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DIVERGENT PATHWAYS IN SEXUAL DEVELOPMENT[1]

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AMONG the outstanding achievements in biology during the past few years are those relating to the physiology of reproduction. Experimental studies on the identification, analysis, preparation and physiological effects of the so-called sex hormones in the various classes of vertebrates have been particularly noteworthy. It is well known that these internal secretions are responsible for the functional development and activation of the sex glands and their associated structures, for when they are properly administered, either by uniting two embryos together or otherwise, the sexual differentiation and sexual function of the developing individual can often be diverted in either the male or the female direction, as desired.[2]

The effects may be scarcely appreciable or decidedly profound, depending upon the species, the sex and the period of administration. In some of the amphibia complete functional sex reversal is possible. In birds and mammals the effects of treatment with hormones of the opposite sex have been thus far limited to alterations in the sex glands or to the accessory sex organs, or both, without achieving complete functional development. Apparently normal germ cells of the opposite sexual type have been experimentally obtained in the fowl, and the production of fertile sex-reversed individuals in the near future appears to be highly probable.

In certain species of amphibia the sex can be controlled merely by regulating the temperature, by delaying the fertilization of the egg or by other means, but I know of no satisfactory evidence that success

[1] Address of the retiring vice-president and chairman of the Section on Zoological Sciences, American Association for the Advancement of Science, Columbus, December 29, 1939.

[2] B. H. Willier, E. Witschi, L. V. Domm and C. H. Danforth, in "Sex and Internal Secretions," second ed., 1939 (Allen, Danforth and Doisy, editors): Richard Avery Miller, *Anat. Rec.*, 70, 1938.

has ever been attained in the control of sex in man or other mammals. The sex-determining and sex-differentiating mechanisms have been known for some years, but as yet all attempts to direct their activities in favor of one sex or the other have either been without effect or have resulted in abnormalities.

The sex ratios can be modified within certain limits by the selection of suitable hereditary stocks, but the innumerable instances in which it has been thought that sex has been controlled experimentally in man or other mammals seem to have been based on insufficient evidence or chance coincidences.

Some species of invertebrate animals seem to have entirely dispensed with males, the races being continued from generation to generation exclusively by females. Others have only one male for each thousand or more females. In mammals also the male may become superfluous under experimental conditions, since reproduction in the rabbit may now be accomplished by the female alone. Pincus has shown that female young may be born when a few drops of a salt solution have been substituted for the conventional father. With that exception, the numerous techniques that have been recommended in recent years seem to have been no more successful in preconceptional sex control than those which Aristotle wrote were in vogue in his time. It must not be concluded, however, that the eventual discovery of a practical technique which will fulfil the desires of prospective parents and animal breeders is improbable.

Some of the sex hormone preparations have already proved helpful in overcoming the defects of imperfectly functioning organs. Their administration to adolescents or adults often has a considerable effect on the nervous system and on the individual's subsequent behavior. Allee has found that the synthetic male hormone testosterone propionate will make a timid hen domineering and cocky. The hormones of both sexes promise to be of much service in the medical practice of the future. But as a boon to the elderly in arresting senility or as a means for reconditioning or rejuvenating the superannuated they seem not to have worked out so well as was predicted several years ago.

We know that partial or complete sex reversal of aberrant individuals of all groups of vertebrates occasionally occurs in nature, either by the failure of the sex-differentiating mechanism to function normally or as the result of some pathological condition in later life. That this is possible may be considered proof not only of the double sexual potency of the undifferentiated embryo but the retention of such potency even after functional differentiation. The sex mechanism is so labile that it can be diverted in either direction by appropriate activating and inhibiting agencies. Experimentally, these may be either chemical or physical.

A functional change of sex takes place normally in a few species of fishes, in many kinds of invertebrates and in some plants. In some of these this occurs not merely once but several times. The transition stages between two sexual phases are similar to those observed in cases of intersexuality and sex reversal in insects and vertebrates. Consequently, an examination of the sexual conditions in a few such forms may be helpful toward an understanding of the general problem which is now under discussion. We shall find that in spite of their diverse manifestations the sexual phenomena of all multicellular animals are based upon a few general principles. Primarily, we shall observe that the organs of the two sexes or sexual phases in both vertebrates and invertebrates have a similar origin from sexually undifferentiated primordia. The diversities result from different activating agencies.

We may first consider an example of *consecutive sexuality* and the problems relating to the influence arising from the association of two or more individuals.

Let us select for this purpose the marine snails belonging to the genus Crepidula, although the representatives of other genera would serve as well. In these snails each of the young individuals functions as a male for a time and afterward changes to the female phase. The male phase thus represents the juvenile condition, the female phase continuing through the remainder of the individual's life. This type of sexual change is strictly hereditary and takes place in all normal individuals. Sex reversal in these snails is consequently comparable with metamorphosis from the larval to the adult condition in insects and amphibia, and like such metamorphosis the juvenile phase can be abbreviated or prolonged experimentally, but the sequence of the two phases can not be reversed.[3]

At the beginning of the female phase the instinctive behavior changes and the individual whose previous activities were so characteristically masculine then becomes strictly sedentary; she receives her mate, deposits her eggs and protects her developing young.

Although this sexual sequence is experienced by all normal individuals, the accentuation and duration of the male phase are highly variable and dependent both upon the hereditary composition of the individual and the environmental conditions. There appear to be two intergrading types of male-phase individuals, as shown by the relative abundance of primary ovocytes in the sex gland and by the behavior of the respective individuals. Those with the more numerous ovocytes, the so-called hermaphroditic males, exhibit a less masculine behavior in that they are less

[3] W. R. Coe, *Jour. Exp. Zool.*, 77, 1938; *Jour. Morph.*, 63, 1938; *Biol. Bull.*, 75, 1938; H. Ishiki, *Jour. Sci. Hiroshima Univ.*, Ser. B, Div. 1, 4, 1936; 6, 1939.

active in their search for females and are less likely to attach themselves in the mating position. They also begin the sexual change at an earlier age and increase in size much more rapidly than those more masculine individuals, or "true males," which have fewer ovocytes and which when isolated may remain more or less restless for several months without changing their sexuality.

One of the environmental conditions which influences the duration of the male phase is opportunity for association with an individual in the female phase. Solitary males or males which are isolated when young usually, but not invariably, undergo sexual transformation much more promptly than those with female associates. In nearly all the species studied such association both accentuates and prolongs the functional male phase, although in none of them is association necessary for the realization of that phase.

It must be admitted that Crepidula has not yet divulged the secret by which this is accomplished. The explanation seems to depend upon the stimuli which the male receives through his sense organs and the associated internal changes occurring at the time of mating. It seems quite unnecessary to assume the transfer of any specific masculinizing substance of hormonal nature from the body of the female to that of her mate.

Adverse metabolic conditions such as abnormally high temperature, lack of oxygen, deleterious substances in the water or extensive parasitism terminate the male phase without inaugurating the female phase. If favorable conditions are later restored the female phase follows, but not otherwise. In some species under adverse conditions the functional male phase may be long delayed and in exceptional cases the female phase may become functional after an aborted male phase.

The transition period between male and female phases may be either brief or prolonged, depending upon the individual, the environment and the species. In all cases the intersexual stages are closely similar to the sex intergrades which appear during the developmental processes of insects and other dioecious forms, including vertebrates, with unbalanced sex-differentiating factors or of those undergoing sex reversal.

In terms of genetics the sexuality of Crepidula would imply homozygosity of both male and female sex-determining genes, with modifying factors which control the initial expression of the male phase, together with associated factors for the termination of that phase and the inauguration of the female phase after a certain stage of physiological maturity is reached. The hereditary mechanism responsible for this consecutive sexuality is in some respects comparable with that which operates during the change from juvenile to adult plumage or pelage in birds and mammals.

We may now inquire as to how this change of sex is brought about. A study of the embryological development shows that although the primordial germ cells are early set apart from the other organ-forming groups of cells they show but little activity until after all the other organ systems have become functional. In the meantime the primordia of the accessory male organs have been formed by the organizing potency of the body in conformity with the plan of organization peculiar to the male phase of the species. The early sex gland is usually differentiated into the two types of primary germ cells characteristic of the two sexes.

As soon as the physiological conditions become suitable the male constituents of the sex gland resume activity. Spermatogenesis begins and at the same time, or earlier in some species, the primordia of the accessory male organs become activated and eventually attain functional development. We have no satisfactory evidence at present as to the nature of the activating agency, whether the induction results from the action of local organizing centers or whether hormones are secreted by more distant groups of cells.

The functional male shows no indication of any female characteristics, as do the males in most vertebrates, except for the ovocytes in the gonad. And yet the individual is genetically determined for femaleness and the male is but the first stage toward that genetically completed individual represented by the female phase.

After a more or less lengthy period of masculine control of the reproductive processes the influence of the female-differentiating genes becomes evident. The ovarian constituents of the sex gland then become active, and thereupon all the spermatogenic cells are destroyed. Then the accessory male organs which had been so perfectly formed are remodeled into organs adapted to the reproductive requirements of the female phase. In some species there is an overlapping of the two sexual phases, but in certain individuals of other species both the sex gland and the accessory sex organs return to a simplified or neutral condition before they are redifferentiated into the female type.

In these sexual changes we witness a long series of developmental processes indicative of the successive responses of the body cells to the activating agencies of the genetic constituents of the nuclei, as well as to the mutual influences of the associated cells. The hereditary organization pattern of full maturity is realized only after the sexual transformation has been completed.

A different aspect of the influence of association on sexuality is shown by a species of chaetopod annelid belonging to the genus *Ophryotrocha,* common alike on European shores and on our Pacific coast. In this species also each of the young worms functions for a time as a male but usually changes to the female phase on reaching a certain size. Under favorable conditions the female phase may continue for the remainder of the individual's life, as in Crepidula, but otherwise the original male phase is resumed.

It has been known for nearly half a century that when the head and a few adjoining segments are severed from the rest of the body of an individual in the female phase it often happens that both fragments revert to the juvenile male phase and produce sperm from the undifferentiated germ cells which they contain. For some individuals a second or a third operation may be necessary. The posterior fragment then dies, while the anterior end regenerates into a small worm similar in most respects to a young male at first sexual maturity. Under favorable conditions this rejuvenated male later changes again to the female phase, and these procedures may be repeated many times. Or the male phase may be continued for long periods by removing the posterior segments with sufficient frequency.

Starvation or other adverse conditions, including various chemical modifications of the sea-water, may likewise cause the functional female to resume the male phase or cause that phase to be long retained. The accumulation of excretions also acts as a masculinizing agency, presumably by interfering with normal nutrition. It has been observed[4] that when two females are placed together in close confinement the more vigorous or more dominating Amazon may obtain a male companion either by biting the other female into two or by devouring all the available food. The more susceptible of the two females may thereupon undergo sex reversal and then, functioning as a male, is available to stimulate ovulation in the remaining female and to fertilize her eggs as they are deposited. After securing her mate she may in some cases keep him in the male phase indefinitely, but more often the recently transformed male again changes sex and becomes in turn the dominant female of the pair, whereupon the sexual relations will be reversed.

In contrast with the condition in Crepidula, such germ-cells as are in process of development during one sexual phase continue maturation in association with those of the opposite type in the newly transformed sex. Self-fertilization may result. It is thus evident that the morphologically undifferentiated germ cells are sexually neutral and that their differentiation is controlled by the conditions within the parent's body. The precise nature of the controlling agency, whether nutritive or hormonal, is still unknown.

Other aspects of this problem of the influence of association on sexuality are found in various examples of parasitism. We must consider the effects of the host on the parasite, of the parasite on the host and of the parasites on each other. First there is the influence of the host on the parasite of the same species. A classical example of this is found in the gephyrean worm Bonellia. Here the male is a relatively insignificant creature, perhaps a thousandth the size of the female on which he is parasitic. After the eggs are shed into the water some of the free-swimming embryos settle down upon the outstretched proboscides of female Bonellias, while others come to rest upon the surrounding sea bottom. It has been known for many years that about 85 to 90 per cent. of the embryos which become attached to the proboscides transform into males, while approximately 95 per cent. of those that find no females become females themselves.

If the larvae are removed from the proboscis after a brief but not too brief period of attachment many intersexual individuals result, since male differentiation may have proceeded too far for normal female development to be possible.[5]

Precisely how the masculinization of the larva is accomplished by its attachment to the proboscis is still uncertain. But it is known that extracts of the proboscis or of the intestine or of the body wall are likewise effective. They are also more or less toxic to other small organisms. Herbst and others have found that many different chemical modifications of the sea water produce the same result. A small amount of a copper or potassium salt, a trace of acid or a decrease in the magnesium content of the water are some of the modifications that have an effect similar to that produced by the proboscis secretion. It is the external influence, then, that determines which of the two alternative paths of development most of the sexually undifferentiated larvae shall follow.

Some of the developing females assume certain characteristics of the male and may even produce sperm before transformation to the definitive female condition. Consequently, it has been suggested that each individual inherits a tendency toward consecutive sexuality and that the female phase is inhibited in those individuals that function as males. Such inhibition is accomplished in nature by the secretion of the proboscis and experimentally by chemical modifications of the water. As mentioned for Crepidula and Ophryotrocha, it appears that relatively small chemical or physical changes in the environment are sufficient to prevent the differentiation of female sexuality, while allowing full expression of the hereditary factors for maleness. Conversely the male phase is usually, but not always, abortive without the stimulating effect of the proboscis secretion.

[4] M. Hartmann and W. Huth, *Zool. Jahrb. Abt. all Zool.*, 56, 1936; M. Hartmann and G. v. Lewinski, *Zool. Jahrb. Abt. all Zool.*, 58, 1938.

[5] F. Baltzer, *Rev. Suisse Zool.*, 38, 1931; 39, 1932; 44,

Here again there appear to be diversities in the genetic endowment of different individuals. Usually 5 to 15 per cent. of the embryos persist either in male or in female development in spite of environmental conditions which control the sexuality of the others. These diversities may be explained likewise on the assumption that modifying factors for sexuality are associated with homozygosity in both male and female sex-differentiating mechanisms.

We may next consider the influence of the host on parasites of a different species. This is well illustrated by some of the nematode worms in which the sexual cycle covers two generations. One of these is free-living and of separate sexes, while the other is parasitic and is functionally hermaphroditic and self-fertilizing. The chromosomal composition of all individuals of the parasitic generation is female, and the early gonad is of the female type. After a period of parasitism, however, the gonad becomes hermaphroditic and functions as such.

Zoological literature contains numerous reports concerning the influence of the host on the sexuality of the parasite as well as of the effects of parasites on each other. Hermaphroditism is characteristic of many groups of parasites, but in some forms that are of separate sexes the sex mechanism is so evenly balanced that the sex may be controlled experimentally, in some cases merely by regulating the number of parasites present. The amount of nutrition available and the effects of excretion products appear to be the controlling factors.

Another aspect of the problem of sexuality as related to parasitism concerns the effects of external parasites on the host in decapod crustacea. In extreme cases the sex glands of the host are almost completely absorbed. Later, after the period of parasitism is ended, the remaining part of the gonad may resume activity. If the host is a male there may be partial or complete transformation to a female condition.

If we may assume either that some of the females have a tendency toward a juvenile male phase (of which there is some evidence) or an antagonistic action of the male and female constituents of the gonad, the removal of the functional portion of the spermary would allow the inactive ovarian elements to assume dominance. The sexuality would then be reversed, and female external characteristics would appear after molting. It seems quite unnecessary to assume the secretion of any specific feminizing substance by the parasite.

The associative influence of dense populations and their accompanying excretions, as well as of other environmental conditions, in controlling sexuality or, more strictly, the method of reproduction is well shown by some of the cladoceran crustacea and rotifers. Some of these can be cultivated for a hundred or more generations as exclusively parthenogenetic females. But males and sexual females can be obtained at any time merely by suitable changes of the temperature, by altering the nutritive conditions or by overcrowding and allowing the accumulation of excretory substances. For a brief period the water in which the animals have been cultured contains the excreted substances, whatever they may be, and controls the sexuality of other individuals of the same species. A decreased metabolic condition is suggested as the possible determining factor.[6]

In some of the algae likewise the filtrate from sexual cultures determines the sexuality of other gametes that may be placed in it.[7]

It has been reported recently that one species of fungus produces four specific activating substances, two by each of the two sexual types. These are secreted in sequence, and all are thought to be necessary for the consummation of functional sexuality.[8] It thus appears that both algae and fungi produce sexual substances of such specific nature that they may be said to be strictly comparable with vertebrate sex hormones.

The examples that I have given as showing the influence of one individual on the sexuality of another must be considered as exceptions to the vast majority of organisms in which no such influence is found. Many of the latter have separate sexes, with genetic sex-differentiating mechanisms that are so accurately adjusted by heteromorphic sex chromosomes that sex reversal is not known to occur. Others are homozygous hermaphrodites, and still others either change their sex during life or have so unstable a sexual condition that their genetic sex can be more or less completely reversed either by natural environmental conditions or experimentally. A few examples of these may be mentioned.

Consecutive sexuality similar to that noted for Crepidula and Ophryotrocha is of wide distribution in invertebrate animals, including mollusks, annelids, echinoderms, nemerteans and crustaceans, as well as in some plants and in a few species of fishes. Most of the invertebrates with this type of sexuality experience but a single change of sex, usually from male to female. An overlapping of the two sexual phases frequently produces a brief period of functional hermaphroditism, at which time self-fertilization may

1937; C. Herbst, *Arch. Entw. mech.*, 135, 1936; R. Goldschmidt, *Genetica*, 20, 1938; *Am. Nat.*, 72, 1938.

6 A. M. Banta, *Am. Nat.*, 71, 1937; Clifford H. Mortimer, *Zool. Jahrb, Abt. all Zool.*, 56, 1936; Kaj. Berg, *op. cit.*, 57, 1937.

7 M. Hartmann, *Arch. f. Protist.*, 89, 1937; B. Hammerling, *Fort Zool.*, 1, 2, 1937; Franz Moewus, *Jahrb. wiss. Bot.*, 86, 1938; *Naturwiss.*, 27, 1939.

8 John R. Raper, SCIENCE, 89, 1939.

occur. Other representatives of the same groups may experience a *rhythmical sexuality,* with regularly alternating male and female phases.

All the species that have been most fully studied agree with Crepidula in having two intergrading types of males, the so-called hermaphroditic males, which soon change to females, and true males. In the former the gonads often have a more or less continuous basal layer of ovocytes, with the spermatogenic cells superimposed near the lumen. This condition resembles the cortical and medullary portions of the gonads of many of the vertebrates. In the true males many or all of the ovocytes in the primary gonads are eliminated, and such individuals retain the male phase indefinitely but not necessarily through the entire life span.

There are some invertebrates in which the sexuality is so labile that it is impossible to predict during one reproductive season the sexual phase which the individual will assume at the next. This type of *alternative sexuality* is illustrated by the commercial oyster of the Atlantic coast, which is seasonally of separate sexes with a strong tendency toward protandry. The proportion of males at the first reproductive period varies from 70 to more than 90 per cent. at different localities and under various environmental conditions.

Following the first reproductive season many of the young males change to females, whereby the sex ratio becomes more nearly equal and there are as many females as males in populations four or more years of age. In the meantime some of the females have changed back to males and then to females again.[9] It is thought that the population consists of two hereditarily distinct types of individuals with reference to their rhythmical tendency and their response to environmental influences.

This alternative expression of sexuality is closely paralleled in some of the flowering plants and in certain species of plants belonging to the lower orders.

In a few representatives of unrelated groups, as nematodes, gastropods, pelecypods, crustacea and fishes, the fully mature individuals are strictly of separate sexes, although all or nearly all the young first function as males. In these species the genetic males (true males) continue to function as such throughout life, while the genetic females (hermaphroditic males) function as males when young and as females thereafter.

More or less numerous representatives of nearly every phylum of invertebrates and of every phylum of plants are functionally hermaphroditic. Here there is no incompatibility between the two types of sex organs, and each adult individual may function simultaneously both as male and as female. Not infrequently, however, this condition is preceded by a brief period of maleness or, occasionally, of femaleness. In some of these species the extent of protandry is increased by unfavorable conditions and can be controlled experimentally.

Incomplete sexual differentiation or intersexuality may result from the crossing of different species or of different geographical races of the same species. While each species or race may have sharply differentiated sex mechanisms, the hybrids often inherit a combination of male as opposed to female determining factors so nearly equal that neither is completely dominant, resulting in an intersexual, sterile condition. Both male and female characteristics may begin development simultaneously or, as Goldschmidt has shown so clearly in the classical example of the gipsy moth, those of one sex may be dominant in the early stages of development and those of the other sex later.

Other sexual abnormalities of similar character may result from endocrine disturbances, irregularities of chromosomal distribution or mutant autosomal genes which interfere with the normal action of the sex-differentiating mechanism.[10]

When closely related species or geographical races of unicellular algae are crossed a series of intergrading sexual types may be produced. Each of these will conjugate readily and form viable zygotes with all other types, including those of the same sex, which are not too closely similar. Sexuality is therefore not absolute but relative, with perhaps several grades of maleness and of femaleness.[11]

Divergent manifestations of sexuality with balanced mating types are also found in local races of unicellular animals. The 16 types which are already known in one common species of Paramecium may be cited as an example.

The question naturally arises as to what bearing all these manifestations of sexuality may have on current theories of sex determination. The answer is that they seem to be entirely consistent with the view that the prospective sexuality of the individual is dependent upon the quantitative balance of the male as opposed to the female factors in the hereditary mechanism. Whether this mechanism primarily resides exclusively in the chromosomes has been a fruitful source of discussion, but undoubtedly the cytoplasm is the agency through which the cellular differentiation is effected.

There are certain types of sexuality that can be explained most satisfactorily on the assumption that the peculiarities of the cytoplasm are such as to in-

9 W. R. Coe, *Biol. Bull.*, 74, 1938; P. S. Galtsoff, *Biol. Bull.*, 74, 75, 1938; *Anat. Rec.*, 72, Suppl., 1938.

10 G. A. Lebedeff, *Genetics*, 24, 1939.

11 M. Hartmann, *Zeits. f. ind. Abst. u. Vererb.*, 54, 1930; Franz Moewus, *Jahrb. wiss. Bot.*, 86, 1938; *Naturwiss.*, 27, 1939.

hibit the full expression of the chromosomal inheritance. It is not improbable, however, that some of these cytoplasmic peculiarities are themselves the result of nuclear activities, while others are inherited directly through certain of the constituents of the cytoplasm and are only indirectly subject to nuclear control.

All the diversities that I have mentioned may be referred to the homozygosity or heterozygosity of the primary sex factors, with their associated modifying factors for the activation or suppression of either the male- or female-determining components at certain stages of embryological development or in harmony with different degrees of physiological maturity. They are all responsive to environmental conditions both within and without the body of the organism.

INTERNAL SECRETIONS

And, finally, the influence of internal secretions on sexuality should be considered. The presumably universal occurrence in vertebrates of hormonal substances necessary for the development and functional activity of the sex organs would seem to imply that secretions of a similar nature must be present in invertebrates. But as yet conclusive evidence to that effect has been found only in crustacea and insects.

It is well known that the removal or transplantation of the gonads in larval insects is without effect on the sexual development or the sexual instincts of the adult. Sex mosaics (gynandromorphs) may have both male and female secondary sexual characteristics perfectly differentiated locally, associated with gonads exclusively of either sex. Hence the evidence now indicates that, although the primary gonads have bisexual potencies, the primary sex-differentiating agents in the insects have only a local influence and are not discharged into the blood. In some species, at least, true hormones supplement these agents in the functional development of the organs. Goldschmidt has suggested that in the moth the activating agent may be released at the base of the imaginal disk from which the part is formed and that its influence then spreads over the disk in the manner of a consecutive embryological organizer.

In most invertebrates there is only a single set of primordia for the accessory sex organs, and these are homologous in the two sexes. The organs which they form may differ greatly, however, presumably because the activating agency in the male is of a different nature from that in the female and activates different parts of the primordia. It is also probable that in some animals the two agencies are differently localized. In individuals with consecutive sexuality the parts peculiar to the primary sexual phase may be reduced to a simplified or neutral condition at the time of sexual transformation. The system is later redifferentiated by the agencies of the succeeding sexual phase in harmony with the functional requirements of that phase. In hermaphrodites some of the parts of the single set of primordia become differentiated into organs of the male type at the same time that other parts are forming the female organs. Thus the activating agencies of both types of sexuality react either consecutively or simultaneously upon those parts of the primordia that have been differently sensitized or localized for their reception.

In the higher vertebrates, on the other hand, the primordia of most of the accessory sex organs are formed in duplicate sets, one set being sensitized for reaction with the male-differentiating agency and the other set with the female agency.

Witschi and others have presented evidence that the cells of the two primary components, cortex and medulla, of each of the sex glands in amphibians and birds secrete antagonistic hormones, the secretion from each component tending to activate the germ cells of that component and to suppress those of the other.[12] Since the cortex represents the prospective female part of each sex gland and the medulla the male part, the sexuality of the individual will depend upon whether the cortex or the medulla becomes dominant. And this is determined both by the genetic composition of the cells and by the environmental conditions. The first effect of the sex hormones is upon the development of the sex glands themselves and later, after diffusion into the blood, the hormones activate that one set of the duplicate accessory sexual primordia that has been chemically sensitized for their reception.

The functional sexuality of the sex gland and then of the appropriate accessory organs are thus under the control of the specific sex hormones. These hormones evidently have no organizing potency in the initial formation of either the sex glands or their associated organs. They merely activate or inhibit the appropriate parts already prepared by the organizing properties of the body as a whole and maintain the functional sexuality of the adult.

Not infrequently, however, the relations seem to be more complicated. Under experimental conditions the results are sometimes contradictory, since the administration of large amounts of the hormones of either sexual type may produce intersexuality or incomplete hermaphroditism by inducing the development of both male and female accessory sex organs simultaneously.[13] In some cases the effects are more

[12] R. K. Burns, Jr., *Anat. Rec.*, 63, 1935; *Am. Nat.*, 72, 1938; E. Witschi, *Biol. Rev.*, 9, 1934; B. H. Willier, T. F. Gallager and F. C. Koch, *Physiol. Zool.*, 10, 1937.

[13] R. K. Burns, Jr., *Jour. Morph.*, 65, 1939; R. R. Green, H. W. Burrill and A. C. Ivy, *Am. Jour. Anat.*, 65, 1939; C. D. Turner, *Jour. Morph.*, 65, 1939.

pronounced with the male than with the female type of hormones. A feminizing effect may also follow the administration of male hormones to males in amphibia. reptiles and mammals or to developing male chicks. To explain these double effects Burns has suggested that the introduced substances either may be changed chemically in the body or may stimulate the secretion of the normal heterotypic hormone. It is well known that the pituitary and other endocrine glands are closely associated physiologically with the sex glands.

Transplantation experiments prove that the primary germ cells of the vertebrates, like those of the invertebrates, are bipotential and that their differentiation into the germ cells characteristic of the one sex or of the other is controlled by the associated tissues. They will become of the male or of the female type depending upon their position within the sex glands; male if situated in the medullary portions and female if in the cortex. Since only one of these two portions is normally retained in each of the functional sex glands of vertebrates with separate sexes, the germ cells remaining are all of the same sexual type. If both portions develop simultaneously hermaphroditism results, but if either one is inhibited for a time and later becomes functional, consecutive sexuality of the one type or of the other, as mentioned for certain invertebrates and fishes, may ensue.

Functional activity, however, is dependent upon agencies additional to those which govern the differentiation of the organs; it requires the mutual interaction of the organs themselves with other secreting and reacting systems, including the nervous system. Only then is physiological sexuality realized and only then do the sexual instincts become operative.

The realization of functional sexuality, therefore, requires the participation of a long series of hereditary reaction systems which are activated one after the other in orderly sequence under the influence of suitable external and internal conditions. The environmental requirements may change during successive stages of development. Each developmental event as it occurs is a response to a preceding action and in turn initiates the one that is to follow. If any one of these reactions fails to occur because of either hereditary or environmental deficiency functional sexuality is not realized. The individual is sterile, and its line of descent comes to an end.

OBITUARY

WILLIAM SNOW MILLER

1858–1939

DR. WILLIAM SNOW MILLER, emeritus professor of anatomy at the University of Wisconsin, died at Madison on December 26, 1939, in his eighty-second year after a brief period of illness and inactivity. Although death came in the fullness of years it appeared especially untimely in one with his mental alertness and scientific activity. In the seventeen years since his retirement from active teaching, Dr. Miller's accomplishment has been such that it might well be the envy of a much younger man. With a daily routine of a morning spent in the laboratory and an afternoon in his well-equipped library, he has furthered the two great interests of his life, the anatomy of the lung and medical history. In the former, his researches of a period of almost a half century were consolidated in his monograph "The Lung," published in 1937. This book had been so eagerly awaited that a first printing of 1,500 copies was exhausted in two weeks. This book he wisely regarded as not the last word on the subject but as a foundation upon which others might build. This work he would leave as his monument.

Dr. Miller's interest in the cultural side of medicine led to the assembling at his home of a library, unusually rich in the classical anatomical works, in medical biography and history and in general medicine. During the past thirty years there has been held in this library a bi-weekly seminar in the history of medicine. This was at first composed of a select group of interested students, and later, after his retirement from active teaching, of colleagues of the medical faculty. Numerous published contributions to the history of medicine have resulted from this seminar. In later years Dr. Miller's own interest has been centered largely in early medical conditions in Wisconsin. Through his efforts a memorial tablet to William Beaumont was set up at Prairie du Chien, where so many of the observations on Alexis St. Martin were made.

It is, however, not only as a skilled, patient and persistent investigator and as cultivator of the historical field that Dr. Miller is to be remembered. He was also a teacher of distinction. In his earlier years at Wisconsin he came into intimate contact with the premedical students with whom he worked. To them he taught histology, neurology, comparative anatomy, topographical anatomy and embryology. Given this extended association with members of small classes, his influence on his students was easily greater than that of any other faculty member. His high ideals, his scientific curiosity and his beautiful, precise laboratory technique were a living example and inspiration to them. That he was a strict taskmaster in requiring of his students similarly honest, clean-cut, independent work did not prevent but rather resulted in a devoted following of young medical men who main-