive quality. He regards the marked predominance of the collateral and discontinuous inheritance over the direct inheritance, the increase of dementia præcox resulting from inbreeding and the numerical relation of those attacked to those remaining normal, as in favor of this view. The significance of a number of individuals of the same family suffering from dementia præcox cannot be questioned. I have personal knowledge of one family in whom no less than 5 individuals have suffered from this disease. Of equal significance are such facts as that the late or last born children of a family suffer more frequently from dementia præcox than the older children, and again, that immediately preceding or following the birth of a præcox patient there is frequently a history of miscarriage, premature birth, or still-birth.

The germ plasm may suffer from other causes still that further affect its general morphological and biological character and profoundly lower its possibilities of growth and development. Among causes which may thus grossly impair the germ plasm we have reason to believe are infections and intoxications affecting the parent. Pilcz, Klutscheff, and others have published suggestive statistics as to the frequency of syphilis in the parents, while Diem, Fuhrmann, Ruedin, Wolfsohn, and others have published studies on alcoholism in the parents alike suggestive and significant. That syphilis plays a rôle in a not inconsiderable number of cases is proved by the frequency of the Wassermann reaction in the patients themselves. Bahr, for instance, found it in so large a proportion as 32.1 per cent. Such facts do not mean that the patients are necessarily suffering from a syphilitic disease of the nervous system, but rather that the organism as a whole has been impaired, made deviate and degenerate in its development by

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the presence of the spirochete and its toxins, *i. e.*, that the development of the organism as a whole—and included in this the development of the glands of internal secretion—has been so inhibited and altered that, at a given point of its life, the organism breaks down by reason of an abnormal and toxic metabolism. Again, it is not necessary that the Wassermann or other tests should yield a positive result. It suffices if the infection has damaged the germ plasm of the parent, and in keeping with this is the fact that clinical evidences of inherited syphilis are absent in the great mass of cases. Finally, that alcohol damages the germ plasm of the parent must, I think, be freely conceded, and its discussion need not detain us here. The question whether other poisons and infections also play a rôle in causing damage to the germ plasm cannot be definitely answered; but such action is neither impossible nor improbable. In any event, however, their action must be vastly less important than that of syphilis or alcohol.

Certainly it is not surprising that, having its origin in a germ plasm so unfavorably placed, the organism should present the evidences of an imperfect evolution. In keeping with this we find numerous evidences of arrest and deviation. Saiz places the frequency of the stigmata at 75 per cent. Among the latter are physical feebleness, retardation of growth, a too prolonged juvenile appearance, malformations or peculiarities of the shape of the skull, deep, narrow and irregular palate, persistence of the intermaxillary bone, abnormalities of the ears, fingers or toes, imperfections and anomalies of the teeth, and other morphological peculiarities such as have been described in the preceding pages.

The above facts clearly indicate the involvement of the organism as a whole. We should remember, too, that the existence of the various evidences of morphological deviation visible to clinical observation also imply that other and perhaps more fundamental deviations are present in the organism throughout. Such an organism must present not only abnormalities of structure but also abnormalities of function and especially of metabolism. Sajous has pointed out the cogent facts indicating the important rôle played by the thymus gland. Various facts point to other structures as well.

Thus, that the thyroid gland may present abnormalities is a matter of common knowledge. Occasionally it is enlarged; more frequently, in my own experience, it is small. Thus, in 7 of my own autopsies in which the thyroid gland was weighed, 5 were little more than half the normal weight, 1 was one-fourth the normal, and only 1 approximated the normal. Again, out of 8 pairs of adrenal glands 5 were greatly in excess, 1 decidedly below normal, and 2 about normal. The most constant findings in the adrenal picture was the small amount of fat in the cells of the cortex; possibly this indicated a lessened functional activity. However, that there are other glands which probably play a rôle in dementia præcox the evidence strongly indicates. Clinically our attention is strongly attracted to the sex glands. We are confronted by the anomalies of menstruation or by the delayed and imperfect establishment of puberty, on the one hand, or of sexual precocity on the other. Again, there is the history of sexual excesses, sexual vagaries, and perversions. A relation to the sex glands is further indicated by the accentuation of symptoms often observed during a menstrual epoch, and by the fact that dementia præcox now and then has its incidence in a pregnancy or in repeated pregnancies, or in a miscarriage, as though sex gland exhaustion played a rôle. Various writers, among them Tsisch, Lomer, and Kraepelin, have assigned an importance to the sex glands. Lomer, particularly, indicated a disturbance of the internal secretion of the latter, but it remained for Fauser to throw an especially illuminating light on the subject. Fauser, as is well known, found in the serum of dementia præcox cases defensive ferments against the sex glands and against the cerebral cortex. It would appear from Fauser's investigations that in dementia præcox a primary dysfunction of the sex glands leads to the entrance into the blood of an abnormal protein, and that in the subsequent breaking up of this protein substances are formed which are injurious to the cortex, and which bring about the destruction, the lysis, of the latter. It is very probable, however, that in dementia præcox toxic action is not limited to the cerebral cortex, but involves the sympathetic and autonomic nervous systems as well. Of this the symptoms presented by the circulatory apparatus and digestive tract are sufficient evidence. Among these are the alterations of cardiac rhythm, the fall of blood-pressure, the lividity, dryness, moisture, or other conditions of the skin and subcutaneous tissues; the atony of digestion, the constipation, and dryness of the digestive tract. It is entirely in keeping with the facts to infer that in dementia præcox the glands of internal secretion have shared in the general failure of development, and that their functions are, therefore, inadequately or aberrantly performed. Further, while a number of glands are always involved—probably the entire chain—certain glands may dominate the picture. Quite frequently the synergically related glands of the sympathetic group, the thyroid, the pituitary, and the adrenals, dominate the picture; sometimes it is the autonomic group; most frequently both groups in varying degrees.

What do we find in the second subgroup, which is made up of the adult forms, the paranoid dementias, the paranoias? The first fact to impress us is again the overwhelming rôle of the heredity. Here heredity finds its full expression. Hereditary factors are here the order of the day, and 85 or 90 per cent. is probably a moderate estimate of the frequency of their occurrence. Second, we are again impressed by the presence of gross morphological arrests and deviations. Thus, the skull at times presents a markedly flattened occiput; sometimes it is oxycephalic, clinocephalic, strikingly assymmetrical, or presents an unusual expanse or prominence of the frontal region, or it may be a forehead that is suggestively receding. Peculiarities may also be noted in the trunk, the limbs, the digits; it may be in the excessive length of the extremities relative to the trunk, in the relative lengths of the various segments of the limbs, in the relative size of the fingers, or possibly in the stature of the individual. Perhaps, too, we may note the presence of female secondary sexual characters in male patients or of male characters in female patients. Such stigmata we have already sufficiently discussed in the preceding pages; regarding their significance there can, of course, be no question. The chief difference between the paranoid forms and the adolescent forms we have just considered is that the deterioration is apparently delayed in the former until the adult period is reached. This, however, is true only of the gross manifestations of the disorder. When it is possible to secure a satisfactory personal history, it is commonly found that the patient already betrayed in childhood and youth peculiarities such as to excite comment. Frequently we learn that the patient was unusually quiet and reserved, morbidly shy and suspicious, that he remained apart from his fellows, did not mix in the play of other children, formed few attachments, had no friends. Often the history reveals that he was morbidly sensitive, introspective, and self-conscious. Later in youth these peculiarities not only persisted, but were accentuated; the patient kept to himself, was distant, diffident, taciturn, and it may be proud and egotistic; he was always occupied with himself. In short, the history is that of a morbid, a pathological childhood and youth.

Such a history reveals the beginning of a deterioration which is later featured by the frank symptoms of a delusional lunacy. The heredity, the morphological stigmata, and the aberrant developmental period permit no escape from the conclusion that the individual was subnormal at his birth; indeed, that his organization was so defective as to lead to an inevitable breakdown. Other facts are in harmony with this view; for instance, delusional lunacy is somewhat more frequent in persons born out of wedlock, probably because women bearing bastards are likely themselves to be degenerate; public women and prostitutes are in large percentage subnormal, while many others who lead irregular sexual lives are likewise defective.

It is very significant, further, that the stage of frank mental disease is ushered in by a period of depression and hypochondriasis which is featured at first by vague, obscure visceral sensations. Faint and uncertain in the beginning or irregular in recurrence, they later become more pronounced. The patient experiences unpleasant, painful, or strange sensations in the stomach and bowels, or in the abdomen generally; distress in the precordia, palpitation, buzzing in the ears, headache, fulness or emptiness of the head, sensations of pressure or constriction; perhaps he will complain of throbbing and other queer sensations in the genitals. Later these sensations, which are clearly hallucinatory in character, may become very pronounced. Special sense hallucinations also make their appearance, as do delusions which have as their basis the reference by the patient of his sufferings to some cause or causes outside of himself. These visceral and other sensations of somatic origin[1] are best explained by a disturbance of the glands of internal secretion similar to that which we have reason to believe exists in the juvenile forms. Very likely this is a disturbance of innervation involving both divisions of the sympathetic. In the early stage, the stage of hypochondriasis and persecution, it is unquestionably the autonomic division—the autonomic group of glands (see p. 141)—which is especially involved; they are, among other things, depressed in function. In keeping with this the patient is in bad nutrition; the gastro-intestinal and associated phenomena—the visceral hallucinations and the delusions of poisoning or what not—are such as to lead to a lessened alimentation and assimilation. In the expansive stage, the stage of grandiose delusions, the reverse obtains; the

[1] In this connection see the section on manic-depressive insanity as to the rôle of the thalamus and cortex, p. 199.

disturbance is now accentuated in the group of glands in the distribution of the sympathetic proper (see p. 140).

With the detailed history of the paranoid dementias, as well as with the history of the so-called non-hallucinatory forms (paranoia vera), we are not here concerned. For us the great rôle of imperfect development and the obvious endocrine involvement are the all-important features; all else is secondary. The rôle of arrest and deviation in the nervous system itself is only in keeping with the general failure of the organism to reach the normal level. The evolution and course of the mental symptoms is also a most interesting subject, but this likewise is beside our purpose. Suffice it to say that gradually and usually very slowly the dementia increases and, in the last stages, if the patient lives, becomes very marked. Usually after the lapse of a number of years—sometimes many—the patient dies of some visceral disease; it may be a disease of the blood-vessels, and a cerebral hemorrhage may terminate the picture.

XX

THE ENDOCRINE FACTORS IN MANIC-DEPRESSIVE DISEASE

We next come to a symptom group which much more nearly approaches a clinical entity than the group of the autogenous degenerations we have just considered. It is the group of the melancholias and manias to which, following the lead of Kraepelin, the convenient term "manic-depressive insanity" has come to be applied. The picture, which is no less interesting than that of the deteriorations, differs from the latter in several important particulars. It is featured, first, by an emotional state, either of depression or of expansion, which dominates the entire clinical picture; second, by a wave-like course of gradual increase, maximal intensity, and final subsidence. Again, as might be inferred, it occurs in attacks. These are commonly of many months' duration. They are rarely followed by any impairment of the mental integrity, and though they tend to recur a number of times in the lifetime of the patient, mental deterioration occurs only exceptionally, and then apparently as the result of special causes such as may obtain at the middle, the post-middle, or the senescent periods of life.

When manic-depressive cases are examined physically we are impressed by the fact that morphological anomalies are not marked features. As compared with the deteriorating group, they may be said to be present in minimal number. Careful search, however, does reveal in given cases anomalies of the ears or of dentition, or, it may be, of stature; or we may find a heart and blood-vessels that do not seem to have attained an adequate development. However, as a whole, it is the exception to find features of arrest or deviation pronounced in degree. One fact, notwithstanding, is very suggestive, and that is the great rôle played by heredity. This has been estimated at no less than 80 per cent.; probably, if the truth were always ascertainable, in an even larger number. It is also a suggestive fact that melancholia and mania occur more especially in individuals of mobile and temperamental extremes, in persons who are emotional, who are readily depressed, or in whom the opposite phase is too readily excited. It is further significant that these affections occur most frequently in youth and early adult life, *i. e.*, about the third decade, though it is by no means limited to this period, for it may occur much later or even earlier. It is the third decade of life, however, in which, as just stated, the symptoms most frequently first make their appearance. This period is one during which the transition from youth to adult life takes place and which is peculiarly liable to emotional upheavals and to emotional stress and strain. It is an age of expansion, pleasure, and happiness, but also of depression, disappointment, and suffering. That persons who are the victims of an inherited neuropathy—a manic-depressive insanity—should manifest this affection, especially at this period of life is, therefore, not surprising. The individual of normal constitution passes through this period unimpaired, but he who is the victim of the manic-depressive neuropathy breaks down, and enters either upon a depressive or expansive wave, or perhaps passes through a succession of both.

In how far are the glands of internal secretion concerned in these attacks? Along with the gradual evolution of the mental phenomena, which it is not our purpose to discuss here, very positive physical signs are noted. Let us first consider melancholia and turn our attention to the period of maximal development of the symptoms. Everything points to a pronounced loss of nervous tone, to a defective innervation. There is now a marked gastro-intestinal atony. The lips and mouth are dry, the tongue is white and pasty, the saliva scanty and thick, and there is marked fetor of the breath. Often there is present an acid indigestion. There is present a severe and sometimes obstinate constipation. The loss of appetite is very profound. The patient may experience a veritable disgust or fear of food. The circulatory apparatus also reveals changes. The force of the beat of the heart is lessened, the arterial tension lowered. The surface of the body is pale, the extremities are cold, and their distal parts are often dusky or cyanosed; even slight puffiness or edema may be noted. The pulse-rate is not much changed; quite frequently it is a little slower than normal; at other times, if the patient be agitated, it is increased. The temperature, more especially the surface temperature, may be distinctly subnormal; more particularly is this true in cases which pass into the stuporous form. The respiration is somewhat slower and somewhat shallower than normal. The urine is usually lessened in amount; its specific gravity is frequently increased, though it may be diminished. The earthy phosphates are increased, the alkaline phosphates diminished. The output of nitrogen, as one would almost expect, is lessened. The skin is abnormally dry and the hair brittle. The perspiration is usually much diminished. In addition, a loss of weight is noted. In women menstruation becomes scanty, irregular, and quite commonly ceases.

The muscles lack tone, the patient is physically weak. He is quiet, sits still, remains apart and by himself. Frequently he will not speak, and if he does, we may find that his voice is low, that his speech is hesitating, his manner abstracted. He speaks slowly, his thoughts are retarded. Often what he says is limited to a few words and short phrases. His face is pale, the head is bowed, the shoulders drooping, the arms hanging, the whole attitude one of listlessness and dejection. Evidently we are dealing here with a symptom group clearly referable both to the glands innervated by the autonomic nervous system and to the glands innervated by the sympathetic proper. The synergically related group of the glands of the digestive tract, the pancreas, the parathyroids, and the thymus, and which are concerned as we have seen with the storing up of energy (see p. 140), is in melancholia profoundly depressed; of this the reduced metabolism and the loss of weight are a sufficient proof. On the other hand, the group consisting of the glands innervated by the sympathetic proper, the chromaffin system, the thyroid, and the pituitary, are also greatly involved, so much so that in the fully developed period the output of energy is diminished to the smallest possible level. It would appear from the evolution of the symptoms that the autonomic breakdown occurs first. In the beginning there is diminution of appetite, delayed and imperfect digestion, and constipation. The patient loses color, the vascular tension falls; there is a lessening of strength and energy; nutrition becomes impaired; the patient, as already stated, loses in weight. That a diminution in the storing up of energy should be followed by a diminished output seems to be quite inevitable. Other things equal, it would seem that the involvement of the group of the sympathetic proper is secondary to the involvement of the autonomic.

Let us now turn our attention to the opposite phase of manic-depressive insanity, that of mania. Setting aside for the time being the mental symptoms present, what are the physical signs? In crass contrast with melancholia we find, instead of physical quiet and torpor, physical restlessness and activity. The patient is in constant motion. His movements are coarse and exaggerated, his gestures extravagant. His manner is aggressive, his expression animated, his color heightened, his conjunctiva tense and brilliant. He laughs and frowns in quick succession. He talks incessantly; he is boastful and declamatory; his thoughts flow with great rapidity and he constantly gives vent to them. He may manifest an actual increase in muscular strength and may make muscular efforts exceedingly violent in character.

When we examine him for evidences of autonomic involvement, we find the tongue clean, digestion unimpaired, the bowels moving freely. The appetite is exaggerated, often excessive; sometimes the patient eats gluttonously. The pulse, which early in the attack may be slightly more rapid—more so in periods of increased excitement—becomes, as the attack progresses, slower, while the force of the cardiac impulse is increased. The urine is increased in quantity, but shows no changes of moment. It is very probable that metabolism is increased, but thus far, possibly because of practical difficulties, satisfactory studies in mania have apparently not been made. In women irregularity or suppression of menstruation is the rule; if the menses appear, there is apt to be an exacerbation of the excitement.

Evidently in mania there is an enormous exaggeration, an enormous increase in the functional activities of both groups of glands—of both the innervation of the autonomic and of the sympathetic proper. Here inferences as to which group is disturbed primarily are not so clearly indicated; however, a hint is furnished by the fact that in mania there is at times observed an antecedent period of depression, during which such autonomic factors as diminished appetite, impaired digestion, coated tongue, and constipation are present. When the mania follows a frank attack of melancholia, which is so often the case, there can be no doubt, of course, as to the sequence of involvement. We have in such an instance a clear indication of the primary disturbance of the autonomic group, a disturbance in which—in the case of mania—the sympathetic group early participates. Indeed, it is difficult on other grounds to escape the conclusion that the autonomic group is involved first. There can be no expenditure of energy by the sympathetic group until the autonomic group by a recrudescence of function furnishes energy to be discharged.

The question now arises, How can the emotional depression and the emotional expansion of the respective phases of melancholia and mania be accounted for? Both divisions of the sympathetic are, as we have seen, in close relation with the cerebrospinal nervous system (see p. 137). It appears, further, that just as the various sensations derived from the special sense organs are represented by special structures in the encephalon, so are the visceral sensations represented by special structures in the encephalon. Naturally, these facts find their simplest expression in the lower vertebrate forms; *e. g.*, in fishes. Speaking of the dog-fish, Herrick states[1] that we may recognize in this fish a "nose brain," an "eye brain," an "ear brain," a "visceral brain," and a "skin brain." Each "brain" is related to certain receptors, and to these only. In ourselves impulses transmitted through the spinal cord and brain stem are received first in the thalamus, the "between brain." Here special way stations, nuclear aggregations, have made their appearance. In the cells of the latter various axones, bearing tactile, visual, auditory and other impacts, terminate synaptically; thence other axones constituting the so-called "sensory projection fibers" pass upward to the cortex. The nuclei in the thalamus which play this rôle of way stations—and one of whose functions is doubtless that of reinforcement—are spoken of as "cortical dependencies." Now among these cortical dependencies, these nuclear way stations in the thalamus, are found cell groups not only for the reception of the

[1] Herrick, Introduction to Neurology, 2d ed., p. 121.

special sense sensations, *i. e.*, for those that have their origin in impressions received through the exteroceptors from the outside world, but also for the reception of impressions received through the interoceptors from the body of the organism itself. Among the latter are included not only the impressions received through the interoceptors from the various viscera but also the impressions received through the proprioceptors; in short, from the organism as a whole.[1] That painful and pleasurable sensations are aroused in the thalamus, just as are sensations of sound or light or heat, there can, I think, be no question. Thalamic pain, for instance, is a well-recognized clinical symptom. Inasmuch as the nuclear aggregations of the thalamus are but way stations to the cortex, it follows that these sensations are transmitted to the cortex. Whether they enter the field of consciousness depends doubtless upon their intensiveness. If sufficiently intensive they force their way in, and, if massive, may dominate the entire conscious state. With the elaboration of the mental symptoms—interesting as they are—we are not here directly

[1] See Dercum, Physiology of Mind, 1922, pp. 110 and 111.

concerned. However, the rôle of the thalamus in hallucinations and the elaboration by the cortex of delusive ideas based upon the latter is a fruitful field for thought.

In the thalamus the sensations present in the visceral nuclear aggregations—the visceral cortical dependencies—are necessarily in keeping with the state of the autonomic apparatus. It is probable that when the autonomic apparatus is functioning normally, these sensations are among those which enter into the general sense of well-being of the organism, although they do not, under normal conditions, enter the field of consciousness individually and specifically. In depression of the autonomic apparatus these sensations are doubtless changed in quality; that this change of quality is the opposite of pleasurable is more than likely. That the cortex must respond to this condition is inevitable, and it must also follow that that response must be a painful one; it certainly cannot be pleasurable. Finally, all emissive avenues being inhibited by the secondary and inevitable depression of the sympathetic group, the attitude of mind must necessarily be subjective; the mind must be taken up with itself and with its own sufferings. Not being able to refer these sufferings to the external world, the patient naturally refers them to his internal world, to himself. Any occurrence, past or recent, trivial or of consequence, now serves as the material for an explanation, the basis of which is always a self-accusation.

That in the paranoid degenerations the patient refers his unpleasant or painful hallucinatory sensations to the outside world, lies, I believe, in the fact that these hallucinations especially involve the special sensations which are normally aroused in the corresponding nuclear aggregations of the thalamus by impressions received through the special sense organs from the *external* world. Naturally, therefore, the patient refers these sensations to this external world and forms his delusions accordingly.

Transmission from the autonomic group of glands to the thalamus doubtless takes place through the centripetal fibers of the sympathetic in the rami communicantes and thence through the cord and brain stem. Clearly, the character and volume of the transmission depends upon the activity of the autonomic group. In the paranoid affections, however, it is extremely probable that abnormal hormones act directly upon the cortical dependencies in the thalamus and thus create the spurious impression of sensations aroused by impacts from without.

The problem that especially concerns us in melancholia and mania is the reason for the remarkable behavior of the two groups of glands —the autonomic and the sympathetic. All of the facts in our possession point to the conclusion that manic-depressive insanity is hereditary and innately neuropathic. If hereditary, there is clearly some factor of organization that is transmitted; if innately neuropathic—that is, if the affection is one not due to external causes, but is autogenous—there must be present some peculiarity of structure or function, something that determines the onset of long periods of quantitative reduction of function or of long periods of quantitative increase. What is this peculiarity? Is it an inherent weakness of the glands of internal secretion, an inherent morphological, structural inadequacy, a biological weakness of the autonomic group, and secondarily of the sympathetic group? It is readily conceivable that such an inadequacy or weakness leads at times to long periods of reduction or even abeyance of function. The autonomic group, the group upon which the continuous supply and the storing up of energy depend, having broken down, a breakdown of the sympathetic group, the group upon which the output of energy depends, naturally follows. So great is the feebleness of the two groups, especially of the autonomic group, that months of inaction—of rest and food—ensue before function can again be adequately established; during this period also the expenditure of energy is reduced to its lowest levels. Little by little, however, energy is regained; gradually the normal level is again reached and the depression, the melancholia, disappears; but very frequently the processes active in recovery do not stop here. Restitution of function having been begun, the slumbering fires of metabolism having been again started, the change proceeds with augmenting vigor. Gradually it gathers in impetus and mass until it passes far beyond the normal line, and soon the opposite condition, that of mania, is established.

As is well known, the investigations of Fauser and others failed to reveal the presence of defensive ferments in manic-depressive insanity, such as were observed in the deteriorating group of mental diseases, dementia præcox and the paranoid dementias. Their investigations included the sex glands, the thyroid, the pituitary, the pineal, the adrenals, muscle, liver, kidney, cerebral cortex, and other tissues. The logical conclusion is that in manic-depressive insanity no specific or other toxins are at work; there is merely a quantitative change in substances normally present. At one time there is diminution, at another time excess. It is a condition, in other words, to which the prefixes "hypo" and "hyper" could be applied both, in turn, to the autonomic and sympathetic groups.

Further, that such an affection as melancholia or mania should pursue a cyclical course, that is, be featured by a period of evolution, a period of maximal intensity, and a period of subsidence, is exactly what might be expected from the facts in our possession. Again, a cycle having been completed, we find that there is no mental deterioration, that mental integrity remains unimpaired. Is this not also in accord with a mental affection in which there is no involvement of the nervous tissue? Is it not in accord with a purely functional disturbance dependent upon a diminution or an excess of substances normally present? Finally, once more, the cycle having been completed and the patient being again at a normal level, there is no guarantee that the attack will not recur, for the patient's organization remains unchanged. As a matter of fact, recurrences are, unfortunately, a constant experience.

When we turn our attention to the mental diseases that occur in individuals previously apparently normal, for example, the mental disorders which follow the infections, we have to deal with problems in which questions of biology at first sight seem to have no place. Among these disorders are the various deliria, febrile, postfebrile, and toxic; also the long periods of confusion—confusional insanity—and stupor, which every now and then ensue after a severe attack of typhoid fever, pneumonia, influenza, or other exhausting infectious diseases or intoxications. However, when we inquire into the family histories of such patients, we are surprised to find in approximately 50 per cent. a neuropathic family history. In other words, it would seem that many of these patients present an impaired resistance; the glands of internal secretion—especially the thyroid, adrenal, and pituitary group—prove inadequate under the strain, and a long period—usually many months—ensues before an equilibrium in metabolism is again established. Further, every practitioner is aware that certain patients become delirious under comparatively slight infections, under slight febrile attacks; indeed, at times, this peculiarity is observed in several members of the same family. So it is with the resistance to alcohol and to other noxious agents; so it is with traumata. Whether or not delirium, confusion, or stupor make their appearance in a given case depends, other things equal, upon the innate resistance of the individual, upon the development and quality of his ductless glands; and all, in turn, upon his heredity, upon the germ plasm in which he has had his origin.

XXI

NEUROPATHY AND THE PROBLEM OF HEREDITY

The consideration of mental and nervous disorders from the point of view here presented leads to new conceptions of what is meant by "neuropathy" and by the transmission through heredity of "neuropathic" factors. Evidently a neuropathy—and we are speaking here, of course, of an innate neuropathy, not an acquired one—is necessarily expressive of a failure, a lessening of the intensiveness of the physical and chemical processes on which development depends; the organism fails to reach the normal level. This failure may reveal itself, as we have seen, either in general or in special ways. Sometimes it is pronounced and striking; sometimes it is slight and but little marked; but the point that vitally concerns us is that it is always morphological. Further—and this is the second point of importance—this failure entails arrests and deviations, imbalances, and deteriorations.

A new light is also thrown upon the transmission of neuropathic factors by heredity. It is readily conceivable that an organism whose chemical and physical processes have lacked the necessary intensiveness to carry it to the normal level of development, can only throw off an impaired, a weakened germ plasm. The weakness of such a germ plasm necessarily reveals itself in the offspring. Further, it would appear that this weakness may not only be general, but may be featured in special ways. In other words, the germ plasm may bear the impress of the special weakness or weaknesses of the parent organism. This should not be surprising when we reflect that the blood plasma from which the germ plas n is built up contains all of the various elements, constructive and catalytic, which the parent organism furnishes. Clearly, if the blood plasma is deficient or aberrant in this or that constituent or constituents, this fact must affect the germ plasm. Such an interpretation is in keeping with clinical experience. Indeed, the facts of clinical medicine permit of no question either as to the hereditary transmission of the various nervous disorders we have considered, or of other affections that are grossly organic, such as Friedreich's ataxia and the myopathies. Here, too, we have indubitable proof of the transmission of "acquired characters." Every hereditary affection, no matter what it may be, always has a beginning in some one generation. True it is that the departures from the normal which are thus transmitted differ from those variations which, occurring in the course of evolution, lead in animals to the formation of new varieties or, it may be, of new species. The departures observed by physicians are, other things equal, expressive of biological failures and weaknesses. Have we not here, notwithstanding, a hint as to the mechanism of heredity in general?

The question naturally arises as to the causes of the weaknesses of the germ plasm which are so fruitful of departures from the normal. Here again, I believe, the answer is to be sought in purely physical causes. Clearly, the factors at work are the stress and strain to which the parent organism or organisms have been exposed; perhaps not for one, but for many generations. Among such factors we have doubtless to deal with long-continued overfatigue and overstrain, with overexposure, with insufficient and inadequate nourishment, and especially with intoxications and infections. There can be no question that factors such as these may, if present in sufficient amount, overcome the normal resistance of the parent organisms and lead in time to a weakening of stock, a weakening which of necessity involves the germ plasm. The weakness of the germ plasm later finds, as we have seen, a manifold expression; it may reveal itself in gross departures from the normal, or merely in subnormalities; or, it may be, in neoplasms and malignancy; or, again, in nervous and mental diseases and deteriorations. All of these states present problems of absorbing interest.

Whether or not we accept the interpretation here advanced of the transmission from one generation to succeeding generations of acquired weaknesses—or to state it in other words—of weaknesses not previously existing in the parent stock, the fact of such transmission cannot be gainsaid. If such weaknesses are to be regarded as something acquired by one generation and which is transmitted to succeeding generations, then we clearly have an instance of the transmission of an acquired factor, though we may with justice hesitate to apply to it such terms used in biology as "character," "variation," or "mutation." However, the transmission of an acquired weakness is a fact of profound significance, for it proves that the germ plasm is not the fixed and immutable thing that some of the modern theories of inheritance, notably that of Weismann, would lead us to believe. Weismann's theory because of the great influence it has exercised over biological thought insistently demands our consideration. Let us, however, first approach the subject from a general point of view. If it be true that the organic forms of the present have evolved from the organic forms of the past, the continuity of living matter is a necessary inference. It is readily conceivable, further, that in unicellular forms of life simple cell division satisfies all the necessities of reproduction and inheritance; it is the same material which is being constantly divided and redivided. Observation has shown, however, that the division must include the nuclear material. The pseudopod of an ameba if separated from the body of the organism dies; in order that it should survive it must contain nuclear material. Thus the nuclear material acquires a great importance. Further, the reproduction of complex forms is not so simple. A living fragment which apparently bears no resemblance to the parent organism is thrown off or, may we say, cleaves off. This fragment may consist of an exceedingly minute particle termed a spore, or of a cell, such as an ovum or a spermatozoid, or, it may be, of other material, which, now growing independently, reproduces the parent form. In any event the continuity of the living protoplasm is preserved. In every instance, further, the material from which a new organism is produced separates into two portions; from one of these the new organism develops; the other furnishes the material for the next generation. Jaeger, who gave this interpretation many years ago, termed the first the "autogenetic portion" and the second the "phylogenetic portion." The latter constitutes the germ plasm. However, it should be added that the separation into these two portions does not occur immediately or even early, save in exceptional instances. In vertebrates the separation or, rather, segregation of the germinal material occurs relatively late. Weismann explained the final appearance of germ plasm under these circumstances by supposing that during the early period of development of the organism the germ plasm is passed on in a latent condition from cell to cell in the successive groups of the latter formed during the process of development until the germ plasm is finally set aside; that is, Weismann believed that the germ plasm, while not separated at once, is, notwithstanding, contained in other cells and is transmitted in successive generations of these cells—and is then finally segregated. The basic idea is, of course, the continuity of the germ plasm from generation to generation of individuals. Perhaps this continuity and the late appearance of the separated germ plasm can be accounted for in other ways; for instance, by supposing that in given instances the separation takes place only when the dividing and redividing cells approach a certain level of differentiation, and that the separation merely means that a differentiated portion of the cell contents and a non-differentiated and still generalized portion undergo spontaneous separation. In any event, and no matter how accounted for, the view of the continuity and persistence of the germ plasm greatly facilitates the interpretation of heredity. Doubt may be legitimately entertained as to the germ plasm being really and innately different from the protoplasm which gives rise to the body of the organism. It is perfectly legitimate to assume that the former, having retained its primitive and undifferentiated character, builds up out of its own substance and the substances acquired in its chemical and physical reactions with the environment, a body which must of necessity be like the parent form. The protoplasm which gives rise to the organism—the autogenetic portion—resolves itself into cells which undergo rapid differentiation; thus these cells lose the function of reproductive cells, cells capable of reproducing another organism. However, they do not lose the power of reproducing themselves and of adding to the mass of the differentiated tissue of which they have become, so to speak, the parent part. Normally they limit themselves to such a form of reproduction, but in those departures from morphology, which we term "diseased processes," they may cease, as we have seen in the preceding pages, to reproduce cells like themselves. They may produce cells of a lower biological level or even cells entirely different from themselves, as in those instances in which muscle gives rise to bone.

Before entering into the details of Weismann's theory let us consider briefly whether and in how far the factor of sex influences the germ plasm and the problems of heredity. Clearly, in sexual reproduction the germ plasm is a resultant, a compound of two individuals; of necessity there is an interplay of hereditary factors. The facts of sexual reproduction are extremely interesting, though they are somewhat remote from our immediate subject. However, as regards the sex transmission of certain diseases, such as hemophilia and the myopathies, they are exceedingly important and have a direct bearing, it would seem, upon problems of the internal secretions. Here we must limit ourselves, however, to a statement of the elementary biological facts. It would appear that the sex cells, both ova and spermatozoids, undergo a division which results in the reduction of one-half of the number of chromosomes. It would seem that each sex cell is thus thrown "out of balance" and requires another "half-cell" of the opposite sex to re-establish its equilibrium. In a sense, the fertilization of an ovum by the entrance into it of the nucleus and cytoplasm of the spermatozoid is a process of "feeding"; and here the inoculation of a frog ovum by Jacques Loeb with a minute quantity of fatty acid, with the resultant development of a parthenogenetic offspring, comes to mind as a most suggestive fact. Surely, whatever the process may be, it is physical and chemical. Indeed, it may even be started, we are told, by the trauma of a needle prick.

The problem that confronts us, however, is the same whether we start with the parthenogenetic ovum of an aphis or the fertilized germ plasm the result of a sexual union. According to Weismann, the nuclear material of the reproductive cell contains the germ plasm, but whether the latter is limited to this structure may well be disputed. According to Weismann, further, the germ plasm is made up of bodies which he terms "idants" and which are identical with the chromosomes. Each idant, in turn, is made up of "ids." In each id is represented an architectural structure upon which the structure of the future organism depends. The ids, in turn, are made up of "determinants," and the latter of other bodies still, termed "biophores." Without pausing to discuss the details of Weismann's elaborate theory, it is quite clear that its fundamental conception is that of an architectural structure, special and definite, in the germ plasm, and which predetermines the structure of the future organism. In a way Weismann's view does not in its essence differ from the preformed homunculus of our ancestors. It is difficult to see, also, how Weismann's views would permit of variations. He assigned the latter to causes in the external world, but then it is difficult to understand—everything being predetermined—how such variations could be transmitted. Indeed, as is well known, the acceptance of Weismann's views has led to the denial of the inheritance of acquired characters.

Many facts throw doubt upon the view that the germinal material of organisms is limited to the so-called reproductive cells. We have but to recall the many instances in which even highly differentiated organisms, such as the higher plants, may be reproduced by pieces or fragments of the stalk or branches so long as these contain buds or the elements from which buds may be formed. A fragment of potato as long as it contains an "eye" reproduces the entire organism. Must we not conclude that the cells of the bud contain a "germ plasm" made up of the same elements as the germ plasm contained in the ovule? We can only account for gemmation in animal forms on the same principle, and a similar explanation must be invoked in the regeneration of amputated portions of the organism in various lower forms. From such facts as these Hertwig inferred that each cell, having been formed by the division and redivision of the ovum, contains some of the original germinal material. It would appear, therefore, that in addition to the special properties entailed by its differentiation, each cell retains latent possibilities in the way of reproduction. In many plants and lower animal organisms such possibilities may, under given conditions, find a full expression. In the more complex forms, as in man, this expression is apparently limited to the production of teratomata. In any event our conceptions of germinal material and its properties must be extended so as to include, in a measure, the substance of the organism in its entirety. Necessarily this leads to a change in our attitude toward the germinal material of the reproductive cells. It would appear that the germ plasm is not the highly differentiated structure that Weismann's theory would lead us to infer, but that, on the contrary, it is a substance relatively undifferentiated, relatively simple, and primitive in its make-up; it takes no part in the complex changes which feature the development of the organism, but remains a generalized mass which, however, contains within itself the same tendencies and possibilities of differentiation as the organism from which it is derived, and of which it was at its inception an integral part. Being made up of the same material, the course and direction and the possibilities and limitations of its growth and development cannot be otherwise than the same. Its differentiations, other things equal, must be the same as those of the organism from which it was derived; of necessity, the same form or a very similar form must be reproduced.

To my mind the theory of Weismann contains two fundamental errors, and in saying this the writer is not unmindful of the debt which the science of biology owes to so great a leader; the opinion of the writer is ventured merely because of the facts of heredity as they are known to the physician; such facts as have already been considered in the preceding pages. Indeed, but for these facts the discussion of heredity would have found no place in these pages. The errors in Weismann's theory the writer believes to consist of the following: first, the assumption of the existence of a fixed architectural structure in the chromosome or idant; second, in the assumption of the existence of "determinants" which play a special and definite rôle in the development of the various parts of the organism. It is exceedingly unlikely that a fixed architecture can exist in living protoplasm. Living protoplasm is known to be an unstable aggregate of many substances, nucleoproteins, fats, carbohydrates, and other materials. The proteins alone entering into its composition are, as is well known, exceedingly complex bodies consisting of combinations of many amino-acids, as many as seventeen if not more. Further, living protoplasm is a colloid; it presents none of the fixity of the crystalloid. Finally, it is constantly undergoing change. It is being constantly built up, but is as constantly being oxydized and reduced. As we have seen, foreign materials, proteins, fats, and carbohydrates are through the action of its contained enzymes fragmented until they become identical in character with the particles of the original protoplasmic mass and become part of its substance. In the continuance of this chemical change and in the continuance of oxidation, the older particles finally become so far reduced that they become inert and make their exit by solution into the surrounding medium. In other words, living protoplasm is the seat at one and the same time of both anabolic and catabolic processes, of both an upward and a downward chemical change. It would hardly seem likely, therefore, that a substance, colloidal in structure, variable in the number and character of its components, and the seat of incessant chemical change, should present an architectural fixity of structure. It might be answered that the germ plasm before the process of reproduction begins does not consist of actively changing material; this objection would hold good only in the instance of certain spores and seeds; it would not hold good for the reproductive material of higher animals which is constantly being formed in relatively vast amount, and can only itself be regarded as the result of active metabolic changes; and, when the process of the building up of the new organism begins, the changes are very active indeed.

The second error in Weismann's theory, I believe, is in the assumption of the existence of "determinants." This directly introduces a teleological factor; it introduces unmistakably the doctrine of design, the doctrine of intention. Assuredly, such a doctrine should no more be admitted into the problem of inheritance than into the problem of the precession of the equinoxes, nor of the formation of a salt by the union of an acid and a base. As has just been maintained, the germ plasm, the phylogenetic portion of the organism, can only undergo the same differentiations that its other half, the autogenetic half, has undergone. The possibilities of this differentiation must lie in the special aggregate of proteins, fats, carbohydrates, and crystalloids that constitutes the general bioplasm of a given organism. The germ plasm must react—indeed, *can only* react—in certain *definite* ways to the nutrient material and other factors present in its environment. It is this which constitutes the "specificity" of the germ plasm of a given organism. However—and here I believe we enter upon a conception of great value—this specificity is not absolute. The germ plasm, contrary to the commonly entertained error, is not isolated, is not placed in a separate compartment, inaccessible to the rest of the organism. We should bear in mind that it is constantly reproduced, constantly manufactured in vast quantities. Nature is wasteful and prolific in the production of germ cells beyond the power of words to express. The germ plasm has its origin, of course, in the first phylogenetic fragment retained in the body of the developing organism, but whence comes the material for its augmentation, for its incessant renewal? This can only be derived from the juices of the host, from the blood plasma in the higher animal forms. The germ cells, like the other cells of the organism, have the power of appropriating and assimilating certain materials from the blood plasma, but clearly in the exercise of this function they are dependent upon the possibilities presented by the materials of the blood plasma itself. The germ plasm in its incessant renewal must build itself up out of such material as comes to hand, and, as a corollary, if the material is changed ever so slightly the germ plasm must change in corresponding degree. It follows that if variations occur—*e. g.*, adaptations to new conditions of the environment—which are of such a character as to affect the internal secretions, that is to say, the metabolism of the animal either in a general or in a special way, this must be reflected in the germ plasm. In such case, the variation may be transmitted by inheritance. If, on the other hand, the variation is such that the endocrine or general metabolism of the organism is not affected, the variation fails of transmission. Viewed in this light, experiments to ascertain the inheritance of physical mutilations become absurd. This explains also the negative evidence of inheritance presented by the age-old practice of circumcision.

We have already indicated in the preceding pages that a weakened organism may, according to the explanation here presented, produce a weakened germ plasm; and that in this way inherited departures from the normal, such as mental and nervous diseases and gross morphological affections, may be accounted for. Evidently we have in such cases to deal with instances in which the germ plasm has undergone gross modifications clearly dependent upon changes in the metabolism of the parent organism.

A word should now be added in regard to the factor of Mendelism in inheritance, though a detailed consideration of this important subject would take us too far afield. In a limited manner only have studies been made—or, for that matter, been possible—in the human subject, but they have indicated the possibilities of the application of Mendelian principles. It will be recalled that Gregor Mendel, an Austrian monk, in 1865 published the results of experiments in inheritance which established the manner in which certain characters termed "unit-characters" are transmitted. It was only long after Mendel's death that the facts came into the possession of the scientific world. Briefly stated, Mendel made experiments in the crossing of different varieties of the common pea. Thus, he crossed the tall with the short or dwarf pea. He found that the peas resulting were all tall. In other words, he found that the character of "tallness" was dominant. If now he allowed these hybrids to undergo self-fertilization, he obtained a generation of which 75 per cent. were tall and 25 per cent. were short. In other words, the dwarfism reappeared as a recessive character. Breeding now the dwarfs among themselves, he found that they always bred true; that is, produced only dwarfs. Breeding the talls among themselves, he found that one-third of the latter bred true and produced only tall peas. The other two-thirds of the tall peas produced results the same as the preceding generation, namely, 75 per cent. of tall peas and 25 per cent. of dwarf peas. In other words, of the second generation of hybrids, 25 per cent. bred true to dwarfism, 25 per cent. bred true to tallness, while the remaining 50 per cent. of talls produced again talls and shorts in the proportion of 3 to 1. This principle of the behavior of dominant and recessive unit-characters has been shown to hold good in the instances of quite a number of animals and plants. For us, however, the facts of inheritance discovered by Mendel have a unique value in that they show conclusively that the processes of inheritance are *purely physical in character* and that they are capable of mathematical expression. Surely mystery no longer has a place in the problem.

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