HORMONES AND STRUCTURAL DEVELOPMENT

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Hormones and Structural Development

BY

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PART I

Embryonic Development and the Internal Secretion Problem

In beginning this series of Beaumont Lectures I must express my appreciation of the compliment you have extended in inviting me to lecture before your Society. I am particularly honored by the opportunity to lecture under the Beaumont Foundation since it bears the name of so distinguished a pioneer in American scientific medicine, and I might say in American biology in general. Dr. William Beaumont as a young army surgeon not only did a significant piece of work in experimental biology under the crudest conditions, but he described his observations and experiments in a classic scientific contribution that has rarely been matched for its charming style. His experiments and observations were conducted with masterly skill and his volume on the gastric juice published in Plattsburg, New York, in 1833, is a model of simple, honest, scientific presentation.

As Sir William Osler has stated, the maxim of this pioneer American physiologist is best expressed in his own words: "truth like beauty, is when unadorned adorned the most,—and in prosecuting these experiments and enquiries I believe I have been guided by its light." The studies of Dr. Beaumont on "that old fistulous Alexis St. Martin" has thrilled the youthful mind of every school-boy who has been fortunate enough to learn about them. In memory of this early thrill I am indeed honored to be your Beaumont lecturer.

Under the general subject—hormones and structural development—I shall make an attempt to analyze the influences active during growth and development which finally determine the quality as well as the quantity of bodily structures. The first lecture considering embryonic development and the internal secretions will be thought by some to belong in a class with the proverbial lecture on the snakes of Ireland. There are no snakes in Ireland, and many will agree that there are no really typical internal secretions present in simple plant and animal forms or during the early stages of embryonic development even in the higher vertebrates. Yet a consideration of the elementary growth processes has an essential bearing in understanding the probable influences of the hormones on the growth and structural changes of the more complex types. The manner in which growth takes place in the absence of certain elements may help us decidedly in appreciating the changes induced when these elements are present. The actual background of the internal secretion problem involves an analysis of certain phases of inheritance and early embryonic development. This aspect of the problem we shall treat in the present lecture, after which we shall be better prepared to consider in the second lecture the influences of the internal secretions on structural growth and individual constitution. As a third lecture the specific case of the gonadal hormones or the influences of the sex glands will be treated in some degree of detail.

THE PROCESS

Among the higher animals development follows the combination of a sperm cell or spermatozoon from the male, with an egg derived from the female. This fertilized egg then proceeds to develop, first, by a process of cell multiplication and, later, in addition to this by foldings and differentiation in various directions, until finally the formed body is produced; this then continues to grow to adult size. Most people are only acquainted with a small portion of the actual development of the individual; that is, they know individuals from the time of birth to death, but they know very little about that important early period of development which is taking place before birth. This prenatal period is actually by far the most important time in development. As the late Professor Charles S. Minot of Harvard has expressed it, "more than 95 per cent of the actual development of the individual has probably been accomplished before the time of birth, and growth from babyhood to manhood represents less than 5 per cent of the important developmental changes which are actually accomplished by the individual." It is easy then to see that these early changes by which the spherical egg—almost microscopic in size—becomes metamorphosed into the seven-pound babe at birth are most astonishing phenomena. We should consider it a very remarkable thing that this complex process of development actually completes itself so well in so many cases, unless, of course, it were due to a very definite and fixed mechanism which was quite immune to the action of outside influences. In order to discover whether any of the outside influences which make up the "environment" have an effect on the developing egg, a large number of experimental studies have been devised, and the entire field of work known as experimental embryology has been developed around the various phases of this problem.

GOOD EGGS AND BAD

It is well known that not every egg under the hen hatches into a vigorous chick. Many fail to develop, others hatch into weak, defective chicks which are unable to live, and still others hatch less defective but still inferior chicks which are in many ways unfit for the purposes of the poultryman. Similar facts are well known to fish culturists. Not every fish egg develops into a normal fish—many eggs die, some develop only a short time and then die, and many of the embryos develop to the point of hatching but are unable to survive as free-swimming fish; but fortunately most of the eggs in a given lot may develop into normal, strong specimens. It is evident that there are actually some "bad eggs" and this is probably due to a fundamentally defective hereditary composition which does not permit normal development.

CONDITIONS OF DEVELOPMENT

Aside from the fate of these bad eggs, are the good, normal eggs able to develop normally under bad conditions? If the environment be slightly modified from that which is considered normal, a number of the good eggs are affected and begin to develop in an abnormal way. The developing egg depends very certainly upon the nature and condition of the environment in which it develops.

The three important factors in the environment which must be stabilized in order to obtain normal development, are water, the oxygen supply, and the temperature. Animal eggs all require a definite supply of water and if water be removed and they are allowed to dry, development stops and the embryo dies. Developing eggs are also dependent, just as the adult is, on a free supply of oxygen. When the oxygen supply is reduced development becomes slower and will finally stop; but if development continues at the slow rate it will give rise to abnormal structures and deformed individuals.

The eggs of almost all species of animals are disturbed by unusual variations in temperature during their development. The embryos of mammals are guarded against temperature changes by the mother's body but the eggs of animals that develop outside the body of the parent must have a more or less constant environmental temperature. The eggs of the common fowl must be warmed up to a temperature of about 103°F., and if they are incubated only a few degrees above or below this, they develop abnormally and many of them die. The eggs of some fish develop in very cold water, almost as low as freezing, while the eggs of other fish develop only in water from 15° to 20°C. Whenever the usual temperature is either raised or lowered beyond a limited number of degrees, the embryo is unable to develop normally.

Thus, in spite of perfect hereditary composition, the egg is unable to develop into a strong, normal individual in other than a particular environment.

LIMITATIONS IN DEVELOPMENT

From these facts we may easily surmise that individuals may inherit the possibilities for a number of characters which they are never able to express. One rarely or never develops all the characters for which he may have the hereditary basis. For example, an individual may be said to inherit the nose from his father or his mother and yet he may develop no nose at all; he may inherit his father's mouth and yet may develop with a harelip and cleft palate, thus in no sense resembling the mouth of his father. It is often difficult to say what we actually have or have not inherited. We simply see the characters which we have been able to express from the fundamental hereditary basis with which we started. We are certainly then a combination of inheritance and development, and the possibilities of neither may be expressed to their fullest extent.

It has been experimentally shown that the factors for many characters may be present in the germ cells and yet the characters are unable to express themselves. I have recently studied a particularly interesting case of this kind in guinea pigs. The guinea pig has three toes on its hind feet and four toes on its front feet—it lacks the big and little toe on the hind foot and the thumb on the front foot. This is a very definite arrangement and probably has existed in the race of guinea pigs for thousands of years. Yet it occasionally happens in stocks of guinea pigs that an individual may occur with an extra toe, representing the little toe of the hind foot. Such individuals may show this little toe as a perfect, well-articulated digit, or else it may be present in all degrees of imperfection down to a tiny toe nail suspended on a mere fiber. The degree of expression or development of the small toe on the hind foot is extremely valuable for study. For if these extra-toed individuals be selected and mated together the occurrence of such toes becomes more frequent and, finally, when animals with perfectly developed little toes are constantly mated together, we derive practically 100 per cent of offspring with four toes on the hind feet. In such a line that had been selected for some time for developing extra toes, an individual finally occurred with a 5th finger, representing a thumb, on the front foot. Thus this animal had five fingers on the front feet and four toes on the hind feet, only lacking the great toe on the hind foot which, if present, would have completed the old ancestral pattern of five digits on each foot.

From these experiments it is very probable that the hereditary basis for five digits on every foot is still present in the germ cells of the guinea pig; yet the ordinary guinea pig in the wild state and in captivity develops an extra or fourth toe on the hind feet only in rare cases. The genes or factors for the five digits are in some way unable to effect a development of these digits. It may be that the interaction among the genes has become somewhat modified in the history of the germ cells in guinea pigs so that the expression of these characters has been prevented; yet the genetic basis for the five-toed foot is definitely present in the germ plasm.

In addition to this kind of evidence showing that the actual body characteristics are not necessarily the definite expression of the complete genetic basis, there are other somewhat different experiments which prove the same thing. Morgan found some years ago that among certain breeds of fruit-flies raised in an unusually humid environment, a germ change or mutation occurred which showed itself in the form of an abnormal or deformed abdomen. This definite genetic character bred as a sex-linked dominant. When flies carrying the abnormal abdomen were transferred to a dry environment they ceased to give rise to offspring with the abnormal abdomen—ali developed into perfectly normal specimens. This line of individuals was bred in the dry environment for nine generations as perfectly normal specimens. They were then transferred to the humid environment and immediately gave rise to the abnormal abdomen in the expected fashion. The ordinary strains of fruit-fly bred in the humid environment do not of course give abnormal abdomens. This particular line of flies had a distinct mutation for abnormal abdomen which had arisen in the humid environment. When a generation was bred in a dry environment they failed to exhibit the mutant condition. This case is particularly interesting since it shows that animals with a definite genetic composition may under certain conditions develop perfectly normal bodies, and under other conditions, abnormal bodies. The genotype may be abnormal and the phenotype perfectly normal or, as cited above, the reverse may also be true. A normal genotype may give in a peculiar environment an abnormal phenotype.

INTERNAL AND EXTERNAL FACTORS IN DEVELOPMENT

From this very brief and simple consideration it seems quite evident that we have made considerable progress towards an understanding of inheritance and development. At the present time no one familiar with these fields would pretend to assert that the entire riddle has been solved—everyone realizes that much of serious importance is yet left to be accomplished. This field of study is rather in full bloom than in complete fruition. From our present knowledge, which is here very scantily reviewed, we are led to feel that the individual is actually a product of the interaction of two sets of factors which we may call the internal factors and the external factors of development. At the beginning, the internal factors are to be thought of as the genetic or hereditary constitution, and the external factors are the conditions of the environment in which the egg develops. As the embryo or individual progresses in development and becomes more and more complex, some of the external factors may actually be thought of as becoming internal, and as the various organs of the developing body begin to form chemical products within themselves these products actually act or react on other organs of the body, and so the condition becomes most complex and it is very difficult to say where the internal factors stop and the external factors begin.

Probably the most practical way of understanding this problem is by a study of the later growth changes which take place in the developing body. There are many structural reactions which give recognizable and often striking evidence of most subtle and delicate processes. An appreciation of these reactions is not only useful for estimating the physiological state of the individual but also for a final and thorough understanding of the chemistry of life processes. So long as we fail to analyze structural expressions we are neglecting one of the most promising fields in a study of growth and disease.

The tendency during recent years has been to depend more upon refined chemical analyses and tests in estimating the condition of the individual, rather than upon a thorough analysis of body changes. Frequently the same chemical test or standard is expected of individuals in various stages of life and the authority deciding the conditions has oftentimes never seen the individual from which the test specimens were obtained. I do not mean to underestimate the value of the physicochemical methods of study and attack, but wish to lay stress upon the modern and future aspect of a consideration of structure which is in no sense opposed to the other methods of analysis and must be correlated with them. Such a method of attack is essentially necessary for a final understanding of all the processes occurring in the living organism.

The *structural reaction,* if one may employ such an expression, is frequently the readiest and sometimes the only indication of deep seated chemical or metabolic changes which are slowly taking place; for example, the modified hair growth and the tendency for the accumulation of fat in normal individuals approaching middle life.

The physician should not contemplate his material as a static mass but must look upon it as the resultant of a long series of growth and structural changes, changes which have occurred not only during the life of the individual but also those earlier and far more minute and delicate changes in the racial history of the germ-plasm which have brought the individual to its present state of evolution.

A consideration of the hereditary factors involved and the developmental processes concerned in the creation of a complex animal body has long been one of the most advanced problems of analytical experiment. The encouraging feature is that the further this analysis proceeds the simpler the underlying mechanism of heredity and development would seem to be.

Following the above review of the rôle of hereditary reactions during early development, our attention may now be centered upon the nature of prenatal or embryonic modifications and their interpretation in a general way. Following this, we shall survey in the next lecture a number of postnatal growth conditions and attempt to fit them into the broad interpretation of all growth and structural phenomena. It must be understood that this is in no sense the discussion of a completed problem, but simply the presentation of certain results obtained during the past several years and an effort to point out what seems to be their meaning. The embryonic modifications are more easily understood than the postnatal changes and my explanation of the latter is based on the analysis of the former and is presented as a conception of the processes rather than as a pretended explanation.

THE LINE OF PRIMARY GROWTH

During the initial stages of embryonic development a line or axis of growth is established which later becomes the actual body axis of the individual. From this axis, other parts grow away or bud off in much the same general manner as the lateral buds or shoots grow from the main stem of a plant. One of the most fundamental structural changes consists in a modification of this primary growth or body axis,—for example, the origin from the egg of two body axes instead of the usual one.

A ready illustration of the initial growth tendencies and budding processes is furnished by the growing plant shoot.

When a shoot of the common privet or hedge bush is examined, we find a growing stem with opposite paired leaves and a terminal resting bud at the apex of the shoot. There is also a resting axillary bud in the axis of each leaf. After a time the resting apical bud begins to grow and in this way lengthens the simple stem. It is the presence of the apical bud which keeps the axillary buds in a resting or non-growing state. If the apical bud be pinched off, the upper axillary buds very soon begin to grow producing branches away from the original stem axis.

In short the primary reaction is an increase in length of the single stem axis by a growth of the apical bud, only one growing stem being formed. After this growth in length of the original stem has partially spent itself, lateral branches arise by the growth of shoots from the axillary buds. However, this tendency to branch may be artificially brought on at any time by injuring the apical bud. We may conclude, therefore, that under natural as well as controlled conditions certain competitive tendencies exist among the buds on the stem. Such competition the German anatomist Wilhelm Roux long ago termed the "battle of the parts."

That the axillary buds fail to grow shoots is not simply because the apical bud grows, but because it grows rapidly and well. If the terminal bud be injured so as to grow more slowly than normal, the upper axillary buds will produce shoots which grow at rates varying directly with the degree of injury or abnormality of growth in the terminal bud.

The apical shoot may grow at a reduced rate and fail to suppress entirely the growth of the upper axillary bud of one side, hence this bud also gives rise to a shoot which occupies a lateral position and is the beginning of a branch away from the primary stem. In still another case both of the upper axillary buds may produce shoots in spite of the growth of the apical shoot. In these two cases one must assume that the apical bud does not consume a sufficient amount of the growth energy or stuff to prevent the growth of the upper axillary buds, or, on the other hand, that the upper axillary buds have developed an unusually strong inclination to grow, strong enough to overcome the inhibitory influence of the apical bud. The former of the two possibilities seems the more probable, since a number of experiments demonstrate the readiness of the axillary buds to grow following any injury or handicap to the apical bud.

The fact of immediate importance to us as illustrated by these plant stems is that there are many buds possessing the potential power to grow although as a rule only one or a very few of them are capable of expressing this potentiality. Does a parallel situation present itself in the developing eggs of animals? Undoubtedly there is in almost all early embryos an initial linear or stem growth which determines the future axis of the animal body. But are there a number of points around the germ-disc or germ-ring potentially capable of producing this axis growth, or is there only one possible growth region or budding point? Is there present only the homologue of the apical bud or are there a number of potential growth points homologous to the axillary buds as well?

TWINS AND MULTIPLE EMBRYOS

Experiments with the eggs of fish and other vertebrates indicate very convincingly that numerous potential growth points do exist in the germ-disc, and I have found with fish embryos that it is possible to induce a multiple growth of embryonic axes each of which may form a complete animal body. Competitive processes are also found to be present in the egg similar to those in the growing stem; for example, when a single axis begins to grow and progresses at a normally rapid and vigorous rate, it suppresses the initial growth tendency at all other points. But when for some reason development progresses at a slow rate it may happen that more than one growth point is permitted to express itself and two or three axes may bud out, giving rise to twins, double embryos and other multiple conditions. Thus actually the process of true twinning, or the origin of two perfect individuals from a single egg which should have given rise to only one, may be artificially induced by arresting the rate of development during early stages before the normal embryonic axis had expressed itself. The case is strikingly similar to the growth of accessory shoots from the axillary buds when the growth of the apical shoot is injured or inhibited.

The double individuals and twin embryos induced by these arrests, supply exceptionally favorable material for a further study of the growth competitions which occur between the two components. When the two buds or components occupy positions of equal advantage on the germ-disc they grow at equal rates and both develop normally just as certainly as a single individual would. When, however, one component attains a growth advantage over the other, the former grows at a normal rate and is large and structurally perfect, while the latter is small and invariably slower in its growth rate and deformed in structure.

The degree of separation of the two components, that is, whether they are completely separate twin individuals, or double monsters of any degree, depends upon how far apart the two primary buds are on the germ-ring. When the buds are opposite one another, or 180° apart on the germ-ring, the resulting bodies become completely separate and twins are formed, but if they be less than 180° apart the caudal ends of the embryonic bodies become common and the double condition is only expressed by their anterior portions. A graded series of double fish may be arranged showing every step from slightly separate heads on single bodies to Y-shaped specimens with separate anterior portions and single posterior ends, and so on to the separate twins.

The degree of doubleness bears no relation to the perfection of development of the two components. Two heads, although slightly separated on a single body, are both just as frequently normal in structure as are the two components of almost completely double specimens. However, as stated above, when one of the two buds chances to be more favorably located, it will grow at a normal rate and develop normally, while the less favorably located growth point gives rise to a slower-growing, smaller component which always develops abnormally. The degree of deformity of this arrested component varies directly with the difference in size between the two components. The large component is actually as large as the comparable portion of a normal single individual, while the smaller component may range, in a series of double specimens, from only a shade under size to a tiny nodule on the larger member. The slightly undersized component may show very little structural abnormality, generally recognizable in poorly formed eyes, coloboma, microphthalmia, et cetera. With an increase in the size-discrepancy, the small component may exhibit almost all known types of eye defects: cyclopia, monophthalmia asymmetrica, microphthalmia or complete anophthalmia. There may also occur pronounced deformities in the brain, in the mouth and branchial arches, and the body may be quite distorted. Finally, the lesser component may frequently be represented by an amorphous mass projecting from the body of its twin, the larger normal component. Should the normal component live to adult size it is highly probable that the nodule representing the attached twin would become inconspicuous and might possibly be included within the body of the adult specimen as a typical twin inclusion.

DOUBLE INDIVIDUALS IN UNDERSTANDING DEFECTIVE DEVELOPMENT

These double specimens furnish most favorable material for the analysis of defective development. In the first place, the two components are known to be derived from a single fertilized egg; their genetic composition is therefore identical and none of the defects exhibited by the smaller component can properly be attributed to hereditary or genetic causes. The defects are therefore clearly developmental or ontogenetic. The environment of the two components must differ only in the slightest degree. No known experimental modifications of development would justify one in believing that the difference in conditions surrounding the normal and the deformed component of the double specimen was sufficient to cause the abnormalities in the smaller component. To what then is the maldevelopment of the lesser component due? It must be due to the only striking physiological difference between the two components, that is, to the difference in their rates of development. The larger component with an initial advantage, which is difficult concisely to define, but yet impossible to deny, inhibits or suppresses the rate of development of the less fortunate component. The slow rate of development of the latter renders it incapable of perfect structural growth. This inhibition resembles that exerted by the apical bud of the growing plant stem over the axillary buds. It is actually the same inhibiting influence which ordinarily suppresses the power of budding or growth in all other potential growth-points of the embryonic germ-disc after one growth-point or embryonic axis has expressed itself.

These facts further indicate that the prevalent idea that twin individuals derived from one egg are structurally identical is not necessarily correct. Such twins, which biologically speaking are the only true twins, have usually been termed identical twins to distinguish them from dizygotic fraternal twins. The latter resemble one another as children of the same parents, whereas the former are thought to be identically alike. Although this is often correct, there are cases in which the two twins differ markedly from one another. In certain instances one individual may be a perfect specimen and the other a quite unrecognizable amorphous mass.

The question may be raised as to whether the above structural reactions are universal among vertebrates. Secondly, does simply slowing the growth-rate of an ordinary single embryo induce deformities similar to those found in the smaller component of the double specimen?

An answer to the first question, is the well known fact that twins and double individuals are frequently found among all classes of animals and are abundantly known in the human species. Having in mind the above facts regarding the relationship in development of the two components of such individuals it will be found on examining the illustrations contained within the literature, that when the components are pictured equal in size they are both normal, but when any marked size-difference is shown between the two components, the larger is represented as structurally normal and the smaller as deformed. A great mass of evidence exists in published descriptions and illustrations to substantiate these statements and yet their significance has not been recognized.

In man it is extremely rare to find any evidence of the cause which brings about the initial doubling in the developing blasto-disc. One such case has come to my notice of a woman in whom two eggs were ovulated at about the same time and evidently began development in the usual way. One ovum became implanted on the uterine wall somewhat sooner than the other, as indicated by the position of the second placenta which overlay the first along their adjacent margins. The tardy implantation of the second ovum pıobably arrested its rate of development at about the time of gastrulation, since two embryonic axes were evidently formed from it and developed into identical twin fetuses. The other ovum developed into a single child which was born at full term and is still alive. Along with the single placenta to which the living child had been attached the twin fetuses which had died three months before were passed out attached to their placenta and enclosed within a common chorion. Three individuals were thus delivered, a normal child and monozygotic twins. The latter were somewhat macerated and had evidently been dead about three months although retained within the uterus.

STRUCTURAL MODIFICATIONS IN SINGLE EMBRYOS

We may now consider the second of the above questions, whether simply inhibiting the rate of development in single embryos is sufficient to induce deformities identical with those exhibited by the smaller component of double individuals. We have assumed above that the only thing which might explain the structural inferiority of the smaller component of a double individual was a difference in the growth rates of the two. We must next turn to experimental evidence for light on this question.

The rate of embryonic development may readily be slowed or inhibited in a great many ways by employing either chemical or physical means. When eggs which develop in sea-water are placed in chemical solutions of certain strengths, foreign to them, their developmental rates are slowed and structural modifications arise. The use of chemical solutions often injures the egg in a complicated manner and renders it difficult to interpret the course of development which is followed when the egg is later returned to normal sea-water. After employing a number of different methods during many years of experimentation on the eggs of marine fish, I have come to believe that the simplest and best method of arresting development is by subjecting the eggs to low temperatures. By this means no injurious chemical stuffs are introduced and the re-establishment of the normal environment is readily brought about by simply raising the temperature.

All methods that have been used tend to induce similar deformities and no specific responses have been obtained as a result of the action of a particular substance. The simple fact is, that all unfavorable treatment whether chemical or physical tends primarily to slow the rate of development, and the developmental stage at which the slowing occurs determines the type of deformity. This is to be appreciated as a fundamental fact which underlies all explanations of the causation of monstrous and twin developments. It may correctly be claimed that all types of developmental defects and modification may be produced by one and the same method of treatment provided eggs are subjected to this treatment during different developmental stages. The reverse proposition is also shown to be true—that the same type of deformity may be induced again and again with many different methods, provided the eggs are treated at a similar developmental stage. The stage of development is the one determining factor for the type of monster produced, and not the kind of treatment. Yet the degree of treatment does regulate to some extent the degree of deformity although not affecting the type.

The double condition of the embryos discussed above is in itself a modification and may be induced by the same methods that induce all other modifications. When the eggs of fish are subjected to a low temperature before gastrulation the developmental rate is slowed and in a small percentage of them more than one embryonic shield may arise on the germ-ring. Such specimens grow to be twins and double individuals. If, however, the fish eggs be subjected to the same treatment at any later stage of their development, double individuals will never be induced since the moment for the establishment of the embryonic shield has passed and a second one can no longer arise in competition with the one already present.

In a similar way there is a particular developmental period, shortly after gastrulation, during which a slowing of the rate of development will bring about various abnormalities in the development of the optic vesicles or eyes. Eggs treated at such a period will produce embryos with small or defective eyes. In others there may be a failure to separate the eye rudiments and a resulting cyclopean deformity occurs in which there is a median eye in the front of the head. There will occur specimens with a normal eye on one side of the head and a defective eye, or complete absence of the eye, on the other side. In a large number of such individuals every known gross deformity of the eye may be illustrated. When, however, the same treatment is applied to embryos of the same kind at a later period of development these gross deformities of the eye do not result.

I have succeeded in locating the developmental periods during which several organs may be greatly modified or entirely suppressed. In addition to the eyes, the heart and blood vessels, the mouth, the gills and the liver may at times be rendered very small or almost absent by slowing development at particular stages. At the present stage of progress of these experiments it is impossible to directly modify the liver with the same degree of certainty as the other organs mentioned. The liver evidently has only a short originating period and this may be somewhat variable so that it is most difficult to know exactly the moment of treatment for suppressing it.

CRITICAL AND PASSIVE PERIODS IN DEVELOPMENT

What in general do the above results mean? They indicate that there are in the development of all or many organs certain periods at which these organs are peculiarly sensitive to any unfavorable condition which may act upon the embryo. Further it may be emphasized that the peculiarly sensitive period seems to be very close to the actual moment of origin of the organ in question. After an organ has arisen and passed through the earliest stages of its development it becomes less inclined to suffer radical modifications in its manner of development as a result of unfavorable conditions. After it is completely formed it is quite resistant. What is peculiar to the organ or part just at its moment of origin that is not true of it during later stages? At its moment of origin an organ develops at the most rapid rate of its entire history and also proportionately at a more rapid rate than other developing parts at this time. We may speak of this as the moment of "linear growth," corresponding to the primary "linear growth" of the plant shoot or the embryonic axis. At this time occurs the most essential growth reaction of the particular organ. The later growth may be termed lateral, an increase in bulk rather than a specific-organ growth. When the primary "linear growth" does not occur, the specific-organ tissue usually fails to differentiate, e.g., the liver cannot develop unless it initially grows away from the gut wall. If at the time this initial budding out should occur, the general state of the embryo is depressed, the early organ bud may be incapable of developing at a normally rapid rate and its expression is subnormal, slow or completely inhibited.

There would seem to be, broadly speaking, *critical moments* of origin for the organs of the embryo, at which periods it is highly essential that the general developmental conditions and rate be at their optimum. When we slow the rate of development, we affect that part which chances to be developing at its maximum rate at that time, while the more slowly developing parts are not so seriously injured, if affected at all. We may imagine, for example, that at a certain period several organs are developing at the rates 20, 30, 45 and 80. If the rate of development be then experimentally lowered so that no organ can progress above 30, the organ which should be developing at the rate of 80 is reduced to 30 and will probably be considerably modified by the arrest. The organ at 45 is also reduced to 30 or lower, also to its disadvantage, while the organ at 30 may possibly be able to almost maintain its rate and likewise the one at 20. We might actually imagine that the two latter organs are benefited by being brought to par with organs which had formerly to some extent dominated them. The last suggestion is rather doubtful, however, since even the slowly developing parts might suffer from the arrest, and if they maintained only a low rate when the general developmental rate was high it is very probable that they must also be depressed by a general slowing of the rate.

There are then *critical moments* in the origin and development of organs when they suffer acutely from an unfavorable change in developmental conditions, and there are somewhat *passive periods* when the given organ may be only slightly affected by the same unfavorable conditions. Arrests of the general development during the passive periods of an organ may give rise to slightly stunted or weakened conditions which are barely subnormal. Many of the late arrests in development give origin to these subnormal conditions while early arrests as a rule produce gross structural defects.

By slowing the rate of development, malformations similar to those occurring in the fish may be induced in all vertebrate embryos. Similarly, the nature of the treatment is not specific in its effects but the resulting injury or abnormality depends upon the developmental period during which the unfavorable condition was effective.

When the eggs of the domestic fowl are placed in evaporating dishes over the fumes of ether, alcohol, or other volatile substances, the fumes penetrate the shell and affect the metabolism of the embryos so as to lower their rate of development and small deformed chicks result. These chicks frequently show monophthalmia and the other defects which can be so readily induced in the fish embryo.

When mammals, guinea-pigs for example, are treated with active chemical substances, the uterine environment is modified and abnormal young are developed of exactly the same arrested types as those seen among the lower forms. Treated female guinea-pigs may abort or absorb their embryos in utero or give birth to small defective young with slow growth rates and high early mortality.

The treatment of male guinea-pigs with injurious chemical substances seems to affect their germ-cells, since there is no other imaginable explanation of the fact that these males sire defective and arrested offspring when mated with perfectly normal females. I have studied these effects for a number of years on long-tested pedigree stocks of guinea-pigs. The effect of the treatments on the sperm seems to be a general one causing them on uniting with eggs to give rise to less viable and less vigorous zygotes than do the sperm from untreated males. There is no reason why a germ-cell as well as a body-cell might not become subnormal in its capacity. A cell may be "half dead" and incapable of proper functions, and as the Hertwigs have already shown, the injured chromatin in the reduction division of the spermatocytes may be sorted out in abnormal fashion thus modifying the later development of the fertilized egg.

The offspring from these defective germ-cells often exhibit defects exactly comparable to those I have just described as resulting from developmental arrests. There is every reason to believe that the injured germ-cell causes a slow rate of metabolism and slow development and the corresponding deformities in the young animal. We know this to be true in the development of eggs fertilized by the sperm of distantly related species. The same defect might in this way arise from either germinal (genetic) or environmental causes. In fact, it is highly probable that certain changes in genetic factors may produce new metabolic conditions which secondarily modify growth reactions and thus give rise to a new type of individual. Many of the strange glandular types are probably brought about in some such manner.

Many recent contributions on inheritance enable us to understand the phenomena of development and growth in a far more exact and definite way than was ever before possible, and allow a much more logical distinction between hereditary and developmental conditions. One may also recognize the combination of these two forces. It is to be remembered that the chromosomes transmit the hereditary factors, the genes, but the developmental conditions may or may not permit the expression of the developing characters. The child may inherit the exact nose pattern of its father yet it may for some cause entirely fail to develop a nose. The inheritance was perfect but the ability to express the structure was lacking.

Finally then, we have attempted to show in this lecture the manner in which inheritance depends upon the conditions of development for its expression, how the growth and development of one part affects the growth of other parts in the organism, and how any condition tending to alter or modify the developmental rate tends also to modify structure.

In the next lecture we shall consider how the action of hormones from the endocrine glands modifies metabolic rate and, therefore, the developmental rate, and, through this means, influences the types of structure.

PART II

Hormones and Constitution or the Nature of the Individual

FETAL AND POSTNATAL GROWTH AND STRUCTURE

Up to this point our consideration has been largely concerned with early embryonic conditions and the influence of modifications in developmental rate upon embryonic structures. We have seen also in the cases of treated male mammals how certain questions of inheritance are involved in analyzing the modified structural reactions. These considerations will now be extended to certain problems of fetal and postnatal growth and to an interpretation of several peculiar structural patterns and conditions seen in man and other animals. In order to make clear the situation, extreme structural peculiarities will first be considered and from these we may attempt to explain the factors concerned in determining the less marked and more usual human types. The growth rate of the individual is determined by both internal and external factors—by its hereditary composition and by its functional activities, the latter being modified largely by surrounding conditions. In regarding the finished individual, no interpretation can be complete without a thorough analysis of the genetic conditions and the developmental reactions.

We may first consider the well-known condition of the cretin, a child born with little or no functional thyroid glands. Is the absence of the thyroid hereditary or due to an arrest in development or to both? Such individuals so far as is known may apparently come from a parentage with subnormal or poorly functioning thyroid glands.

However, no one has yet analyzed this condition sufficiently to determine exactly its genesis. It is not known for example whether the subnormal thyroid of either parent affects the germ-cells so as to modify those genes which determine thyroid development and structure. We may have reasons for believing that the thyroid of the embryo and fetus is capable of developing independently of the thyroid hormones in the blood of the mother, but there has not been sufficient experiment to make it certain that the mammalian embryo does not need the thyroid stuff in the mother's blood for its proper growth functions.

We may simply state that the cretin is a thyroid dwarf which has attained an incomplete degree of development but cannot go further without the application of the thyroid stuff. This we know, but why the condition arises we have yet to determine. It is obvious that the origin of the condition is the important thing to know and the mere treatment of the abnormal end-product can supply little knowledge of its cause.

The one instructive thing to us at present is that the human child without a thyroid gland can only develop to the stage shown by the typical cretin. This stage might be called the early larval condition of man. The most definite and clear cut experiments done on the influence of the internal secretions on development are those which show that the thyroid is essential for the metamorphosis of the amphibian larva to the adult stage. The human cretin without thyroid will not metamorphose or develop into an adult. Also the human individual with a subnormal amount of thyroid may be expected to be more childlike and less adult than the individual with a normal supply of the thyroid secretion. There is a great bulk of evidence, impossible to mention within the limits of this lecture, to show that the amount or quality of thyroid secretion present in the developing individual is an enormously important element in determining the rate of its growth. This, the thyroid does by primarily determining or affecting the rate of metabolism. The significance of this we have pointed out above by showing that the rate of development is the most profound factor in determining the quality and amount of structural production.

The cretin is an abnormal or pathological individual. Its conditions would preclude the breeding of a race of such specimens. It is not in itself a type, it is an arrested child stage, but the cretin furnishes an extreme growth condition which is most helpful in fully appreciating the influence of the thyroid gland on the growth of the so-called normal types of men.

If time permitted we might review other peculiar developmental and structural specimens that could in some manner be attributed to the unusual action of several other glands of the body which modify growth. Many striking pathological growths are familiar to all; let us, therefore, proceed to consider certain strange and unusual individuals constituting real types, which cannot properly be classed as pathological.

The various dwarf types of man are very instructive in a study of growth reactions and structure. In this regard it is passing strange that all biological analyses of these people are not made from the points of view of inheritance and the factors modifying growth and development. Many of the dwarfs are in most respects normal, and they simply differ from the common type as the small breeds of several domestic animals differ from the large. The cause of such types we can determine by considering both the genetic and developmental modifications possibly concerned in their production. The statement that this may be the same large problem as the origin of any species or type should not be discouraging since certain peculiar types may be more likely to reveal their causes than the more common long-existing ones.

DWARFS

The simplest dwarf type of man from our present growth standpoint is the small African pygmy. These are childish, silly Africans of very low intelligence as well as small size. When one examines pygmies closely, particularly their physiognomy, a striking similarity of features is found between them and the thyroid cretin. In both the mouth, nose, forehead and brow are closely similar in form and proportions. On administering thyroid to the cretin these features become rapidly modified by progressive development and approach the normal picture. One can scarcely resist the temptation to suggest the experiment of administering thyroid to the young pygmy. The pygmy may be looked upon as a not fully metamorphosed large negro, a mild and slow growing condition of cretinism. They are not true dwarf types but certainly people with general growth arrests. The few that I have seen are quite cretinous in their behavior which is certainly unlike the fully grown African of the coast countries surrounding them. The fact that they are capable of reproduction does not argue against this standpoint, since partial arrests are so commonly known in which all organs are not equally affected. With our present knowledge it is impossible to say whether the pygmies are a true genetic breed, or whether they simply live in an environment unfavorable to complete development.

There are other true human dwarfs, however, about which we may speak with a greater degree of certainty since they have been studied for a long time and a considerable mass of data exists regarding them. Much of the data has been well presented by Rischbieth and Barrington of the Francis Galton Laboratory for National Eugenics in England. These workers, however, discarded one of the most valuable means of understanding such human types, by deciding that they show only an apparent resemblance to the similar types found among lower animal breeds. This attitude I believe is a vital mistake since certain animal breeds not only closely resemble the human dwarfs but very probably arose and developed in an exactly similar way. The understanding of the origin and development of the one is certainly of the highest value in a biological consideration of the other.

Among the true dwarfs, the achondroplastics may be discussed first since other dwarfs often also show some degree of achondroplasia. The typical achondroplastic dwarf is very short and stocky, the head and trunk are large, being often as large as those of an ordinary individual, but the extremities are short and somewhat twisted, on account of the peculiar development of the long bones. The muscles are short and thick, standing out in a knotty fashion, particularly on the extremities. They are very active, often acrobatic and quite bright and intelligent. Their head-growth and face-shape is characteristic. The base of the skull is short. The ossification and cessation of growth in the basal cartilage between the occipital and sphenoid bones frequently occur before birth, instead of after 22 years as is the usual case. This failure to continue the growth of the skull base after birth renders the head short and consequently disproportionately wide. Such dwarfs are, therefore, brachycephalic. The lack of growth at the base of the skull also causes a failure to push forward the nasal septum. The nose bridge remains low and often actually sunken in below the overhanging forehead. The upper jaw likewise is not carried the usual distance forward, so that the fully developed mandible projects beyond the maxilla, the teeth do not properly lock, and the "undershot" jaw condition prevails. The entire face is flat, vulgarly termed a "dish-face."

Achondroplastic dwarfs have been accounted for in many ways on the basis of disturbance in the glands of internal secretion which regulate growth. Several have attempted to associate their entire peculiar makeup with an unusual action of the hypophysis. But many of these dwarfs seem to show some peculiarity in the structure of the thyroid and for this reason they have been thought to be the result of unusual thyroid function. Sir Arthur Keith, for instance, has referred to them as having a "minus-thyroid" condition. Be this as it may, the real cause for these dwarfs is more fundamental and deep-seated, and the probable effects of the glands are secondary. We know from the monograph by Rischbieth and Barrington that the condition is already present far back in the early fetus. The extremities are originally far too short for the trunk size and length and the early bones are typically peculiar, not as in rickets or any other known condition. This definitely peculiar growth continues throughout development until the adult dwarf condition is attained. The question may arise as to whether their dwarf condition may be due to peculiar glands in the mother. That this cannot be true is shown clearly in the pedigree table of Rischbieth and Barrington where the condition is transmitted by the father. The male could only transmit such a state to his offspring through the spermatozoon, and if this be done, the condition is truly hereditary. Rischbieth and Barrington record the case of a typical achondroplastic dwarf man married to a normal woman. Two children resulted from this combination, a boy and a girl that lived to become adult, and both were completely achondroplastic dwarfs closely resembling the father. There are other such cases on record as well as similar dwarfs produced by achondroplastic mothers. Ordinary parents may sometimes produce a typical achondroplastic dwarf along with several normal sisters and brothers.

One strange fact regarding these dwarfs is that they frequently die at birth from unknown cause. This and their sporadic occurrence in families make it seem possible that the complex may be a Mendelian dominant that is only viable in the heterozygous form. When there is a double dose of the dominant and the zygote is homozygous a lethal expression follows and the child is incapable of living after birth. Morgan and others have pointed out several cases of this homozygous dominant lethal in their genetic studies. Such cases show why, although a character may be dominant, it is unable to establish itself in a homozygous condition, and may never become abundant in the race.

These are only isolated facts from human cases of achondroplasia but in the light of our present knowledge of inheritance and development they leave little doubt that the fundamental or primary cause of the complete achondroplastic dwarf condition is a germinal mutation or sport, and the condition is definitely hereditary.

Turning from man to the domestic animals, we have on hand an abundance of material for the study of achondroplastic dwarf conditions. Achondroplasia occurs in various degrees among several of the domesticated species, but the most varied and remarkable examples of the condition exist among the fancy breeds of dogs. With these animals nature and man have performed an enormous experiment lasting for hundreds of years, and today they present the investigator with material of remarkable value for a real analysis of the process of inheritance and growth concerned in mammalian achondroplasia. There are breeds of dogs, such as the small French bull, which show a complete achondroplastic condition exactly duplicating the typical human achondroplastic dwarf. The head-form, extremity and trunk conditions are all closely comparable. Other dogs show a marked skull and head type without fully developed achondroplasia of the extremities. Still others show the most pronounced condition in the extremities with the usual head-form, as seen in the dachshund, Scottish terrier, Bassett and others. Finally there are several dog breeds, Pekingese and some peculiar terrier forms, combining various degrees of achondroplasia with an ateliotic or midget condition. This combination of achondroplasia with ateliosis is also very often seen among human midgets.

If we choose either the best type British or French bulldog we find on close study and comparison, point for point, a resemblance to the human stocky dwarf. All have the short wide head with flat muzzle giving the sunken "dish-face." The base of the skull has failed to attain its usual length through failure in growth of the basi-sphenoid and more especially the basi-occipital bone. A shortened, disproportionately wide condition necessarily follows. The nasal septum is not carried fully forward and the root of the nose is flat or actually sunken in. The maxilla is also, for associated reasons, in an unusually backward position and the unaffected mandible, therefore, projects in front of the maxilla. The teeth fail to meet in the normal biting position and the common under-shot jaw condition exists. The entire facial expression and head carriage of the bulldog and the stocky human dwarf are strikingly the same and are due to the same structural background. The condition of the extremities in these dogs and in the dwarf are also structurally alike. The proximal segment in all four extremities is very short and somewhat bowed or bent, being the most modified segment of the limb. The fore-arm and leg segments are also short and somewhat bowed though not so shortened as the arm and thigh. The hands and feet are very much of the ordinary shape and proportions and are about as large as those of the common large breeds of the species. The muscles of the extremities are short and knotty and the entire animal makes a most muscular and stocky appearance. The trunk as well as the head may be about as large as in the ordinary animal. This is more evident in the British than in the French bull, the latter being more of a terrier. The external genitalia are generally of normal size but the extremely short thighs give the male genitalia by contrast an abnormally exaggerated appearance.

With no attempt to make a serious subject frivolous, it may be added that a most striking and convincing comparison is obtained on holding a fine pointed French bulldog up on its hind feet by the side of a human achondroplastic dwarf, or the identity of the types is equally well shown by placing both the man and dog down on all fours.

Breeders of various achondroplastic varieties of dogs often find that a considerable mortality occurs among the pups at birth, and also recognize that they are difficult to feed and rear during the first few weeks after birth. Following this period the survivors are fairly strong, long-lived and hardy. These observations scarcely warrant in themselves scientific consideration, but they suggest the desirability of obtaining comparative early mortality records, since the high mortality at birth of human achondroplastic dwarfs seems well established as well as the records of hardy long lives for those that do survive. As mentioned before, such records may indicate that the survivors in these breeds are possibly heterozygous for the dominant achondroplastic condition, and that homozygous achondroplastics with the two dominant doses have some lethal complex that causes their elimination or death about the time of birth or before.

It may be possible, however, that the double dominant condition in man would give a lethal effect, while among the achondroplastic dogs this would not necessarily be the case, and the bulldogs might thus be a pure homozygous breed. Yet their out-crosses do not indicate them to be altogether homozygous, provided achrondroplasia is a dominant condition.

The general attempt to explain achondroplasia as due to peculiar actions of the glands of internal secretion, either the hypophysis, thyroid or any other, leaves out of account the numerous examples of partial or localized achondroplasia so commonly seen in man and the lower animals. If the internal secretions in the blood produce these peculiar growths, why do they not always act on all similarly growing parts in a similar manner? How is it possible that one humerus may be typically short and twisted and all other long bones unaffected? How does it happen that the dachshund and the Bassett hound have the most pronounced achondroplastic legs and yet the heads of these dogs are like the ordinary head of the common large hounds? Numerous other examples of partial and localized achondroplasia could be cited which make it difficult to account for the condition as simply due to unusual internal secretions. Yet we might imagine that certain tissues or parts, such as one humerus, could inherit a peculiar sensitiveness to certain internal secretions which would cause this one bone to respond differently from all others, though such an hypothesis is difficult to conceive.

All that we know of the breeding records of dogs of the above varieties and the fragmentary data from human dwarfs indicates most strongly that these are true varieties or breeds of animals that probably have arisen by some mutation or sport from the ordinary form. They breed fairly true to type, but not perfectly so, since great variations in the condition constantly arise, and for this reason most careful selection is necessary in order to maintain a high standard stock. Such selection is, of course, entirely unnecessary in maintaining the stock of a wild species, for example, the wolf or fox.

The point of much importance to recognize is that these strange forms, in spite of all said to the contrary, may be transmitting peculiarly acting glands of internal secretion. This modified gland is being inherited, and possibly causes the production of the strange structural type. The types are definitely the result of clean-cut growth reactions and these might be secondarily brought about by the primarily strange type of internal gland. There is much argument both for and against such a position on the basis of the apparent facts available at present. It must be recognized that these problems are still largely unsolved. My remarks on the cases above, as well as what is to follow, are given as a conception of the situation, a conception which will no doubt require modification before it becomes an established explanation of these important phenomena of growth and inheritance.

ATELIOSIS

A final dwarf type of interest from the standpoint of growth and structure is the tiny ateliotic midget. Some of the most celebrated dwarfs have been of this type. They differ from the achondroplastics in having the bodily proportions and general outline of the normal large individual. Their trunk and arms and legs are all of the proper proportionate length. The head is properly small and the body is often delicately and gracefully formed. A sexual infantilism with poorly developed genitalia is very common in the ateliotic, yet many are normally developed sexually and there are numerous records of their having produced offspring.

A midget fully grown may resemble in head and body-size a child of six. Yet midgets are frequently alert and very intelligent. They seem to grow normally for 5 or 6 years after birth and then stop. The wrist and ankle cartilages fail to ossify, the epiphyses or the long bones do not fuse with the shaft and the skeleton is about like that of a child of seven. In nature this is clearly a genetic condition. One or more midgets may be born from perfectly full size parents along with full size brothers and sisters. There is a case of three midget sisters who claim to have two large brothers and two large sisters who were born alternately with them from large parents, the father being Dutch and the mother German.

Although the ateliotic condition may occur in the simple form described above, it very frequently has associated with it a certain degree of achondroplasia. When one examines a great number of midgets, it will be found that many of them have unusually short arms, the fingers reach only to the hip joint or great trochanter instead of striking almost half way down the thighs. The faces of these are closely alike and usually sunken at the nasion, just as in the achondroplastic, though not so pronounced; but the under-shot jaw condition is rarely present in the midget.

Again we find dogs of exactly similar type,—for example, the head and face of the Pekingese is in shape, outline and expression almost a picture of the human midget. The psychology of the two is much the same for general behavior reactions. The extremities and head of the Pekingese are also quite achondroplastic as is so frequent in the human midget. There are several other tiny breeds of dogs which are slender and have a sharp muzzle, real ateliotics, with no achondroplasia. Many of these tiny dog breeds also seem to have some infantilism and individuals are frequently sterile.

Bantam chickens and other miniature animal forms are probably the same in origin and type as the human ateliotic dwarf.

All of these dwarf forms give us valuable suggestions for an interpretation of many usual types of growth and development. And when a study of them is associated with an investigation of the opposite extreme, the giants, a remarkably complete series of growth and structure conditions is supplied.

EXCESSIVE GROWTHS

The giants and acromegalic individuals are so well known from many recent studies that only passing mention need here be given. I simply wish to point out certain features of these types before we attempt the final estimate of what may be considered the usual human types from a growth and development standpoint.

The fine youthful giant is a properly proportioned lithe and active individual often with a well chiseled prominently featured face. This is simply what might be recognized as a splendid human specimen of gigantic size. The giant forms of lower animals are frequently of this type of supernormal growth with proper proportions. Among the dogs, the Great Dane is a splendid example of this kind,—alert and youthful with no acromegalic symptoms.

Just as most human midgets show some achondroplasia, so do most human giants present some degree of acromegaly. Achondroplasia and acromegaly are apparently opposite reactions in bone growth and both conditions are probably associated with definite hypophyseal states. It may safely be added that the usual or so-called normal bone growth and the ordinary hypophyseal condition stand just between the two. This strikingly illustrates the delicacy of the growth balance in the normal individual,—if the scales waver in one direction a countenance mildly suggesting acromegaly accompanies a large framed body, whereas a tip the other way gives a flattened face on a small person with a somewhat long body and short extremities.

The usual giant is particularly apt to become acromegalic as he grows older. It should be recognized, however, that a great many normal people, as well as other animals, also show various slight degrees of acromegaly as they approach middle life. The general thickening up and increased body weight after the age of 35 is something of this nature though complicated in other ways. Many pronounced acromegalics were big boned and stocky as young men. The diseased condition of the hypophysis may come on gradually after the long bones have ossified their growth-cartilages so that no further increase in height or length can then take place. The bones merely become larger and heavier and the features thicken to greatly exaggerated size. Early photographs of patients taken before acromegaly had developed generally show a face which, of course, would and did pass as normal, but which has a very decided touch of those symptoms which later develop in so pronounced a fashion. In other words, as a rule an uncertain hypophysis that is later to become deranged fails originally to give an extremely delicately modeled face.

There are certain human types presenting what might be called anatomical, or normal rather than pathological, acromegaly. These types may be pronounced in a certain family or even in a localized region where pathological acromegaly is not unusually abundant. This is also true among lower animals. There are some acromegalic species. Several of the large dogs, the St.

Bernard, the Mastiff and others, show recognized symptoms of acromegaly along with gigantism. But in the dogs, as in man, acromegaly may exist apart from gigantism. The blood-hound is a splendid example of the acromegalic type without gigantism, and his facial expression and general appearance is closely similar to the human acromegalic.

Many breeds of dogs have been selected and perpetuated for centuries. The breeders selected those specimens having certain well pronounced characters and features that they desired to preserve. They also thought that these characters were the things primarily inherited, but we may be certain for many breeds at least that the visible marks for which they are selected are simply the external symptoms of a particular quality or action of glands of internal secretion. These peculiar glands are the fundamental things that the breeders have unconsciously been selecting, since when they choose animals with the desired structural symptoms they are also blindly choosing the glandular cause. Thus a certain gland type may be inherited, and the dog breeders have produced the experimental proof of this over and over again.

ACUTE STRUCTURAL REACTIONS

Extremely abnormal or pathological cases could be cited in great numbers to show the acute action of the glands of internal secretion on growth and structural responses, but many of these are so well known as to be taken for granted in following the present discussion. However, before we pass to a brief final consideration of the normal human being, one of the most striking experimental cases will be cited to illustrate the remarkable possibilities of these glands for determining personal types.

In the breed of fowls known as the Golden Sebright

Bantam, the plumage of the cock is almost exactly like that of the hen in both coloring and feather form. The rooster's head, however, is decorated with the usual large fully developed comb and wattles of the male. Morgan has studied the conditions found in these chickens and has obtained most striking and valuable results. He finds that when both testicles are completely removed from the hen-feathered rooster, a striking revolution in its appearance takes place at the next moult. The castrated male now develops the fine plumage of the rooster, with plume-like hackles and saddle feathers, and long sickle plumes in the tail. In plumage and color the capon no longer resembles the hen but is a perfectly feathered male. This is not all that has taken place. The large comb and wattles have now degenerated in size until the head is much like that of the hen in appearance. The removal of the gonads has induced a sudden and extensive structural change. Morgan states, "Feathers that may have started their development at the time of the operation show the old influence at the tip of the feathers and the new one in the rest of the feather. The change is abrupt, although the transition is perfect." We could have no more striking evidence of the important influence of the gonads on bodily structure and appearance, nor of the changed action of something else in the body which calls forth the fine plumage after the gonads have been removed. We might suppose that since the comb and wattles were large before castration, their condition was due to some action of the testicles, but the subsequent feather development following castration is certainly not the result of gonadal secretions; it is very probably due to a change in hypophyseal action after removal of the gonads, since this gland seems to modify the growth of hair and feathers in individuals when gonadal degeneration begins.

In this study on hen-feathered cocks Morgan added another very important fact; the hen-feathered condition of the male is inherited in a perfectly definite way and is due to two dominant Mendelian genes. In other words, this means that the strange gland condition which underlies the peculiar plumage of these birds is definitely inherited. The character of the plumage is merely the symptom indicating the presence of the unusual gland complex.

This experiment is of still further interest to us in connection with certain general changes that occur during the life of human individuals. It will be found on observing a group of men that at about the age of thirty-five or a little later, a coarse growth of hair begins on parts which in youth were not so hairy or on which the hair was fine. Strange coarse hairs grow in the eyebrows, on the pinna of the ears, and at the entrance to the auditory meatus. The beard becomes coarser and heavier, and coarser hairs develop on the trunk and extremities. The man now possesses a more pronounced male hairiness than he did when under thirty. On first thought one might consider him to have fully arrived at the completely developed male state. This is not correct, however, since the gonads of such an individual have actually begun to decrease in their sexual power. The coarse hair growth is a plumage expression resulting from a decline in the male gonadal activity, rather than the attainment of its zenith. The change is gradual but of exactly the same nature as that suddenly produced in the Sebright bantam by castration. In man this is truly to be recognized as an early indication of senility.

It is also known that castration generally favors an extra accumulation of fat in mammals. The ox is more readily fattened than the bull. Here again in man at about the same time the coarse hair growth appears an accumulation of fat also takes place. The anterior abdominal wall often becomes prominent, and a decided increase in waist measure occurs. These mild symptoms seem to accompany the physiological castration which is gradually taking place. The structural changes occurring at the menopause in women are similar in character, but more pronounced and rapid in their development than the above changes in men, and very probably because the physiological castration in women is at the same time much more complete.

Thus we see that all normal human beings are experiencing developmental and growth changes which are noticeably due to the usual fluctuation in function of the organs of internal secretion. The existence of these very evident changes serves to illustrate the fact, that if we study closer the entire developmental history of the individual, it will be found that growth and expression are constantly being influenced and molded by the amount and quality of the internal secretions that have been inherited in the breed to which the individual belongs.

NORMAL HUMAN TYPES

When the reader reviews his personal acquaintances or any group of human beings it is evident that many of them show slight degrees of one or another of the peculiar structural conditions which we have surveyed above. There are those with short arms and flattened faces, others with heavy features and large wide hands, others with long narrow faces and delicate hands, some with rough hairy skin and others with smooth, until we may simply admit the bromidic remark, that each is sufficiently peculiar to be distinguished from all the rest and addressed by name. We also recognize certain family and national resemblances which aid us in classing or grouping our acquaintances. Such resemblances have been more or less taken as a matter of course and simply explained as being inherited, but, actually, to what are they due? Anthropologists have never explained why some heads are long and others wide, although they lay great stress on the fact that such is the case. Would it be possible for any baby to grow either a long or a wide head?

Does a great heterogeneous population lend itself to a system of classing or grouping from the structural standpoint? If such is possible, to what cause or causes is this division into structural groups due? The first question is very old, and almost endless fanciful groups and classes have been arranged by various students of the subject. As a rule each has begun with a few classes, but later these have been divided until in the end a return to confusion resulted.

One premise we may depend upon; namely, that all structural form in animals results from processes of unequal growth. Equal growth in all directions from the original spherical egg would result in a sphere. Spheres may differ in size but in form all are alike. Should the growth processes be exactly the same in two specimens their final structures will also be exactly alike. Whenever the growth processes of the two differ, the resemblance is modified. Thus the problem of human types is a problem of growth and all individuals that may be grouped together under one type are individuals with closely similar growth histories. The main theme of this lecture has been to show that in the embryo and the fetus the type of structure largely depends upon the rate of growth. A rapid growth and development gives one result and a slow growth produces, even in a twin individual, an entirely different result. The peculiar adult human and animal forms that have been described were also interpreted as due to modification of the usual growth processes by the actions of substances which affect metabolism and, therefore, growth rates. Certainly, from the time of birth, numerous growth-affecting substances are being produced in the body and the action of these stuffs regulates and modifies the rate and type of growth. Their usual effects are simply to increase or decrease the rate of metabolism and to cause the individual to grow faster or slower than another, thus giving rise to the variations above and below the mean.

It is necessary to recall at this point several propositions before mentioned in introducing the present conception of human types. In the first place initial growth and rapid growth tend to produce linear structure. In all plants and animals there is this primary tendency to form an axis or line of growth. Following this a lateral growth in width takes place. Crudely stated there is a tendency first to attain length and later width. Secondly, there is a certain degree of competition between these two tendencies so that as a rule the growth in width only expresses itself after the length growth has worn itself down and become slower.

It follows that any organ capable of affecting the rate of metabolism or oxidation would necessarily affect the growth rate and must likewise affect the form and structure of the individual. The one organ in the vertebrate body which seems above all others to affect the rate of metabolism is the thyroid gland, and we actually know from convincing experimental proof that this gland also greatly affects the rate of growth and structural development. It is a fact that the cretin without a thyroid gland is incapable of growth and development. The tadpole without thyroid does not metamorphose into a frog. The thyroid is essential for growth from babyhood to maturity. Very probably the thyroid is not alone in its action, it may be affected by many other things and so may growth rate, but the point of primary importance is that the thyroid is the central body tending to control the rate of oxidation, and therefore growth rate in the individual. An active thyroid gives fast growing, rapidly differentiating structures, and linear rather than large lateral type individuals.

It is impossible here to go into questions of the interactions among the internal glands, and it is only necessary for our present purpose to state that if a substance such as the secretion of the thyroid does regulate growth it must also tend to determine structural types. And since the rate of growth is the important thing in structural type, we should expect not more than two extreme types which will grade regularly into each other. The thyroid is so delicate in its response, and is so certainly different in its action in different environments, that the two types may be quite well separated, the one due to highly active thyroid and the other due to a low acting thyroid. The intermediate, ideally balanced, or indifferent condition, would be the most difficult to attain on the part of the sensitive gland.

The two groups into which almost all ordinary persons fall more or less exactly may, therefore, be termed the *linear type* and the *lateral type*. The linear type is the faster growing, high metabolizing, thin, but not necessarily tall group, while the lateral type is slower in maturing, and is stocky and rounder in form.

Taking the tip of the nose as the extreme anterior point of the body and viewing the figure laterally, we may draw a line which would indicate the morphological lateral line. This line on each side of the body separates the truly dorsal from the truly ventral surface regions. When these lines on the two lateral surfaces of the head and body are thought of in space we may imagine that the nearer they come together the more linear is the individual, and the wider apart they diverge the less linear and and more lateral the individual type will be.

It is clear that when the lateral lines are near together the head is of course narrow or dolichocephalic. The interpupillary distance is short and the eyes are close together, the nose bridge is narrow and therefore generally high, the palate arch is narrow and for the same reason generally high, the lower jaw is small and narrow and usually not strongly developed. The teeth are usually crowded and somewhat ill-set. The neck is long and small in circumference, the shoulders are square, high and angular, the extremities are long and slender with long slender muscles and slender bones, the trunk is short and narrow tapering to the waist. The intercostal angle is quite acute. The stomach in such a person is long and narrow and rather vertical in position, and the liver is generally small.

The shape of the eye in this type is such that it is usually physiologically far-sighted though not pathologically so. They need no glasses on the street unless for astigmatism, or some pathological condition. They are under weight for height according to the crude average tables now in use, and are often so as children. They arrive at puberty rather early than late, and differentiate rapidly so that the males develop a large strong larynx and a low pitched bass or barytone voice. Their skin is thin and sensitive, as is also the epithelial lining of their alimentary tracts. They are as a rule active, energetic and nervous, quite self-conscious, and thus constantly exerting considerable nerve control. When in normal health they rarely laugh aloud and when suddenly shocked they resist the reflex jump and never scream. In this way they pass for cool calm individuals with steady nerve, but as a matter of fact the body is almost constantly held under nerve control, and they are actually nervous, usually suffering more after the shock than on the occasion.

The lateral type when fully expressed is the antithesis of the linear type in all of the respects mentioned. The lateral lines are far apart and the head grows wide and not long (brachycephalic); the interpupillary distance is wide and the eyes are far apart, the nose bridge is wide and often, though not necessarily, low. The mouth arch is wide and low, the teeth are not crowded and are usually smoothly set. The lower jaw is large and strongly developed. The neck is short and large in circumference. The shoulders are round and sloping. The extremities are not long, and are stocky, with large bones and thick short muscles. The trunk is inclined to be long and full, not constricted but bulging at the waist. The intercostal angle is quite obtuse. The stomach in such a person is large and tends to be transverse in position, the liver is generally large.

The eye in the lateral type is so shaped as to be anatomically near-sighted instead of far, and such persons frequently wear glasses on the street. This type is well rounded and over weight for height, and also shows great fluctuation in weight, often gaining or losing as much as 15 or 20 pounds in a short space of time. Those of the linear type on the contrary do not experience rapid weight changes but maintain a very constant weight, and may during the twenty years from about 19 to 39 vary only a small number of pounds. The lateral type arrives at puberty a little late and is slow differentiating, the larynx of the male does not develop so suddenly as in the linear type and does not usually grow so large. The voice is thus high or tenor instead of bass. When men are under 30 years old the heaviest bass voices are almost always found among the thin linear individuals and these are very rarely tenors. The finest tenor voices are those of the round lateral type. Everyone recalls that the fine tenor is a fat man while the heaviest bass is a tall thin man.

The two types are more clearly expressed in men than in women, since the growth and glandular reactions are more decided in the male than in the female, and are also freer from physiological disturbances. Many more physical points of difference and contrast could be cited for the groups, but the above list is sufficient to make the differences clear.

The actual recognition of the two types is not new. They have long been recognized just as we should expect, since if the contrasting features are really of any significant value anyone studying the physical characters of men should have discovered the types. Numerous workers have realized the existence of the two types and they have been designated by many names. The most recent, and what seem to me about the best physical distinctions have been recorded by Bean, and his data bring out in a statistical way a number of physical differences which could be added to those mentioned above. My linear group Bean formerly termed hyperontomorph, meaning high developed structure, but he has since changed the term to hyperphylomorph, indicating a high phyletic origin. This change in terms means that Bean considers these types largely as fixed phyletic or hereditary entities rather than as ontogenetic or developmental results as his former terms indicate. The lateral type is close to his mesophylomorph. He arranges five types in all in considering the world races. It is a usual procedure to think of the races as grouped into separate types and this accounts for the change of term from onto- to phylomorph. It is the method of grouping end products to which I strongly object from the developmental and growth standpoint. I do not question the value of thoroughly analyzing the physical race differences but it must be more clearly recognized that there are frequently extreme type-differences within the race groups. These type-differences are often very probably of a genetic origin, but they are complicated in other ways, and in all cases they are directly the result of definite growth and developmental reactions. The hereditary type is transmitted but the expression or development of this type depends upon numerous environmental influences, and although a feature may be definitely inherited it may never be developed or expressed, just as the Sebright bantam cock inherits the male plumage but is unable to develop such plumage until his testicles are removed. Without this operation a casual observer might conclude that the rooster plumage had failed to be inherited when it has actually failed to be expressed.

In the same way, the human types are modified and changed by environment and the problem of expression or development is equally as important in understanding them as are the involved questions of heredity. The two types actually occur among all races and nations of men, but some races or groups show a great majority of one type and only a few of the other. So that, in general, it may be said that one race is of the linear type and another of the lateral, whereas the actual ancestry or stock of the races may have been closely similar. The "upper classes" of people in England and Germany illustrate the point. Almost all of the Englishmen of this cast are linear in type, thin and dolichocephalic, while almost all of the Germans are of the lateral type, stocky and brachycephalic. Yet some of these Englishmen are decidedly lateral and some of the Germans are decidedly linear in type. All in all, however, the English may be called a linear type race, and the Germans a lateral type race.

We may go still further and claim that these types among the English and Germans are more largely the result of the effects on growth of the environments in which they live rather than of hereditary differences in the stock. That is, the differences are more ontogenetic than phylogenetic in origin. This position will be borne out if we consider the types in conjunction with the geographical distribution of the people of the world. The linear types are usually found along the coastal planes, in maritime climates where there is a good supply of iodine in the environment and where the thyroid gland is normally active or even hyperactive. The lateral types are largely central continentals living in an inland environment away from the iodine supply of the sea. The thyroid gland functions poorly in these central continental regions, colloidal goitre is common and cretinism occurs in the extreme situations. This is a brief general statement of type distribution, all that space permits. At once a number of exceptional cases occur to the reader but these have also occurred to me and when they are fully considered and analyzed they may be fitted into the general scheme. The high volcanic islands often have in certain of their central valleys lateral type people, but the environment may not be actually maritime though it is insular.

It is a well recognized fact that when the distribution of an animal species becomes very broad the species is frequently broken up into a number of varieties, each typical for a given geographic region. There are also certain similar characters developed in the varieties of different species in a given geographic region. The bluejay has several geographic varieties, as has also the bobwhite and other birds in different parts of the United States. The northern varieties of these birds are as a rule larger than the southern, and the Florida types are often the smallest and frequently have longer feathers. The small mammals, squirrels and others, also show numerous geographic varieties. There are reasons to believe that food and other environmental conditions are the primary factors that have brought about these varieties.

When we consider wider geographic ranges, it becomes rare indeed to find the same variety or even species of bird or mammal living in two different continents. The greater the degree and time of isolation for a given region, the more the species differ from those of all other world regions, as is illustrated in Australia, New Zealand and other such regions of long isolation.

A species of such wide distribution as the primitive man of several thousand years ago, with only limited means of world migration, must necessarily have broken up into the geographic varieties which we now find. But the species has in all of its ranges either a tendency to produce a majority of the linear type, long narrow individuals, or a majority of the lateral type, stocky round persons. Whichever the tendency may be we attribute the result to the action of the environment on the function of the thyroid gland and the type is the result of either a fast or slow rate of development. It is a growth reaction.

In diagnosing these types it is very essential to take into consideration the age factor. The well expressed typical condition may only be depended upon during the twenties; at times younger than this the type may not be fully expressed, and at periods above thirty it is becoming modified by age changes. It is, of course, possible to diagnose the type at any age, but it is far more difficult and must be done in detail on the young and post mature, while during the twenties it may with practice be done very readily.

During the twenties the linear type is always rather thin, but after thirty-five many of this type become fat and rounder and may at first sight be mistaken for a lateral individual. A change in the pituitary condition has probably occurred, but on close examination the head shape, interpupillary distance, tone of voice and other characters that do not change make the linear type recognizable.

The study made by Boas a number of years ago on the children of immigrants in New York City furnishes most important data on the environmental modification of types. Central continentals from Europe with brachycephalic heads and lateral type characters when bred in a maritime environment for several generations tend to become dolichocephalic and of the linear type. The gland quality that produces the type is certainly inherited but the action of the gland itself is actually modified by the environment, and the race stock in the new environment is changed in spite of heredity, the possibilities of which Morgan's experiments on the chickens so beautifully illustrate.

Again there are persons who do not properly fall into either type, nor are they typical intermediates, or blends of the two types. These individuals may possess well marked, fully expressed features of the linear type along with typically developed lateral features. They may be dolichocephalic with near-sighted eyes, wide palate arches, and tenor voices, combinations that are at once out of harmony. Such individuals are almost invariably found to be derived from parents of opposite types, and they are very common among the offspring of race mixtures. The fact that the purest type individuals are derived from two similarly pure type parents emphasizes the hereditary elements concerned. In spite of this there is much evidence to indicate that environment may modify the growth regulating mechanism, and so tend to change the brachycephalic into the dolichocephalic head.

If two distinct types actually exist in a wide population we should fail to obtain a usually proportioned figure by averaging a large number of physical measurements. A striking illustration of this fact is now at hand. Accurate physical measurements were collected from a great number of men in the recent army draft by Davenport of the Carnegie Institution. From these data averages were obtained for each of the several measurements collected. A statue of the human figure was then built on the basis of these averages. This might be called a statue of the average young American male. Yet any anatomist examining the figure would at once recognize a number of abnormal proportions. The abnormally long trunk renders the arms disproportionately short and throws the mid-point of the figure entirely out of position. Other unusual details render the figure that of a person one would rarely ever see. In melting together the accumulated measurements an unusual or almost deformed figure was produced, instead of a combination of commonly seen proportions. This is just such a result as would be expected when measurements from two or more distinct types are averaged. Failure to obtain a commonly seen figure from such measurements is very good evidence for the existence in the population of at least two distinct anatomical types. These are, I believe, those termed above as the "Linear" and the "Lateral" growth types.

The basic psychology of an individual is probably associated with his structural type. Two persons of the same race and region that chance to be of opposite types show contrasted mental reactions. The lateral type is careful and painstaking, observing details and valuing them and making little effort to get at the meaning of things or draw conclusions until a mass of detail has been accumulated. This type is emotional and expressive, laughs aloud and shows impulses and feelings towards things, the eyes easily fill with tears and the point of view is rarely concealed. The linear type on the other hand, has great difficulty in accumulating detail or in working a subject out thoroughly. These individuals have mild respect for details and tend to draw conclusions and see the meaning of things after only a hurried survey. They are not emotional and do not laugh aloud since their reactions are generally under control and their reflexes are suppressed. They conceal their impulses and would be ashamed to shed a tear. This type is self-conscious and nervous, while the lateral type is not self-conscious and not really nervous in the common sense of the word. The linear type has great self-control and among savage tribes the chief is almost always of this type, but among civilized peoples the lateral type with near sight and emotion are often rulers of great ability. The lateral type rulers are popular and aware of the details of the immediate situation but are not apt to perceive the great principles of the future. So the linear type Presidents of the United States are honored long after their terms of service, but are often not popular during office; on the other hand, lateral type Presidents perchance of equal ability and equal greatness have been the idols of their time but leave nothing to be remembered in the future.

CONCLUSIONS

In conclusion the following points may be emphasized:

The rate of development, which depends upon the rate of oxidation or rate of cellular metabolism, is a fundamental factor in determining structural formation. The rate of development is inherited by the protoplasm of the species, but it may be modified experimentally or by changes in the environment. A modification in developmental rate is followed by modifications in the structure of the species.

All developmental abnormalities known in nature may be induced by any one method of treatment, provided the eggs are subjected to the treatment at different developmental stages.

The reverse is also true,—the same abnormality may be constantly produced with a number of different treatments provided the eggs are always treated at the same developmental stage. Thus the type of abnormality does not depend upon the kind of treatment, but upon the embryonic stage during which the rate of development was modified by the treatment.

There is in the development of the body and its individual organs a primary linear growth, initially rapid and then becoming slower, to be followed by a lateral growth or expansion. In all plant and animal forms there resides a generalized capacity of growth capable of producing the simple and earlier structures, but to this generalized growth has been added the specialized growth reaction necessary to give rise to the complex body of the higher species. The fetal and postnatal structures of mammals are more complex than the generalized growth capacities are capable of producing, and special centers have developed giving rise to hormones which push the developing parts forward to their highly complex and finished state.

The important function of the glands of internal secretion is this influence on growth and development, regulating their rate and thus determining their result. An understanding of these glands is greatly facilitated by a knowledge of their actions during the development of the individual, and at present what we know of most value about them has been gained from such studies.

The rate of development may be slowed by many methods so as to give rise to structural modifications, but only the internal secretions have been experimentally used to cause increased rates of embryonic development and unusually rapid maturity.

The quality of the internal secretions is inherited, and this quality as well as quantity tends to determine the developmental results to follow. The developmental result is, however, not only due to the quality of the secretion, but also to the nature of the body upon which the secretion acts.

PART III

Hormones of the Sex Glands or the Biology of the Gonads

GONADS CONTRASTED WITH OTHER ENDOCRINES

The gonads or sex glands are extremely complex even as compared with other glands of internal secretion. This complexity is largely on account of the fact that the gonad is not only a gland of internal secretion but is also the reproductive organ of the individual and is, therefore, intimately involved in the entire sex problem. It is a point of some biological interest that the gonads are the only endocrine organs in the vertebrate which may be directly compared with a similar organ in the body of the invertebrate. All other vertebrate glands of internal secretion are either absent from the invertebrate body or have been homologized with most dissimilar structures. Although gonads are present in the two grand divisions of the animal kingdom, yet, the gonads of the invertebrate seem comparable only to those of the vertebrate in being organs of reproduction or germ glands, there being no recognized internal secretion. The comparable parts of the gonads in the vertebrate and invertebrate are simply, then, the germ glands, and there is actually no endocrine tissue in the invertebrate to be directly compared with the internally secreting cells of the vertebrate gonad. The internally secreting mechanism has apparently been added as a new part of the vertebrate gonad, and we are as ignorant of its phylogeny or origin from the invertebrate body as we are of the origin of endocrine glands in general.

The hormones secreted by the gonads in higher vertebrates exert definite effects on structural development during three different periods of life. *First,* during embryonic development their secretions seem to regulate in a definite way the formation and growth of the primary internal and external genital organs. The proof of this statement is beautifully shown by the studies of Lillie and of Tandler on the development of the "free-martin" calf. When twins of opposite sex are produced in cattle, it frequently happens that the arteries from the two placentae become anastomosed or fused, so that the blood from each embryo circulates through the body of the other. Under this condition the male calf develops normally but the development of the gonads becomes arrested in the female twin and the uterus, oviducts and external genitalia of such a female individual are abnormal and poorly formed. The reproductive organs of the "free-martin" calf never recover from this early modification and the adult cow is defective and sterile.

After birth there seems to be little activity on the part of the gonads until just before the stage of puberty, then the *second phase* of gonadal effect begins. At the time of puberty sex-gland activity increases, and the gonadal hormones become important factors in bringing about a fully completed expression of the secondary sex character. The active secretion is necessary for the full development in the male of adult external genitalia and body hair, and in the female for similar developments as well as the mature growth of the mammary glands. If the gonads are destroyed by disease or removed before puberty, these secondary sexual developments are never fully expressed.

Third, following this heightened activity at puberty the gonadal secretions continue to be very important in influencing the general growth and development of the individual up to the state of complete adult size and form. There is evidence which would lead us to believe that the gonadal secretions actually influence, perhaps in a secondary way, head shape and the general body shape and height of the individual. It is well known, of course, that the eunuch does not present the typical shape and stature of a normal individual. Other well recognized structural changes occur after menopause and during senility, which may be either primarily or indirectly associated with the disappearance of gonadal secretions.

In addition to this general life cycle of varying effects the endocrine tissues of the gonads also show a most pronounced short interval rhythmic activity. No other endocrine gland shows such well marked rhythms. The secretory rhythm of the ovary, what might be termed the chemical rhythm of the female, brings about a corresponding rhythm in the genital tract and in reproductive activity. The rhythmical occurrence of ovulation in the female is associated with rhythmical changes in the secretions of the gonad.

A final important point of distinction between the endocrine tissues of the gonads and the other internally secreting glands is that the gonadal secretions seem more particularly associated with reproduction and the preservation of the species, while the other glands are more directly concerned with the preservation of the individual or self-preservation. Removal of the thyroid, adrenals or pancreas will result in great inconvenience or death to the individual, while the removal of gonads does not greatly handicap the individual's welfare but completely does away with the possibility of reproduction.

These complex influences on growth and development and on the general sex rhythm furnish many varied points for attack in attempting to analyze the nature and play of the gonadal secretions. The study of these secretions is a broad, intricate biological problem that must be considered from many angles if it is to be properly analyzed.

RESULTS OF CASTRATION

We may now briefly review a number of general facts bearing on the nature and action of the gonadal secretion. The simplest means through which we have gained insight into the influence of these secretions has been a study of the changes taking place after the removal of the glands.

There has been considerable investigation of the result of castration in human beings. The eunuchs of the East and the religious sect in Russia known as Scopec have been recently studied by Tandler and Gross and by Martin. The age at which castration is performed is a point of importance in the nature of the structural changes which follow. Typical body changes occur in both males and females after removal of the gonads. In all such individuals the thyroid becomes small (probably associated with increase in body fat) and it is claimed that the hypophysis becomes enlarged, particularly in the female after ovariotomy. After castration in lower mammals there is a pronounced degeneration of the seminal vesicles and prostate and of the external genitalia. The human castrate grows tall, the shape of the pelvis is somewhat modified, and the general bone growth takes place as if reacting to a changed condition of growth regulation.

The removal of the gonads from birds produces changes quite comparable to those seen among mammals. In the case of the domestic fowl, the castrated capon shows a very reduced condition of its comb and wattles, while on the other hand, the general plumage of such a bird is developed even beyond the gaudy male pattern. The general metabolism is changed, and the body weight here increases as it does in the castrated mammal; thus, as is well known, the practice of castration is largely used for commercial purposes. When the ovary is removed from the hen she assumes after the next moult the plumage of a rooster and may grow spurs and actually behave in many ways like the male. If similar operations be performed on ducks or other birds the results are very closely the same.

It is of considerable interest to note that the removal of gonads from the mammal causes both sexes to assume a state quite like the usual female type, while the removal of the gonads from birds on the contrary causes both sexes to develop plumage of the usual male type. In both groups, therefore, the characteristics of the operated individual approach in general the homozygous sex which has in its cells the two X-chromosomes instead of one. In the mammals this homozygous two X-chromosome condition is in the female and among the birds it is in the male sex. This chromosome arrangement is supposed to be of prime importance in determining the sex of the individual at the time the egg is fertilized by the spermatozoon.

Among the invertebrates there are some beautiful examples of sex dimorphism, the male and female being widely different in both form and color, yet this seems entirely independent of the gonads. In some insects the male, for example, may have wing color entirely different from the female, or one sex may be wingless while the other is winged. The removal of the gonad even from the embryo of the invertebrate seems to have no effect whatever on the expression of either body form or color. It is, therefore, probable that there is no internal secretion from the gonad of the invertebrate comparable to that in the vertebrates, and here sex dimorphism is regulated in a manner entirely different from that of the vertebrate.

TRANSPLANTATION AND INJECTION OF GONADS

The action of the gonadal secretions has been extensively studied by transplantation experiments. We sometimes think of this as being a very modern method, yet John Hunter 165 years ago attempted to transplant the gonads in fowls and apparently succeeded in obtaining slight results. Recently this method has become very popular through the work of Steinach, Sands and many others. There have been feminization and masculination experiments in which certain body structures were made to change and resemble the opposite sex. Most of these modified characters are those which actually exist in both sexes, such as the mammary gland, hair, size, etc. Definite sex limited structures such as the uterus and tubes in the female and the ducts of the male are not changed over toward the opposite sex. It would seem in general that sex determination in mammals at least seems to be definitely complete and the one sex cannot be changed into the other.

There have been many experiments on the effects of feeding with sex glands but none of these have given clear or reliable results. This would seem to indicate that the secretions of the glands are not effective through the alimentary tract at least in the forms administered. The injection of extracts has given more definite results. This again is not an ultra modern practice since Brown Séquard in 1889 injected testicular extracts subcutaneously in man. He believed that effects were obtained. The present results from such injections are probably very little different from his—certainly we are hardly yet at a stage of definite practice on human beings. Much work of this nature has been done on lower animals. The results, however, have all been very indefinite, as might readily be expected since there has been no proper method for standardizing the gonadal extracts used either on animals or the human being. This work must be followed to a stage of definite accuracy.

THE SECRETORY TISSUE

Since it seems so certain that both the testis and ovary actually produce important secretions, the question arises as to exactly what cells or tissues in these organs are the important secretory elements.

The case of the testis is simpler than that of the ovary. Here the discussion has been as to whether the interstitial cells or the true generative cells produce the secretion. With a pertinent bearing on this question it has been found that a marked eunuchoid type might actually possess perfect spermatozoa while, on the other hand, a perfectly developed male type might have completely degenerate germinal epithelium. Such conditions as these make it seem that the interstitial cells are the important element in bringing about the fully expressed sex characteristics. The action of the embryonic secretion from the testis before there is any active germinal epithelium, as shown by Bissonnette in the 'free-martin' studies, is also a case in point. X-ray treatments destroy the germinal epithelium at least temporarily without modifying the body type. The removal of most of the testicular material seems to have no effect on the body form—only a small remaining portion of one testis is apparently sufficient to maintain the normal male body condition. There is no hypertrophy of portions of the testis following the removal of a part. The evidence thus seems to show that in the male gonad the interstitial cells, and not the germinal epithelium, produce the internal secretion.

The case of the ovary is more complex. It must not only influence growth conditions but must later regulate uterine rhythm, placentation, and probably other phenomena. In the ovary a number of different kinds of cells have been thought to produce various secretions. There are here interstitial cells believed by many to arise from atretic follicles, follicular cells, cells of the corpora lutea, and the ovum itself. It is very difficult of course to completely separate or isolate the activity of any one of these types in an experimental way. When one ovary is removed the other hypertrophies to a great extent, and a small piece of ovary will grow into a whole organ. The single ovary tends to ovulate or give off eggs as abundantly, or even more so, than both ovaries did originally. The ovarian secretions, as pointed out in considering the gonads in general, exert different effects on growth and development at different life periods. The ovary at menopause completely degenerates and yet the individual may live for years with no more rapid ageing after menopause than before the degeneration of the ovary. This fact in itself should make one question whether the lowering of the gonadal secretions is a primary cause of old age rather than one of the symptoms.

The secretions from the male and female gonad have been thought by many to be antagonistic in their actions. In order to test this, adult rats of opposite sex have been artificially grafted together, producing a condition of parabiosis. There was first thought to be antagonistic effects which caused the gonads of both components to become degenerate, but it was later found by several workers that a castrated animal might be fused to a normal animal of the same sex and yet the gonads of the normal animal would tend to degenerate under such conditions. Recently very interesting experiments have been made by Burns at Yale in grafting together tadpoles before the development and differentiation of sex, in order to determine whether one sex in its development might influence the other. It happened that every pair of grafted tadpoles that lived to reach a stage where the sex could be identified were invariably a single sex pair, either two males or two females. In this experiment, either all grafts of opposite sex have died, which seems somewhat probable, or else it might be that one component in the pair transforms the sex of the other so that both members of the pair are always of the same sex.

It should be remembered in considering all specific hormone effects produced by the gonads that other endocrine glands may very probably be involved. The nervous system is also concerned. The removal of eggs from the nest of a bird may cause a single female to produce as many eggs in forty days as she might have ovulated in five years. This is a definite effect on the ovary through the central nervous system of the bird in reacting to the taking away of her eggs from the nest. In line with this is the fact that menstruation and ovulation may be suppressed by hypnosis in the human female. Thus the central nervous system exerts a definite effect upon the hormone secretion of the gonads, and vice versa; the presence or absence of gonadal hormones exerts a marked influence on the physiology of the nervous system.

Hormones from other glands of internal secretion also play a rôle in regulating the behavior of the gonads. The effect of the removal of the thyroid gland on the ovary is well recognized by most physicians, and it is well known that among lower mammals a considerable degeneration of the ovary takes place after removal of the thyroid. Papanicolaou and Bagg in our laboratory have recently found that radium radiation on the thyroid in guinea pigs may cause a hyperactivity of this gland. The ovary in such animals gave a very marked reaction to this thyroid condition. Ovogenesis is greatly activated and the new cells migrate down into the stroma and form new Graafian follicles. There is also a change in the cellular picture of a smear made from the fluid of the vagina after radiation of the thyroid and the resulting stimulation of the ovary. This is quite an opposite reaction on the part of the ovary from that which follows the removal of the thyroid gland.

INDICATOR FOR TESTING GONADAL SECRETIONS

All of the foregoing discussion shows the importance in the body economy of the endocrine secretions from the sex glands. Yet all of the phenomena so far discussed are simply qualitative changes resulting from a hit or miss method of experiment, and none of the results mentioned are definitely measurable or quantitative in type. This is necessarily true, since up to the present time there has been no definitely established indicator against which the gonadal secretions could be definitely measured or standardized. The results of experiments may be spectacular, but they are of little definite value unless quantitatively expressed and subject to accurate repetition. The chemical preparations or extracts of gonadal hormones must be brought up to some such point of standardization as that already obtained for the suprarenal substance and insulin. In order to attain this aim there must be devised some indicator against which these secretions may be accurately measured and tested. For the past eight years Dr. Papanicolaou and the present writer have been studying the ovarian reactions in guinea pigs by using the changes in the uterine and vaginal epithelia as an indicator for the ovarian condition. The action of ovarian hormones on the uterus and vagina are very definite in giving certain cellular expressions which may be accurately recognized.

In making daily smears from the content of the vagina it was found that the cellular appearance changed in a very exact way in correspondence with the sexual stage of the animal. These observations were controlled by both operations and autopsies so as to establish a definite connection between the appearance of the smear, the condition of the vaginal wall, the uterine wall, and the ovary. These relations have been so clearly analyzed that anyone may examine a smear of the cells from the vagina and know very definitely what the condition of the uterus and ovary are at this time. By such a method one is actually able to predict within the hour the exact time of ovulation. These experiments have been repeated by a number of other workers—Long and Evans with the rat, Allen with the mouse, Hartman with the opossum, and a number of others using different mammals. In all these animals it is readily possible to definitely diagnose the oestrous stages or sex periods, and to know the exact state of the ovary from examination of the vaginal smear. It now becomes evident that any treatment or experiment which tends to influence the condition of the ovary might readily be detected by some modification in the vaginal smear. In the anatomical laboratory at Cornell we have studied the effect of a number of modified conditions such as starvation and underfeeding, and various operations, and found that in certain cases ovulation could be completely suppressed and the vaginal smear would definitely indicate the fact. If ovulation was accelerated this of course could be recognized in the same way. Allen by employing this method was able to detect the effect of the chemically extracted follicular hormone on the uterine reaction of female mice from which the ovaries had previously been removed. In this way Allen and Doisy have learned many points of importance about the follicular hormone, and the possible means of its chemical separation.

A group of us in the laboratory at Cornell Medical College have been able to measure very definitely the quality and strength of several chemically fractioned ovarian preparations. There has been obtained a definite acceleration of ovulation in the guinea pig by injections of an ovarian hormone, and an equally clear-cut delay in ovulation as a result of measured tests of a purified lutean extract. Papanicolaou has recently reported in some detail these findings.

It seems quite evident from the amount of investigation already conducted that *the vaginal smear method offers a most accurate indicator for the study of ovarian extracts and of ovarian reactions, and by the use of this indicator it is believed that the endocrine products of the ovary may be as accurately extracted and measured on the basis of unit doses as is now possible in the case of insulin.* Certainly much work remains to be done, but it may clearly be followed along these lines.

An attempt to extend this work to human beings is now being made and through coöperation considerable progress has been attained. Dr. Papanicolaou finds that the various stages of the ovarian cycle in the human may be detected with considerable probability by examination of vaginal smears. The human smear is somewhat more difficult to analyze than that of the lower animals, but with experience it seems perfectly practical to use it as a general indicator. In working with the human cases it has also been found that early stages of pregnancy and other abnormal conditions of the ovary and uterus may possibly be detected by characteristic changes in the cellular appearance of the vaginal smear. Papanicolaou has already reported in a brief way the general nature of the modified smear of pregnancy, and his study is being actively continued at the present time. Much chemical investigation is necessary in order to understand the changes in the pregnant uterus which may modify the nature of the vaginal content.

Finally, we are encouraged to hope, in the light of the recent advances which have been made by the use of the vaginal smear method, that much accurate quantitative knowledge is soon to be obtained regarding the various functions of ovarian secretions. This method of study also furnishes a clear-cut means of detecting the influence of the secretions from other endocrine glands on the ovarian reaction. The relationships between the thyroid and pituitary and the ovary may be further elucidated by the present methods of study.

In concluding we may emphasize the remarkable fact that this histological indicator is as accurate and clean-cut in its response to chemical changes in the body as any other type of diagnostic reaction, and it may aid in facilitating the more accurate chemical isolation of the gonadal hormones.