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THE DIFFERENTIATION AND ABERRATIONS OF SEX CHARACTERISTICS*

BY

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At first thought the choice of a subject on which to address an assembly comprising students passing through different stages of their careers seems difficult, for the topic should be one with which all are to some extent familiar. But the difficulty is not real, since every scientific aspect of medicine fulfils this requirement, and it is only in the clinical application of scientific knowledge that the final-year student is in advance of the rest.

For to-day's discourse I have selected "Sex" as my theme. With this your biological (including physiological) training should have been concerned; and in your clinical studies you will frequently be called upon to unravel the complexities which surround it, for just as we recognize normal sex-linked characteristics distinguishing the sexes, so we acknowledge hereditary sex-linked disorders, of which, perhaps, haemophilia is the best known.

It must frankly be admitted that the subject is, in the present state of our knowledge, of considerable intricacy, and is one which it is not easy to discuss lucidly in the time at our disposal. Sex in man is, however, of so much sociological, legal, and medical importance, that a brief survey of certain basic considerations may be of interest and may stimulate thought.

In the present study our objective is, then, to bring our knowledge of the biology of sex to a focus, as definite as may be, in the human subject.

NATURE OF SEX

The term "Sex" is derived from the Latin word *sexus*, itself a derivative of the root of the verb *secare* (to divide). Cicero, Livy, and other classical writers who used the word *sexus* could have had no inkling of the aptness of the term in relation to modern cytology; they used it merely to divide the members of any given species into two groups—male and female. It must not be supposed, however, that the ancients, especially the Greeks and Romans, were ignorant of the anatomy and physiology of the genitalia and of gross sexual anomalies such as hermaphroditism; they were not, as the works of Aristotle prove and as the word "hermaphroditism"† itself reveals.² Moreover, they were well versed in probably all of the psychical sex aberrations which are known to us

to-day. Naturally, before the microscope came into use there could be no recognition of the nuclear processes which lead to cell division, of which we now have some information in relation to the mechanism of sex differentiation, and to this I shall refer again presently.

Yet, with all our biological knowledge of the processes of reproduction, it is difficult to perceive the meaning or significance of sex. Professor Crew, who has done so much to illuminate the subject of genetics,⁸ recently declared: "On this matter I must perforce be silent, as the biologist no longer is concerned with the search for an understanding of the nature of sex itself. . . . The more one knows of sexual differences, the less one seems to know of sex itself."⁹ He goes on to say: "Sex can only be recognized by bringing it into essential relation with reproduction. Thus sex becomes the mechanism which Nature uses for the preservation of the species and the continuance of the race." But, he adds, the evidence of a purpose in sex is not a contribution of biology; and he reminds us that reproduction may be asexual.

Strictly speaking, we are not concerned in the present study with asexual reproduction, which is a natural mode of reproduction in protozoa;* nor are we directly interested in the phenomenon of parthenogenesis—that is, the segmentation and development of the asexually fertilized ovum—which occurs normally in some metazoa (for example, *Hymenoptera*), or may be artificially produced in the eggs of the sea-urchin, for instance, by simple chemical and physical stimuli.† Still, it seems difficult to dissociate entirely such mechanisms from the processes underlying sexual fertilization, which, moreover, is to some extent at least responsible for sex differentiation; indeed, we cannot afford to pass over any fact of reproductive method in our search for the truth. It may, indeed, well be argued from the phenomenon of parthenogenesis, that femaleness (with eggs) is the essential instrument of reproduction, and that maleness (with sperms) is an added factor. Since, however, evolution has not yet reached

* It is, however, known that in many forms of protozoa fission alternates with conjugation, sometimes with the common encystment of two individuals; and the nuclear changes which follow have been compared with those occurring with sexual fertilization in metazoa.

† Parthenogenesis with mitosis has been observed in protozoa when a period of reproductive depression follows a long series of generations by fission. Parthenogenetic development is, however, a constant and normal process in some insects, especially the *Hymenoptera*—for example, the honey-bee (*Apis mellifica*). In these the resulting generation is composed of one sex only—namely, of males (drones). On the other hand, the sexually fertilized eggs give rise to females (workers and queens); abnormally, but very rarely, a few males develop along with females. What has been called "accidental"—that is, occasional—parthenogenesis has been noted in the silkworm moth (*Bombyx*) and the gipsy moth (*Lymantria*), when both males and females develop from the eggs. With artificial parthenogenesis in the sea-urchin and the frog it has been noted that males are usually produced.

* A lecture, with lantern illustrations, delivered before the Medical Students' Society, Manchester University, on February 5th, 1935.

† Hermaphroditos—the son of Hermes (the messenger of the Gods) and Aphrodite (Venus)—was so beloved by the nymph of the well Salmacis that she begged the Gods to unite them for ever. The Gods answered her prayer very literally. The result was no doubt quoted by the ancient Greeks as a typical example of the divine origin of pathological conditions. Hippocrates, commenting on this belief, expresses his agreement in a general way, but in his scientific wisdom adds: "Each condition has its natural principle, and none exists without its natural cause."

finality in the matter of sex differentiation, and bisexuality, with structural evidence of both sexes in each individual, exists in the highest mammals, the whole truth can hardly be more than foreshadowed.

Before we pass on to consider the cause, or causes, of sex differentiation in metazoa over which hangs the paradox of bisexuality, I would like for a moment to refer to what is known as the monoecious state as opposed to the dioecious, for this is an interesting and curious bisexual phenomenon.

In the monoecious condition, which may be observed in many of the invertebrates, we see what may be described as true hermaphroditism; that is to say, fully developed and functional sex organs of both sexes are found in each individual: in them bisexuality is equally balanced. In some (for example, *Distomum*), not only are sex glands (gonads) of both sexes active in each specimen, but self-fertilization is also performed. A similar consummation happens at times in others (for instance, *Ciona*), in which, however, reciprocal cross-fertilization also occurs. Others, again (as *Lumbrieus*), are capable of cross-fertilization only. In these creatures it is hardly possible to describe a male and a female sex.

Higher in the scale of sexual evolution we encounter the dioecious state in which, although there is still bisexuality, sex differentiation in one direction or the other is much further advanced in the fully developed animal, and the bisexual tendency is unequally balanced, ovaries or testes being associated with evidence of bisexuality elsewhere. It is possible in these circumstances to speak of a male and a female sex. The differentiation is both quantitative and qualitative. On the one hand, there is a certain general preponderance of maleness or femaleness, as the case may be; and, on the other, there is a qualitative difference in the nature of the sex cell (spermatozoon or ovum) produced by the gonads.

DIFFERENTIATION OF SEX

As already indicated, in the case of asexual reproduction nuclear division—either by simple fission (amitosis) or by mitosis with redistribution of the pigmented nuclear filaments (chromosomes)—follows intrinsic (physical or chemical) stimuli. When sexual reproduction, a complementary mechanism, became imposed, as it were, on the simpler process, a variety of complications were immediately introduced. The explanation of this imposition is the meaning of sex.

I need not here discuss the simple progression in the number of cells produced by mitotic division during somatic growth, or the more complicated method whereby what is called maturation of the sex cells to form the male and female gametes is effected. It is sufficient to recall that in the latter mechanism the original number of chromosomes common to the somatic and to the oögonial and spermatogonial cells is reduced to half, that on fertilization the normal number may be re-established in the zygote. It is, moreover, essential to the subject under discussion to remember that there are chromosomes of two kinds—namely, autosomes, chiefly responsible for general somatic characters, and sex chromosomes, which are usually two in number, and which carry sex-linked genes. It is these chromosomes in the gametes which have a directing sex-influence in the zygote.

In the monoecious state, to which reference has just been made, the sex chromosomes, male and female, must be similar, or equally sex-balanced, in character. But in the dioecious state, in which males and females are formed, we have knowledge of physical, and even numerical, differences in the sex chromosomes. It has been shown by Morgan and others that in the fly, *Drosophila*, there are two similar female sex chromosomes, which are known as X-chromosomes; and that these

differ in appearance—that is, in shape—from one of the two male sex chromosomes, which is called the Y-chromosome, the other being an X-chromosome like those in the female sex cell. Union of a male gamete containing the sex chromosome Y with a female gamete (sex chromosome X) results in the formation of a male (XY), while the conjunction of a male gamete containing the sex chromosome X with a female gamete (sex chromosome X) leads to the production of a female (XX).

This is the normal mechanism so far as the sex chromosomes of the fruit-fly (*Drosophila melanogaster*) are concerned. It is, however, interesting to note that in the gipsy moth (*Lymantria*)—in connexion with which the work of Goldschmidt¹¹ is classical—an opposite state of affairs in regard to the sex chromosomes obtains: the ovum has an XY nuclear sex constitution, and the sperm an XX. The X-chromosome is here the male-influencing factor, and the Y-chromosome the female. This means that there is a variable sex chromosome, which we call Y, but that this, as such, is not sex-specific.

Furthermore, it seems that the degree of maleness or femaleness in any individual depends on the numerical relationship of the sex chromosomes to the autosomes. Of this one illustration will suffice. It has been found that in *Drosophila* an additional set of autosomes with the normal number of female sex chromosomes (XX) leads to a state of intersexuality. It is therefore presumed that the autosomes themselves are male-influencing. There are many other variations in chromosomal constitution affecting the sexual make-up of the progeny, which I cannot now discuss.

Here we may pause for a moment to seek an answer to the question "Why has sexual reproduction been imposed on asexual mechanisms?" in order to discover the meaning of sex. Much thought has been given to this matter, and while many plausible arguments and feasible explanations of a general character have presented themselves, most of them deal with incidentals, rather than with the essentials of evolution, which, presumably, are variation and mutation, with the production of new species having the desirable qualities of the old. Apart from the changes due to the known effects of environment, especially in the lower orders, variation must be greatly facilitated by the commingling of sex chromosomes and sex-linked genes. If this be so, it would appear that sexual reproduction is not only for the inevitable, but temporary, perpetuation of the species, but also for the production of varieties and in time of new species. If this be the purpose of sex it is surely a biological issue.

It might be argued against this view that, with cross-fertilization between different species of the same families, such, for example, as the *equidae* and the *carnivora*, the progeny, if any, is often infertile, as in the cases of the mule and the tiger-lion. Still it is now known that infertility in these circumstances is relative to the taxonomic distance between the species concerned—the nearer, the less chance there is of the offspring being infertile. On the other hand, it must not be forgotten that too great a degree of individuation, which may, perhaps, in this connexion be defined as *fixed characterization*, in the lower animals may lead to a decrease in fertility, as Herbert Spencer¹⁵ has stated.

To return, is sex-chromosomal constitution and distribution the beginning and the end of the differentiation of sex in dioecious creatures of which Man is one? It is not; although the brilliant work of modern cytologists in regard to sex-chromosomal factors has undoubtedly tended to overshadow other considerations.

In the first place, behind the variation in sex chromosomes there must be some hereditary influence, for the chromosomes carry sex-linked genes, among which are not

only those concerned with physical characteristics, but also those responsible for the frequency of occurrence of the sexes, fertility, and many other phenomena. Although in the long run in Man the production of males and females is probably equal, and although fertility and infertility may be due to other acquired factors, heredity acting in accordance with Mendelian principles cannot be left out of account.

In the second place, while these presiding agents—heredity and chromosomal factors—inaugurate the sex-direction of the larva or the early embryo, their influence, although in insects it may be, is not necessarily sex-determining, owing to the persistence in evolution of bisexuality. Larvae may be affected by the food supply (as are *Hymenoptera*), or by other environmental circumstances (as in the case of *Bonellia*), to so great an extent that the final sex-determination may be the result of these alone.

Again, to take the case of the human embryo, for six or eight weeks following conception no indication can be recognized histologically as to whether testes with male ducts or ovaries with female ducts will be developed; and in some of the lower mammals sex is not manifest even at birth.

Putting aside environmental factors, which are practically ruled-out in the higher mammals by intrauterine life, let us consider the intrinsic mechanism which eventually confirms and gives effect to the sex-predisposition of the embryo, and without the decisive action of which many sex aberrations arise, even though the chromosomal constitution be normal, owing to the ever-present complication of bisexuality. There can be no doubt, I think, that the determination of the final sex state, at any rate in the higher vertebrates, is due to the influence of hormones.

It is necessary to be quite clear what we mean by this. Reference has been made to the directing factors of heredity and of the chromosomal constitution of the fertilized ovum—the zygote—and these influences, as I have long insisted, are carried to the incertory organs, especially to the suprarenal cortices and the pars anterior of the pituitary, and eventually to the developing gonads, which remain indifferent for a short or for a longer time. For this reason I have always described the organs of internal secretion as being among the primary characteristics of sex; and, indeed, over twenty years ago¹ I suggested that instead of the older view, that the physical and mental attributes of a woman were dependent on the ovaries alone (*Propter ovarium solum, mulier est quod est*), it was more in accordance with facts to say "*Propter secretiones internas totas, mulier est quod est*."

It might, however, be more accurate to say that a woman is a woman because she has not been made a man during embryonic life by masculinity-producing hormones. It is true that for the present but few direct physiological facts are known in regard to the influences of the other organs of internal secretion which have been mentioned, although much pathological evidence, to which I shall refer, is well authenticated. In the case of the suprarenal cortices, however, certain normal phenomena of importance have recently been described. Broster and Vines² have found that certain fuchsinophil cells in the zona reticularis and zona fasciculata influence the development of masculinity, and that in the male human embryo these cells are demonstrable from the ninth to the nineteenth week of life, while in the female embryo they appear in the eleventh and disappear in the fourteenth week. Again, Noble Chamberlain³ has made the following interesting observations. In the suprarenal cortex of the buck rabbit he obtained an average percentage of 7.4 of cholesterol, and a cholesterol ratio (amount in milligrams of cholesterol in

both suprarenals divided by the body weight in kilograms) of 16. In non-pregnant does the average percentage was 12.3 of cholesterol—a difference from that of the male of 66 per cent.—with a cholesterol ratio of 23. In pregnant does this remarkable difference disappears. The average percentage of cholesterol in other organs is practically the same in the two sexes.

That sex-determining hormones circulate in the blood of the embryo, and that those producing masculinity can override the weaker—perhaps, negative*—factors associated with femininity is demonstrated by a natural phenomenon—an experiment of Nature—to which attention has been directed by Lillie.¹² This investigator found that the so-called "free-martin" in cattle is a female twin, whose characteristics have been so altered in embryonic life by the sex hormones of a male twin that partial hermaphroditism is produced. In such cases Lillie found a definite anastomosis between the arterial and venous vessels in the chorion of the binovular twins. On the other hand, he showed that, if there be no anastomosis between the chorionic vessels, a female twin to a bull calf is not a "free-martin," but a fertile cow. We know of no similar observation in Man; but it can hardly be doubted that this sequence of events may sometimes occur in the human subject, although it is not the explanation of most cases of partial hermaphroditism.

Results of Sex-differentiation

From what has been said it will be clear that there are time stages as well as distribution phases in the differentiation of sex; and it is probable that but for the overriding by the dominant male hormones the recessive condition of femininity would obtain.* In this connexion the determination of the nature of the gonad itself is of interest, for it is a somewhat late manifestation, as we have seen, and is dependent on the sex character of the suprarenal cortex and the other sex-influencing endocrine organs. This last fact, especially, makes it difficult to divide the features of sex into primary and secondary characteristics only. The question has been well discussed by Lipschütz.¹³

In the matter of time during the development of the vertebrate embryo the endocrine glands—apart from the gonads—stand first, and are therefore primary. Next, and as an isolated event, the nature of the sex gland becomes determined, and its sex-influencing and sex-controlling functions become linked to those of the other incertory organs to form a genital hormonal system. Dependent on this system, the appropriate genital ducts and external genitalia are formed next, and certain other of the sex characteristics—skeletal design, body contour, and so on—follow suit. Last of all, the more outward physical signs and functional phenomena, which appear at puberty, give full and final expression to the determined sex.

It must be emphasized, however, that in Man, and possibly in other dioecious animals, the degrees of development (differentiation) of the ultimate characteristics vary enormously, as is only natural, perhaps, in view of the ever-present bisexuality. We may see what we describe as masculine women and feminine men; and it is important to remember that in such circumstances *all* the late characteristics, including mentality, are of a similar somewhat opposite or intermediate sex type, although the character of the genital organs may appear more or less normal to the individual concerned. This condition is a minor grade of intersexuality.

A very large number of physical and psychical characteristics have been studied and described. It would

* After this lecture was in the press a paper by Wiesner¹⁴ appeared. Comparison may be made with this statement and the views expressed by him.

serve no useful purpose to enumerate all of them here. It is enough to know that they exist and are capable of great variation, and, indeed, of alteration in abnormal circumstances. So great is their variability, owing to the existence of bisexuality, that it is somewhat difficult to lay down a standard of normality. Rough social estimates and legal requirements may do nothing but injustice to what is often a very perplexing sex-balance, for the assessment of which the most careful scrutiny may be needed.

While recognizing all these phenomena in the make-up of the individual we should, nevertheless, remember the philosophical remark of Ray Lankester:

"Among the multicellular animals, certain cells are separated from the rest of the constituent units of the body as egg cells or sperm cells; these conjugate and continue to live, whilst the remaining cells, the mere carriers as it were of the immortal reproductive cells, die and disintegrate."

These words should prevent our glorifying the individual and discounting his high purpose of reproduction. Yet we must not be led astray by resounding phraseology. We now know that the "mere carrier," when human, can influence favourably his offspring by the cultivation of health and by mental experiences, and can impair its life by transmitted feebleness or disease and by intellectual apathy. The significance of all this—individual life on the one side, and sexual selection and fulfilment on the other—demands the earnest consideration of all thinking men and women who are interested in matters of moral and sociological import bearing on the destiny of mankind. There is much regrettable ignorance, indifference, and even evasion concerning the complications which the mind of Man has introduced into the biological field.

ABERRATIONS OF SEX IN MAN

It will be evident from what has been said that abnormalities of sex constitution in all its ramifications may be congenital or acquired. The congenital arise in embryonic life, while the acquired are post-natal. The congenital may affect the character of the sex gland and the other genitalia, as well as the later characteristics. Acquired sex derangements alter the last only, if we except the clitoris.

Congenital Anomalies: Intersex

In embryonic life the sex direction imparted by heredity and chromosomal variations, and the sex-determining influence of the endocrine organs, may be indefinite or irregular; consequently all grades of intersexual types may be observed, from masculinity in women (congenital virilism) and femininity in men to the most outspoken examples of partial hermaphroditism. In man, however, functional hermaphroditism is unknown. The more masculine a man is, and the more feminine a woman, the more normal they are according to our present beliefs. The chromosomal variations relative to these eventualities have been studied in insects, in which "super-males" and "super-females" have been described.

Normal as the intersexual condition is in certain invertebrates, and common as it is in vertebrates, I propose to discuss here intersex only in relation to man. It is a pathological manifestation of his bisexual inheritance. Unfortunately, in my opinion, it is customary in medical and legal circles to ignore or view askance, rather than scientifically, the minor grades of intersexuality. In such persons the late-formed characteristics incline to the sex opposite to that represented by the genitalia. Of these characteristics the mentality of the individual, especially in respect of sex attraction and desire, is the one that causes most concern, for it may lead to homosexual practices into the details of which I need not enter.

It seems strange, however, that persons suffering from the effects of chromosomal irregularity or endocrine indecision should be treated as criminals instead of as abnormalities. The explanation of this want of discrimination appears to be a general inability to distinguish between mere sexual vice, often due to the lack of opportunity for normal contact, and abnormal inclination, the result of disordered function. Sexual vice must, of course, be restrained in civilized life, but homosexual aberrations should be viewed in a different light, and pity, not punishment, should be accorded to them.

A more advanced state of intersex is seen in the various forms of partial hermaphroditism (pseudo-hermaphroditism). The qualifying adjective "partial" is used to indicate the fact that functional as well as structural hermaphroditism does not occur in Man.

Partial hermaphroditism is described as being glandular in nature when the gonads are involved. Usually, in these circumstances, a combined male and female sex gland is present—an ovariotesis, as it is called. Only a few cases of glandular partial hermaphroditism have been recorded.³ Gynandromorphism—that is, the lateral division of the body into male and female portions—which has occasionally been seen in birds, is unknown in the human subject.

It will be remembered that the anlage of the gonad is of an indifferent sex type, and that what may perhaps be described as cortical female, or medullary male, gonadal development is a comparatively late embryonic manifestation. This it is which makes possible a mixed (hermaphroditic) sex gland.

Partial hermaphroditism is said to be tubular in nature when the genital ducts and/or external genitalia and other sex characteristics are anomalous in respect of sex, as represented by the gonads.

It is interesting to note that when the external genitalia are feminine in type they are usually normally formed, but when they are masculine they are generally hypospadiac in appearance. Hence it is important that hypospadias with undescended testes be not mistaken for partial hermaphroditism.⁵ So, too, when there are ovaries these are almost always structurally normal though infantile; whereas when the gonad is testicular in nature it is much less developed than an ordinary undescended testis. It is, in this respect, important to observe that the interstitial cells are, however, always in the greatest profusion, constituting, in fact, the bulk of the organ. How is it, if the interstitial cells of the testes normally play a part—some believe a determining part—in the production of the male secondary characteristics, that in these cases, in which they are best developed, the secondary characteristics are feminine?⁴

Several varieties—external, internal, and complete—of tubular partial hermaphroditism have been described; but I need not discuss them and their variations here, for they have the same general interest in that the characteristics of sex, apart sometimes from certain internal genital structures, are of a sex nature opposite to that of the gonad. I may, however, say that types other than that which is known as external partial hermaphroditism must be very rare in Man—indeed, I myself, in a large number of cases, have never seen the so-named internal and complete varieties. In passing, it may be remarked that gross lesions of embryonic life have been noted in the suprarenal cortices far more often in those cases of partial hermaphroditism which have male general characteristics than in those which have female (15 per cent. against 0.7 per cent.).^{10 14}

It must be obvious that no surgical or other treatment can do more than modify the congenital state present. It is therefore with the lives of these persons and their status as citizens, that we are chiefly concerned.

To the best of my belief, and I have been unable to obtain any legal opinion to the contrary, the law takes no cognizance of the sex characters of the suprarenal cortices, the pars anterior of the pituitary and the other endocrine organs, except only of that last sexually determined—namely, the gonad. The general characteristics, too, are apparently of no account. If this really be so, the sex and status as a citizen—for there are still a few hereditary advantages in respect of titles and property appertaining to a male—of a glandular partial hermaphrodite with a combined ovary and testis, and of one who in all respects except the gonadal constitution is a female, is paradoxical, if not absurd. Could the last-mentioned inherit a peerage and an estate? Can “she” be indicted for homosexuality because “she” has married a man; and is “her” “husband” entitled to a decree of nullity? If a man is castrated he is still legally a man, and a woman remains a woman after her ovaries have been removed. But would the removal of the underdeveloped testes allow such a “woman” as that I have described to become a woman in the eyes of the law?

With regard to the points raised, lawyers would no doubt support the view that inheritable—especially entailed—possessions should pass only to persons presumably themselves capable of procreating a heir; but what a commotion such a ruling would cause. An indictment for homosexual practices could hardly be sustained; but suits for nullity would, of course, be wrongly entertained. As to the last question, in my opinion, whatever the legal authorities may say, a “woman” from whom imperfect testes have been removed is a woman.

However, the main point is: what can we, as doctors, do to help those unfortunate people? I have dealt with the question at some length elsewhere,^{4 5} and now have time only to mention a few problems that may be presented to us.

We may be asked to decide the sex of a baby. This will occur when the external genitals are equivocal. Hypospadias with testes, and enlargement of the clitoris with ovaries, constitute the difficulties. The former is a male, although some regard hypospadias as evidence of hermaphroditism, and the latter may be a partial hermaphrodite. The question of sex must be determined before the child is many years old. If a hermaphrodite, there will almost certainly be sexual precocity, with hair on the pubes within the first few years. It must then be decided whether the ovaries shall be removed and the child brought up as a “male,” or whether a suprarenal gland shall be excised, the enlarged clitoris amputated, and the subject brought up as a girl.

As I have said, when the external genitalia are really feminine the other general characteristics will be in accord, and the subject in these circumstances is reared as a girl. No doubt there are many such “women” with testes, the character of their gonads not being known. Indeed, in all the cases I have seen of this type, and I have known four who married, the nature of the sex organ was discovered by accident—in two cases it was removed with a hernial sac. There can, I think, be no doubt that the testes should always be removed from these “women” when discovered, and the person be allowed to live “her” life as a woman, which, in my opinion, she really is, owing to the preponderance of late characteristics, including her psychical traits.

Acquired Abnormalities of Sex

We now come, last of all, to the consideration of an interesting and important aspect of our subject—namely, the transformation of the general characteristics of sex as the result of lesions of the endocrine system. With this I can only deal shortly in the time at my disposal.

It will be clear that the organs which are responsible for the final determination of sex will control the post-natal development of the characteristics and the functions normal to the established sex predominance. Any serious post-natal disturbance of the genital system of endocrine organs may, then, lead to alterations in sex characterization. No doubt there is a reciprocal relationship between the various internal secretions, although, as we have seen, the male determinants can override those of the weaker sex.

The difficult question of a specific sex hormone as an entity for each determined sex—such as oestrin for the female, although this is also found in the male—needs no special attention here. If such hormones exist they are subsidiary in nature.

The clinical features now to be taken into account are: (1) sexual precocity; (2) virilism in females; (3) feminism in males.

Sexual Precocity

By the term “sexual precocity” we mean that puberty supervenes in childhood with the appearance of the outward bodily characteristics of adult sex and, in some cases, with the functional development of the genital organs. Now, as might be conjectured, the causes of precocious puberty in girls differ from those which lead to precocity in boys.⁴ In girls sexual precocity with menstruation is, so far as we know, caused only by ovarian neoplasia and hyperplasia. Still, only a small proportion of ovarian neoplasms in girls cause precocity, and then, no doubt, they produce an excess of the so-called female sex hormone (oestrin), for after early removal of a unilateral tumour of this kind menstruation ceases and the precocious external characteristics, such as hair on the pubes and mammary enlargement, tend to disappear. It is possible, but not definitely known, that in those cases in which menstruation is absent while the other adolescent features are present, lesions of the pineal may be responsible for the precocity. Care must always be taken not to mistake cases of partial hermaphroditism, with virilism and the early appearance of hair on the pubes, for feminine sexual precocity in which the characteristics of the female, not of the male, are developed.^{4 5}

Sexual precocity in boys is most commonly caused by neoplasms and hyperplasia of the suprarenal cortex, but also by neoplasms of the testes, and probably by hyperplasia and neoplasia in the pituitary, and, as some believe, by lesions in the pineal. It must, however, be emphasized that in a very large percentage of all cases (probably over 90 per cent.) sexual precocity in girls is related to ovarian lesions, and in boys to suprarenal cortical tumours. The “infant Hercules” is not uncommon, and some of you may have had an opportunity of seeing at least one of these “freaks.” At an early age they are muscularly powerful, sexually potent men of small size, with the general appearance, as has been said, of brewers’ draymen; oddly enough, however, hair is usually absent from the face. No doubt the successful removal of the suprarenal tumour might lead to retrogression of the precocity, but unhappily the neoplasm is usually malignant in nature, consequently the end-result desirable is not often, if ever, attainable.

Virilism in Females

I now come to the question of acquired virilism in females, which is unassociated with a minor congenital tendency or with partial hermaphroditism. This acquired form may, but does not often, appear before puberty. Should it occur in the prepubescent period it is practically always due to a malignant tumour of the suprarenal cortex.¹⁰ After puberty it may be due either to a hyperplastic or to an innocent neoplastic enlargement of

a suprarenal cortex, and only occasionally to a malignant tumour.

Not infrequently hyperplasia or neoplasia (adenoma) of the pars anterior of the pituitary also leads to virilism in women. With hyperplasia there is usually acromegaly. It is interesting to note that a marked change to virilism does not occur in women as the direct result of these lesions after the menopause, although, as we know, in many after that epoch certain masculine characteristics, such as hair on the face, are common. Similar changes may follow oophorectomy with the artificial menopause.

With cortical suprarenal tumours the changes observed in women are remarkable. Many grow beards, and some appear in fairs as the well-known bearded women. They may have the voices of sergeant-majors, and be rough and aggressive in manner. When seen early, removal of the offending tumour may lead to retrogression of most of the masculine characteristics, but the altered larynx never reverts to its former shape and size.

With acromegaly there is a limited change towards masculinity with amenorrhoea. The voice invariably deepens. In one case I found that the clitoris had become so greatly hypertrophied that it was causing the patient much distress. Acromegaly in men, as Harvey Cushing has shown, causes increased virilism, just as do suprarenal tumours.

Feminism in Men

A change in characteristics towards femininity is seen in men who have destructive lesions of the pars anterior of the pituitary, such as may be caused by cysts in that organ or by suprasella tumours. In these circumstances the syndrome known as dystrophia adiposogenitalis is present. Hair disappears from the face and pubes, while the contour of the body and limbs assumes a feminine type. After castration, too, a certain degree of feminism develops. No doubt in all these circumstances the masculinity-maintaining mechanism is interrupted.

SUMMARY

The relation of the sex-directing factors of heredity and sex-chromosomal constitution have been discussed, and the continued sex differentiation in vertebrates through the sex-determining action of organs of internal secretion has been described, together with the nature of the later general sex characteristics brought into being by the endocrine genital system.

Sex aberrations from biological, sociological, legal, and medical points of view have been considered.

REFERENCES

- ¹ Blair-Bell, W.: The Genital Functions of the Ductless Glands, *Lancet*, 1913, i, 809, 937.
- ² Idem: Hermaphroditism, *Liverpool Med. Chir. Journ.*, 1915, xxxv, 272.
- ³ Idem: So-called True Hermaphroditism, *Proc. Roy. Soc. Med. (Obstet. and Gynaecol. Sect.)*, 1915, viii, 77.
- ⁴ Idem: *The Sex Complex*, second edition, London, 1920.
- ⁵ Idem: Hermaphroditismus Externus Femininus, *Amer. Journ. Obstet. and Gynecol.*, 1925, x, 778.
- ⁶ Broster, L. R., and Vines, H. W.: *The Adrenal Cortex*, London, 1933.
- ⁷ Chamberlain, Noble: Sex Differences in the Cholesterol Contents of the Tissues, *Journ. Physiol.*, 1929, lxxviii, 259.
- ⁸ Crew, F. A. E.: *Animal Genetics*, London, 1925.
- ⁹ Idem: Discussion on Sex, its Nature and Abnormalities, *Proc. Roy. Soc. Med. (Obstet. and Gynaecol. Sect.)*, 1934, xxvii, 87.
- ¹⁰ Glynn, E. E.: The Adrenal Cortex, *Quart. Journ. Med.*, 1911-12, v, 157.
- ¹¹ Goldschmidt, R.: *Mechanismus und Physiologie der Geschlechtsbestimmung*, Berlin, 1920.
- ¹² Lillie, F. R.: The Free-Martin, *Journ. Exper. Zool.*, 1917, xxiii, 371.
- ¹³ Lipschütz, A.: *The Internal Secretions of the Sex Glands*, Cambridge, 1924.
- ¹⁴ Neugebauer, F. L.: *Hermaphroditismus*, Leipzig, 1908.
- ¹⁵ Spencer, Herbert: *The Principles of Biology*, 1867, ii, 460.
- ¹⁶ Wiesner, B. P.: The Post-natal Development of the Genital Organs of the Albino Rat, *Journ. Obst. and Gynaecol. British Empire*, 1934, xlii, 8.

THE SUBSTANCE RESPONSIBLE FOR THE TRADITIONAL CLINICAL EFFECT OF ERGOT

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In 1932 one of us (C. M.)¹ drew the conclusion from clinical experimentation that the characteristic and traditional effect of ergot was caused, not by ergotamine, ergotamine, tyramine, or histamine, but by a substance still unidentified. Previously it had been generally held by pharmacologists that aqueous extracts of ergot were valueless because they lacked the supposedly essential alkaloids. The experiments then described showed that, far from being inert, the much-criticized *B.P. 1914* liquid extract of ergot had a most remarkable oxytocic activity, and we believed that the clinician was fully vindicated in his dogged belief in the efficacy of the old-fashioned preparation. In spite of some criticism and scepticism our clinical and chemical observations kept us convinced of the truth of our conclusions, and we are now able to prove their correctness by reporting the isolation of the substance to which ergot rightly owes its long-established reputation as the "*pulvis parturiens*." We propose to name it "ergometrine."

Isolation of Ergometrine

The rapidity of action after oral administration of appropriate crude ergot extracts suggested that the active substance was a relatively simple compound, and our preliminary chemical investigations supported this view. We found that it was precipitable by phosphotungstic acid, and that when submitted to the Kossel-Kutscher method of fractionation it appeared in the "lysine" fraction. We also observed that it could be precipitated by mercuric sulphate and recovered from the precipitate by decomposition with hydrogen sulphide.

Large quantities of *B.P. 1932* extract were accordingly fractionated by a combination of these methods, but although we repeatedly obtained from the "lysine" fraction material which showed typical activity, we failed consistently to obtain any crystalline salts or derivatives of the base which was undoubtedly present. When we found that the active "lysine" fraction gave colour reactions similar to those of the known ergot alkaloids, and that the active substance could be extracted with chloroform from alkaline solution, we suspected that it was a more complex base than we had originally imagined. We therefore modified our procedure, taking advantage of the chloroform solubility of the substance in order to avoid the laborious application to crude extracts of the methods for the isolation of bases that we had until then employed. Our new method of extraction led us with unexpected rapidity to the isolation of the substance for which we were seeking, and was carried out in the following manner.

Defatted ergot powder was extracted with hot dilute sulphuric acid. After filtration the liquid was treated with barium hydroxide solution in slight excess. The precipitate was discarded, and excess of barium was removed by treatment with carbon dioxide. The filtered alkaline solution was then concentrated in a vacuum to small volume and treated with alcohol, which precipitated much sticky material. The alcoholic solution was con-

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