CHAPTER I

GENERAL BIOLOGICAL INTRODUCTION

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I. INTRODUCTORY

Sex is a nearly universal attribute of living things as determined by various criteria of which amphimixis, or union of gametes, is the most general. It differs from other universal organic functions such as metabolism, or irritability, in requiring two individuals for its complete expression. This antithesis between sex and other bodily expressions is popularly expressed in the saying that "the driving forces of mankind are hunger and love": by "hunger" meaning the control of all those functions concerned in the preservation of the individual, and by "love" meaning the exercise of those functions concerned in the preservation of the race through reproduction.

A brief definition of the biological conception of sex is impossible. As a matter of fact we do not know "sex" but only sexes. There is no such biological entity as sex. What exists in nature is a dimorphism within species into male and female individuals, which differ with respect to contrasting characters, for each of which in any given species we recognize a male form and a female form, whether these characters be classed as of the biological, or psychological, or social orders. Sex is not a force that produces these contrasts; it is merely a name for our total impression of the differences. It is difficult to divest ourselves of the pre-scientific anthropomorphism which assigned phenomena to the control of personal agencies, and we have been particularly slow in the field of the scientific study of sex-characteristics in divesting ourselves not only of the terminology but also of the influence of such ideas.

In the strictly historical sense of the words a male is to be defined as an individual that produces spermatozoa; and a female one that produces ova; or individuals at least bearing the characters usually associated with these functions. But, by extension, these terms have come to be applied also to the gametes themselves, to the determiners of male and female characteristics, and to the zygote destined to produce a male or a female.

Intersexual conditions of various kinds introduce other difficulties of terminology and even lead to absolute contradictions in terms, as in the case of animals that are of one sex with reference to their genetic determiners, but in structure and function of the other, as in cases of so-called sex inversion.

Such difficulties can hardly be completely avoided, and it appears inadvisable to attempt to restrict the use of the terms male and female to their historical simplicity of meaning, as Link (1929) has suggested. On the other hand it is necessary to distinguish carefully the radical difference between the qualities of gametes which fit them for the fundamental function of amphimixis, and the qualities of the differentiated individuals which bear the two kinds of gametes.

Sex of the gametes and sex in bodily structure or expression are two radically different things. The failure to recognize this elementary principle is responsible for much unsound generalization. The differentiation of gametes is with reference to the function of amphimixis; the sexual differentiation of somatic parts on the other hand consists, *primarily*, of adaptations of the soma, carrier of the gametes, to ensure normal functioning of the gametes. It is therefore wrong to regard sex differences in general, including gametic and somatic, as parts of a single scale of phenomena; for instance, as Castle (1930) expresses it, "plus and minus variations in a single scale of gradations." Such a conception, expressed in terms of plus and minus either with reference to some unknown quantity, or to rates of metabolism, inevitably leads to paradoxes.

Quite different points of view concerning sex manifestations have been presented by students of protista and of the lower plants from those current among zoologists and physicians and the laity, who derive their ideas of sex from higher animals for the most part. This is because the former deal largely with sex of gametes, and the latter with somatic sex characters. When the zoologist or the physician speaks of sex in a general sense he almost invariably has in mind the sex behavior, structures and manifestations of persons, carriers of gametes, and not of the gametes themselves. When on the other hand students of the simplest organisms speak of sex they generally have in mind the structure and behavior of gametes, and not of persons, which either do not exist as distinct from gametes in these organisms, or else exhibit slight sex differentiation, or none at all.

The evolutionary history of the gametes, as inferred from taxonomic position, is exceedingly simple. Starting out from gametes, alike so far as microscopical structure is concerned, but which are postulated as physiologically different, dimorphism of gametes is soon attained, one larger and less motile and the other smaller and more motile. Evolution from

this condition to that of the immotile female gamete or ovum and the typical flagellated spermatozoon is realized in the Protista. Throughout the whole range of the Metazoa there is no further sexual evolution of the gametes. It is true that the ova and spermatozoa of every animal class, order, etc., down presumably to species, are morphologically distinguishable, and that each is specific in a genetic sense; but with reference to their qualities as gametes no evolution is traceable in the metazoan series.

This presents a most amazing contrast to the sexual evolution of the individuals that carry the gametes. There is no chapter in evolution more varied than the evolution of the biological, psychological and social characters of the individuals that bear ova on the one hand (females) and spermatozoa on the other (males). On the biological level organs are evolved for the reception and storage of the gametes, for their transfer from male to female, for protecting the development of the fertilized ovum without or within the body, and for the care of helpless young. These are almost endlessly varied in the different animal groups. Parallel with these goes the evolution of appropriate forms of behavior of the sexes with reference to mating, nesting and care of young; and, in association, the evolution of social relations in the various animal groups. Sex becomes a dominating factor in psychological and social life.

The primary function of somatic sexual differentiation, that of ensuring the union of gametes, may thus become more or less submerged by secondary conditions, which become endlessly elaborated in ways sometimes difficult to interpret in a functional sense. It is as though variety and beauty had become ends in themselves in the evolution of secondary sex characters, as exemplified in the plumage of birds, and in the strife and amenities of human social relations.

One of the most interesting and promising lines of experimental biological investigations of the present century has been in the biology of sex. It has been discovered that sex characters in general are subject to certain simple mechanisms of control that operate throughout the life history, and which determine whether male or female characters shall develop in the individual. In species where sex differences are few and simple such differences may be controlled by a single very simple mechanism; in other species, where differences between the sexes are many and complex, the same simple mechanism *may* nevertheless control them all, or additional coöperating means of control may also appear. But in any case the mechanisms of control are exceedingly simple compared with the sex machinery itself. This simplicity of control enables the experimenter to produce far reaching results.

This book deals predominantly with a method of control of sex characters, which is especially characteristic of vertebrates including man, mediated by hormones circulating in the blood. Of these, the specific internal secretion of the testis, or male sex hormone, and the specific internal secretion of the cortex of the ovary, or female sex hormone, are the most important, and probably occur in all vertebrates.

The great advances that have been made and consolidated, especially in the chemistry and chemical relationships of the male and female sex hormones (Chapters XII and XIII), and in the study of relations between gonads and hypophysis and of the gonadotropic hormones (Chapters XVI, XVII and XVIII) have served to complicate rather than to simplify our conceptions of the mechanisms of control of sex characters. Such advances have emphasized peculiarities of different species in certain important respects with reference to control of sex characters and functions. Under these circumstances it seems inadvisable to include in a biological introduction the newer chemical terminology. The old terms male and female sex hormones carry the implication of control of sex characters, and represent conceptions that would still be valid whatever the outcome of further chemical and physiological analysis. The terms male and female sex hormones are used to indicate substances that are functional within the organism, and also in order to avoid unsolved questions of identification with specific chemical substances isolated or synthesized.

II. MECHANISMS OF CONTROL OF SEX CHARACTERS

In this book sexual differentiation is discussed from the analytic viewpoint. On the other hand it is obvious that sexual differentiation as a whole has a primary function with reference to reproduction, and thus in relation to social processes and to organic evolution; in these vast movements sex is an elementary phenomenon, in which the essential unity of sexual differentiation and of the sex drive is to be emphasized: the fitness of the sexes for one another in the perpetuation of the species. This viewpoint is essential for consideration of the analytic results, and as a matter of fact is in the background of all such studies. Placing it in the foreground occasionally has the advantage of warning us of the possibilities of attainment of the functions of sexual differentiation by different mechanisms and of aiding us to avoid premature generalization. Each species has something special to tell us, and contains a warning against the expectation of discovering some single principle of explanation.

Sex characters appear in the course of the individual life history, considered as beginning with the fertilized ovum which usually has no sex

characters of its own.[1] Sex characters thus appear, as do other characters, in a certain order of succession. The study of their experimental control therefore belongs to the more general field of the physiology of development.

It follows of necessity that there is a period at the beginning of development before any sex characters have appeared when the future sex of the embryo is indistinguishable save by reference to chromosome composition (see Chapters II and III). This has been called the period of sexual indifference. It may be of longer or of shorter duration depending on the degree of sexual precocity of the species. It was formerly believed that all embryos of a species were alike with reference to the ultimate determination of their sex during this period, and that some condition in the environment, as for example, in the case of mammals better or poorer nutrition of the mother, determined the sex. But it has been shown that nuclear determiners exist during this period, in most groups of animals at least, which act so as to direct the development of characters either in the male or the female direction. The nature of this mechanism is discussed in the next chapter; here we need only note that the determining conditions are established at fertilization in the union of the gametes. This is not inconsistent with the conception of external influences acting on sex characters; but it would imply an intermediary of internal regulatory mechanisms between the environment and the affected sex characters and functions.

The term sex determination is usually used to designate the establishment of internal conditions leading to the development of one or the other set of sex characters in the embryo and adult. The term thus applies to the sex of the organism as a whole; and, when this is unequivocal, as is usually the case, its use raises no difficulties. But it has been shown that sex determination is not irreversible predestination; and in cases where the original determination is overridden, either in certain organs, parts, or characters, as is often the case, or even in all, which occasionally happens in nature or may be produced experimentally, either intersexes occur or complete reversal of the "determined" sex of the individual results.

Such facts and others have led geneticists to the conception that primary determiners for both sets of sex-characters are present in each zygote, but with a quantitative superiority established at fertilization of one kind over the other. From this results the principle of balance of sex determiners,

[1] In certain organisms the female-producing egg and the male-producing egg may be distinguished by size, as for instance in Phylloxera and in Dinophilus; but such conditions are rare.

which has been worked out in somewhat different ways by Goldschmidt and Bridges (see Chapter II).

Intersexual conditions may result either from an upsetting of the balance of the sex determiners by hybridization or by nuclear abnormalities; or again, given a normal balance of determiners, by conditions arising in the course of development. Thus, for instance, an embryo calf determined as female becomes intersexual with a curious intermixture of male and female characters, if blood of a male calf of the same age mixes with its own blood during critical stages of sexual development. This happens when twinned with a male calf *in utero* owing to the anastomosis of placental blood vessels that usually occurs; the resulting intersexual female has long been known under the name of free-martin (cf. Chap. III).

It is clear that we must make a radical distinction between sex determination and sex differentiation. In most cases the factors of sex determination are chromosomal, and subject to the usual laws of Mendelian inheritance. The phenomena of the sex ratios of populations, and of sex linked inheritance are readily explained on this basis.

In the phenomena of sex differentiation on the other hand the matter is more complicated. We have two major mechanisms in the animal kingdom. In the case of the first, best known in insects, and especially in the fruit fly Drosophila, the mechanism of sex determination is believed to act also as the mechanism of sex differentiation throughout the life history; there is apparently a complete or almost complete absence of control of sex characters by any extra-nuclear mechanism; and as a result any abnormality in the sex chromosome mechanism that occurs during the life history is transmitted to all derivative cell areas thus resulting in sex mosaics or gynandromorphs (cf. Chap. IV). In the case of the second, best known in the higher vertebrates, the mechanism of sex differentiation is taken over by extracellular agents, the male and the female hormones; but it is necessary to postulate that the endocrine cells producing them are first determined by the nuclear mechanism (see Chap. VI).

Castration in insects is usually without effect on the differentiation of sex characters; but in the higher vertebrates sex differentiation and sex functions are profoundly affected by this operation. If the sex hormones have taken over the entire business of sex differentiation in the latter, it would be expected that male and female castrates would be alike, subject to irreversible conditions before the operation. This extreme position has been taken by Lipschutz (1924) in his theory of the asexuality of the embryonic soma, and by Zawadowsky (1926) in his theory of equipotentiality. One cannot, however, entirely rule out nuclear control, at least in certain minor characters, such as sexual differences in the plumage of certain birds

(e.g. the English sparrow, and relative width of bars in barred Plymouth Rock fowl) or the spurs in fowl (Kozelka 1932). But in spite of such exceptions the general rule stands that secretions of the gonads exert primary control of the differentiation of sex characters in the higher vertebrates, including the secondary hormonal and nervous mechanisms.

In insects the differentiated asexual condition necessarily remains unknown, for it has not been possible to eliminate sex genes entirely; but in vertebrates the asexual condition can be fully explored in castrates of both sexes, subject only to the experimental condition of time of operation, a purely technical difficulty easily overcome in amphibia, though rather difficult to realize in birds and mammals. The vertebrates therefore offer great advantages in experimental work in the biology of sex.

Inasmuch as the entire set of sex characters in any individual constitutes one action system, everything must be subordinate to one set of controls. The greatest possible simplicity is arrived at in insects where one set of controls, male determining and female determining genes in proper balance, is provided for the entire life history. In vertebrates greater lability is provided by the second pair of controls, the male and female hormones, dependent for their origin on the first, and regulated in their operation by still higher controls, both endocrine and nervous. But whether genes alone act, or sex hormones dependent for their origin on genes, each agent controls functions of a degree of diversity that is limited only by the possibilities of the biological system. The matter cannot be conceived in physico-chemical, but only in biological terms; for even if we knew the entire physico-chemical set-up for the development of each sex character, it would be impossible to explain the harmonious coördination of the results in terms of the physical sciences.

III. SEX DIFFERENTIATION

The appearance of sex characters, as of other characters, in the life history is based upon the principles of physiology of development. The characters themselves are accordingly subject, not only in their quantitative expression, but as regards their male or female nature also, to conditions arising during the course of development, even though the genetic determiners of such characters, as of other characters, are present in the zygotes. Determiners are not characters; and in general there is no differentiation of sex characters in the life history until after the fundamental segregates and primordia of the organs and regions concerned arise in the embryo.

In the following discussion we shall restrict ourselves to the sex hormones as controllers of sex characters. The experimental results to be described in succeeding chapters show that the general possibilities of sexual differ-

entiation, and, frequently at least, even the most special, are the same for all individuals, when the entire life history is taken into account, whether the original determination be male or female. This means that the same segregates and organ primordia are formed in all life histories, and that sex differentiation depends upon alternate and contrasting forms of behavior of the same things. Thus primordial germ cells of a given embryo may under experimental conditions be caused to produce either ova or spermatozoa; or feather germs of a fowl may be caused to produce feathers of either male or female type at will in an individual of either sex. Such examples might be multiplied; but the fact that complete sex inversion, i.e., the production of a functional male from a genetically determined female, or *vice versa*, has been experimentally realized in such diverse groups as insects and amphibia, and has been closely approximated in birds, is the definitive proof that the possibilities of either form of sex differentiation inhere in all developmental histories, whatever the original determination.

In mammals and man complete control of the differentiation of sex characters has not been attained. It has so far been impossible to produce the experimental conditions needed for a complete testing of the generalization in these forms. There are, however, many indications in abnormal sex conditions that make the extension of the generalization to mammals and man appear reasonable.

Every zygote is thus potentially hermaphroditic in the sense that it is capable of giving rise to characters of either sex, or, subject to conditions of determiners, to characters of both sexes, i.e., to individuals that are actual gynandromorphs or intersexes. Conditions of determiners fixed for functional hermaphroditism have, as is well known, evolved separately in various branches of the animal kingdom.

In the development of every individual, therefore, there occurs, at some time at least, the rudiments of all sex characters, whether male or female. Each such rudiment is capable of either the male or female form of development depending upon the nature of the determiner or mechanism of control within the individual. All sex characters thus have their homologues on a basis of community of origin in individuals of the opposite sex.

The conception of homologous, i.e., paired and contrasting, sex characters requires further definition. Everyone can furnish a whole host of illustrations that apply. Confusion would arise only if the pairing of characters were made on a functional instead of an embryological basis, i.e., if the principle of analogy rather than the principle of homology were applied. If, for instance the male gonoduct (vas deferens) were paired with the female gonoduct (oviduct), we would be following the principle of analogy; the *homologues* of the vasa deferentia are, in the female, the ducts of Gärtner;

and the homologues of the oviducts and uterus are found in the male in the hydatids and uterus masculinus.

As there are two sets of sex characters, so there are two sex hormones, the male hormone controlling the "dependent" male characters, and the female determining the "dependent" female characters. The primary sources[2] of these hormones are the testis and the cortex of the ovary respectively, as shown by the experiments recorded in Chapters VII and VIII. These hormones have been isolated in the form of closely related pure compounds of relatively simple chemical constitution (see Chapters XII, XIII and XV). Zondek believes that "the specific chemical characterization is solely due to a quantitative regulation of the general process of metabolism" and that "the male hormone represents an intermediate product in the formation of the female one." The regulation of metabolism involved in the preservation of functions peculiar to the actual sex can at present be left only to the imagination. The greatest triumphs of biochemistry commonly raise such difficult questions. However this may be, there is reason to believe that the same compounds may be the effective agents of sex differentiation in all classes of vertebrates; it has at any rate been conclusively shown that sex hormones of human origin may control the differentiation of sex characters in fowl. The isolation of these substances has given an immense impetus to research on the experimental control of sex characters.

Two theoretical possibilities exist as to the mode of operation of the sex hormones with reference to the differentiation of sex characters, viz.: (1) The primordium of any pair of sex characters might be induced to develop in the male direction by the male hormone, and in the female direction by the female hormone, each primordium being responsive to both hormones but in opposite ways. (2) Of all the sex primordia some might be responsive only to the male hormone, others only to the female hormone. In such a case only the male or female form of any pair of sex characters would be a "conditioned" sex character, and the contrasting sex character would be "unconditioned" in the sense of being the same as in the castrate.

In the first case, if both sex hormones were present simultaneously, a

[2] The fact that female sex hormone (folliculin or estrogen) is found in the urine of humans in both sexes and at all ages, and that it can be shown not to be derived from food, indicates extra-gonadal sources, for the most part unknown, though the placenta furnishes a rich supply (Chapters X and XIII). In the case of the male hormone it is found that colts and geldings excrete only about one third of one per cent of the quantity excreted by stallions in the urine (Chap. XII). The functional testis is extraordinarily rich in male hormone. While it seems certain that both male and female sex hormones are produced from extra-gonadal sources, experiments demonstrate that only sub-threshold amounts can be present after castration (Zondek, 1934).

condition readily produced experimentally, there should be an "antagonism" of the two hormones, each striving, so to speak, to control the development of the sex character in question. Such an antagonism was in fact postulated by earlier workers in this field, e.g., Steinach (cf. Steinach and Kun, 1926); but more recent work, especially that of Moore (1931, 1932), seems to remove the necessity of assuming any antagonism in the simultaneous action of the two hormones, by showing that each operates independently within its own field. Other experiments furnish evidence tending in the same direction, and support the conclusion that of any pair of anatomical sex characters only one is conditioned, the other being an unconditioned sex character (cf. M. M. Zawadowsky, 1922).

The unconditioned sex character is usually to be classed among the so-called rudimentary structures, as for instance the mammary glands of the male, or the homologues of the genital ducts in the sex in which they are not functional. This is, however, by no means always the case. The best example of the latter condition is the plumage of most breeds of fowls. The form of plumage found in the male is not modified by castration except in a slight quantitative sense; the castrated female, on the other hand, takes on, after moulting and replacement of feathers, the capon, i.e., approximately the male, type of plumage. The plumage of the males of such breeds is thus independent of the male hormone. But the injection of female hormone into a castrate of either sex produces female plumage. The plumage of the male is a most pronounced sex character nevertheless, though it is to be regarded as racial or asexual in its origin, whereas the plumage of the female is hormone-conditioned.

There are, however, certain breeds of fowl, of which the Sebright bantam is the best known, in which the males are feathered like the females, and in which complete castration of either sex leads to the development of a male-type or capon plumage. The plumage of the normal male in this case is conditioned also by the testis hormone, as shown especially by Roxas' (1926) experiments; but the plumage has ceased to be a sex character inasmuch as there is no distinction in respect to plumage between males and females (Chap. V).

Certain sex characters appear to be quantitative variations of a common base rather than sharply alternative conditions. This is especially striking with reference to sex behavior; whether the distinction between conditioned and unconditioned sex characters has any real application in such cases raises some interesting questions (Chap. XXIII).

The morphological sex characters of any given individual may thus be divided on the basis of mechanism of control into conditioned and unconditioned characters. In the male of the brown leghorn fowl for instance the

conditioned characters are the comb, wattles, ear lobes, vasa deferentia and sex behavior; the unconditioned characters are the plumage and spurs which are among the most striking male sex characters of the breed. In the female of the same breed, the plumage, spur rudiments, oviduct and behavior are conditioned sex characters; the head furnishings are somewhat doubtful, and it is difficult to point to any undoubted sex characters, except the rudimentary ones, which are wholly unconditioned.

Another way of stating the same principle would be that all sex primordia or rudiments and, possibly, all sex tendencies, assumed to be common to the life-history of both male and female individuals of a species, may be divided in two classes, those that respond positively to the female hormone, and those responsive to the male hormone, each class being uninfluenced by the opposite hormone. In each pair of contrasting sex characters one is thus a conditioned character, whether by the male or the female sex hormone, and the other an unconditioned character.

In the development of the normal individual in the higher vertebrates one kind of hormone is dominant. This is assured in the male by the complete absence in the testis of any rudiment of the ovarian cortex, which is the specific source of the female hormone; but the female possesses in the medulla of the ovary the homologue of the testis endocrines, apparently usually in a functionless state. In the female therefore complete absence of male hormone is not assured with the same degree of certainty, as absence of female hormone is assured in the male. The female is therefore more liable to a certain degree of intersexuality in its development. However, as this is not marked in normal development, it must be assumed that in the critical stages of sex differentiation of the female the medulla of the ovary is actually functionless. Nevertheless the possibility of intersexual development is actually inherent in the female of higher vertebrates due to the presence of the male endocrine component in the ovary (Chap. IV).

Recent researches have also demonstrated that the gonadal endocrines are not autonomous systems; in fact that their functional regulation lies entirely outside, through influences that are exerted partly by other endocrines especially the hypophysis, by nervous effects, and perhaps also by more general organismic influences. In the female of mammals supplementary mechanisms of control of certain reproductive functions or cycles also have been evolved. The physiology of the corpus luteum has proved especially significant in this respect. These subjects are treated in Chapters VIII and XV.

Those who are concerned with human sex manifestations, whether as parents, physicians, educators or legislators would do well to study and think over the results of modern researches in the biology of sex, which are

not yet generally appreciated or properly evaluated. On the one hand there is the conservative tendency to think in terms of outworn ideas, and on the other to overestimate the practical value of some new discovery or point of view; both extremes have harmful results (Chap. XXIV). One of the aims of the present book is to present the most important results in their most recent form by the hands of the investigators themselves, so that there may be available an authoritative work of reference to the present state of researches carried out in so many parts of the world and published in numerous sources inaccessible to any but the specialist. In a subject that is advancing so rapidly no finality can be claimed for many of the subjects presented; the results should therefore be accepted in a critical spirit.

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