SOME GENETIC ASPECTS OF SEX[1]

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I. SEXUALITY

FROM the genetic point of view it is advantageous to begin by considering sex in the broader sense of sexuality. It is not generally realized that genetics has finally solved the age-old problem of the reason for the existence (*i.e.*, the function) of sexuality and sex, and that only geneticists can properly answer the question, "Is sex necessary?" There is no basic biological reason why reproduction, variation and evolution can not go on indefinitely without sexuality or sex; therefore, sex is not, in an absolute sense, a necessity, it is a "luxury." It is, however, highly desirable and useful, and so it becomes necessary in a relativistic sense, when our competitor-species also are endowed with sex, for sexless beings, although often at a temporary advantage, can not keep up the pace set by sexual beings in the evolutionary race and, when readjustments are called for, they must eventually lose out. Thus sexual beings form most of the central and the continuing portions of the evolutionary tree from which ever and again new sexless end-twigs sprout off.

Whatever the secondary needs of present-day somatoplasm may be, there is no fundamental protoplasmic need for rejuvenation of the germ plasm through sexual union, no reason to believe that "protoplasmic stimulation" is *per se* produced by mingling of unlike germ plasms, nor any evidence that variation of the hereditary particles is induced by "panmixia." A more reasonable claim might be made out for the new genetic concept of "heterosis" as furnishing the function of sexuality and

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sex. By heterosis we mean the increased vigor of hybrids, as compared with pure breeds, which is caused by the preponderant dominance of the genes favoring survival and growth furnished by both parents. But a more searching study of this matter shows that, in the main, heterosis affords only a compensatory advantage, in that it makes up for deficiencies that sexual reproduction is itself mostly to blame for. Heterosis arises only when cross breeding is wider than it has been on the average in previous generations. But if this wider cross-breeding is kept up, deleterious recessive genes will accumulate until a new equilibrium is reached, at which stage there is a sufficient abundance of such genes to cause even these more "mixed-blooded" individuals to exhibit as many recessive defects as did their "purer blooded" ancestors. *Vice versa,* if we increase the intensity of inbreeding, the more rigorous selection ensuing will eventually lead to the inbred line being purged till it has as great vigor as its more cross-bred ancestors. The closer the inbreeding, the less does sexual reproduction depart, in its genetic effects, from asexual reproduction, and we may conclude that at the limiting state, that of asexual reproduction, there would not (after the attainment of a state of equilibrium) be less vigor than in sexual organisms. The attainment of equilibrium in regard to the number of harmful mutant genes present may, however, require a very considerable time, and in the meantime sexual reproduction would be of advantage through its induction of heterosis. Heterosis may therefore have been of immediate value, in the first origination of sexuality, and so it may explain how sexuality happened to become established in the beginning, as Altenburg has suggested in an as yet unpublished work. But heterosis can not explain the major function of sexuality and why it has persisted in the long run, and acquired such complicated accessories.

Among the primary and accessory features of sexuality there must be considered not only the differentiation of

male from female germ cells, the differentiation of male from female sex organs, the separation of the sexes, with its associated mechanism of sex determination, and the differentiation of secondary sexual and "sex-limited" characters in general, but also the mechanism of Mendelian heredity itself, involving segregation of homologous chromosomes, independent assortment of non-homologous chromosomes and crossing over. Without sexual reproduction, the latter mechanisms are not called for, and would not continue to operate. Which, however, among the attributes mentioned, occupy a more primary and which a more secondary status? It is clear that not only is sexual reproduction necessary for the operation of segregation and recombination of chromosomes and chromosome parts, but, conversely, the latter are necessary in order that sexual reproduction may have any permanent value, while all the other characteristics of sexuality, though enhancing, are dispensable. Of the two major features, segregation and recombination,[2] only recombination is in itself of evolutionary value, but it can not take place without segregation and so we must suppose the two to have sprung into existence at nearly the same time. Mendelian heredity must therefore have arisen almost full fledged, when sexuality arose. This complicated step, which probably required a peculiar concatenation of accidents, along with selection, seems to have been taken in the green algae, and from them to have been inherited by animals and higher plants alike.

The essence of sexuality, then, is Mendelian recombination. Not increased variation in the sense of more change in the hereditary units or genes, now that we know there are these units, but the making and the testing out of all sorts of combinations among these gene mutations which would arise and become evident any way. Sexual-

[2] It is not possible at present to decide definitely whether recombination of whole chromosomes or crossing over was first evolved; either would have been sufficient to give value to sexuality. But it seems more probable that crossing over was a later development.

ity, through recombination, is a means for making the fullest use of the possibilities of gene mutations; thus it is itself an accessory process, accessory to the primary process of gene mutation.

There are two ways in which recombination of gene mutations is valuable. One, by far the lesser way, is the providing of an opportunity for continual shifting and readjustment of the relative abundance of different types as external conditions vary back and forth, and here and now one, there and then another combination becomes more advantageous for the maintenance of the species. In this process heterozygosity is an asset, and the disadvantageous combinations continually produced are an insurance against the day when some of them will be needed.

The other, the major value of recombination, is the production, among many misfits, of some combinations that are of permanent advantage to the species and that eventually become fully established in it as a part of its normal constitution. Without sexual reproduction, the various favorable mutations that occur must simply compete with each other, and either divide the field among themselves or crowd each other out till but the best adapted for the given conditions remains. In asexual organisms, before the descendants can acquire a combination of beneficial mutations, these must first have occurred in succession, within the same lines of descent. In sexual organisms, however, most of the beneficial mutations that occur simultaneously, or in different original lines of descent, can increase largely independently of one another and diffuse *through* one another, as it were (see Diagram 1). (Our diagram does not accurately represent this spread of genes through one another; it would hold only if the individuals and genes were fixed in geographical position and unable to disseminate freely amongst one another. If their positions were completely random, we should need a new dimension, at right angles to the previous ones, to represent the diffusion of each

new mutation. The actual situation lies somewhere between these two extreme alternatives.)

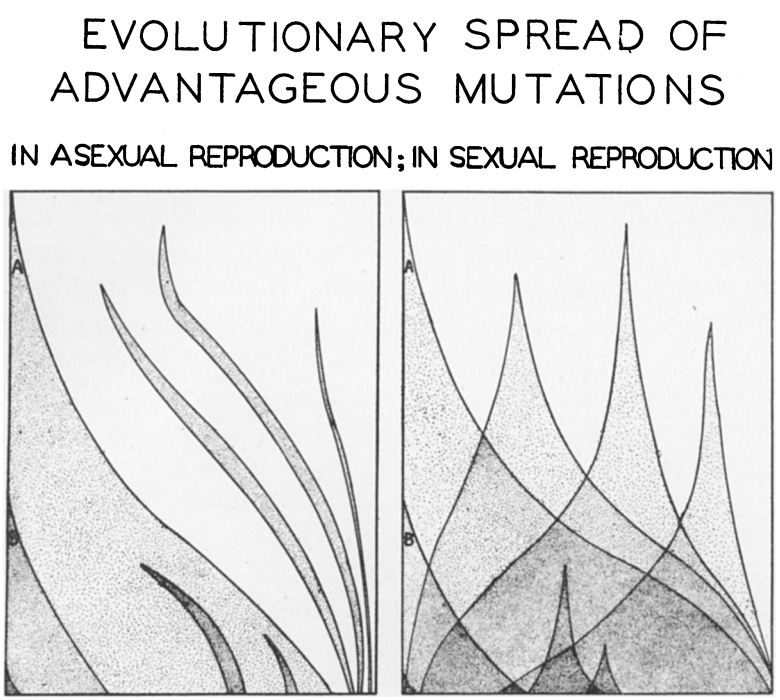

DIAGRAM 1. Showing the method of spreading of advantageous mutations in asexual and sexual organisms, respectively. Time is here the vertical dimension, progressing downwards. In the horizontal dimension a given population, stationary in total numbers, is represented. Sections of the population bearing advantageous mutant genes are darkened, proportionally to the number of such genes. In asexual organisms these genes compete and hinder one another's spread; in sexual organisms they spread through one another. See, however, qualifications in text (p. 121), explaining limitations of a diagram in only two dimensions. The diagram is simplified in a number of other ways as well. For example, all mutants represented are shown as spreading at nearly the same rate, if they do spread, and this rate is shown as about the same regardless of the extent to which they have entered into combination with one another.

Now it can easily be shown that the ratio which (on the average) the number of individuals in the most favored line of descent, counting from the time of occurrence of one favorable mutation (A) to the time of occurrence, within the same line, of the next favorable mutation (B),

bears to the number of individuals in the population as a whole in the same period (in Diagram 1, the ratio of the left-hand mutant shaded area A to the total area, in the region between two horizontal lines drawn through the points of origination of mutant shaded areas A and B) would represent roughly the speed of evolution in an asexual as compared with a sexual organism,[3] provided a correction, making the situation still more favorable to the sexual organism, is made here, namely, multiplication of this ratio by a factor representing the greater speed of increase of the favorable mutations in the sexual than in the asexual organisms, due to the fact that in the former the different favored mutations do not have nearly so much tendency to interfere with one another's increase. When such calculations are made, using any reasonable-seeming premises for mutation rate, selection and population size, within very wide limits, it is found that the advantage of sexual over asexual organisms in the evolutionary race is enormous.

In these calculations, and in the diagram, the assumption has been made, for the sake of simplicity, that the advantage of a mutation is the same regardless of the combination in which it occurs. However, the value of a combination of mutations will sometimes be far greater than the mere sum, or even the product, of the values of each mutant condition taken separately. Therefore, as Wright has recently pointed out, it is sometimes possible, by means of recombination occurring before selection, to get valuable combination-types which would not have come into existence at all, or only with far greater difficulty, if the "complementary" mutations composing them had had to occur and then to become selected in succession, as must happen in asexual reproduction.

[3] For while, in the given time, only one new advantageous mutation (B) became available in the favored line (A) of the asexual organism (the mutation rate being such as to give one in this number of individuals), in the sexual organism as many new advantageous mutations would become available, for combination with A, as the area of A goes into the total area.

While it is true that only the findings of modern genetics could enable our conception of the function of sexuality to take on the definite form above outlined, and only they could furnish real proof of this conception, nevertheless it should be recognized that the core of the idea—the formation of new combinations of "determinants," having a selective value sometimes greater than the original combinations—was conjured up long ago by the genius of Weismann, who herein, as in a number of his other major contentions (non-inheritance of acquired characters, reduction division), to-day stands brilliantly confirmed.[4]

II. On the Origin of Sex and Sex Determination

The advantage of the division of labor between sperm and eggs has long been obvious to biologists. Perhaps it is also needless to point out that the further differentiation, leading to the existence of the two sexes in separate individuals, is of advantage in the same way as any other division of labor in which more individuals than one are mutually involved, in this case rendering the performance of the respective tasks of finding a mate (or causing the male gametes to reach the female), and of giving the offspring a good start in life, respectively more efficient. But in cases where conditions are such that these functions in the same individual would not greatly interfere with one another—as is often true in organisms that are slow-moving any way and that need not be otherwise even for mate-finding—the efficiency may not be increased enough by dioeciousness to compensate for the effect of the latter in halving the number of individuals giving each type of gamete and in reducing the proportion of contacts which would be of service in fertilization, and so these organisms may have retained or developed hermaphroditism. This relation too has been pointed out by Altenburg in the work above referred to. His con-

[4] I am indebted to Professor S. J. Holmes for having redirected my attention to this important historical fact, subsequently to my address at New Orleans.

tribution concerning the relation of "reproductive load" to hermaphroditism is especially valuable in this connection, but we do not wish to anticipate it here. On the other hand, in dioecious species, it is not so evident why it should be most advantageous for them to have almost exactly equal numbers of the two sexes, as is usually the case, but perhaps this proportion exists simply because it is the easiest to produce, genetically.

If, as seems likely, hermaphroditism was the more primitive condition, dioeciousness may sometimes have arisen, as recently obtained artificially in corn, by means of two separate mutations which caused male-sterility and female-sterility, respectively. These mutations may in some cases have been linked (lying in homologous chromosomes), but such an arrangement would not be in the direction of the more prevalent mechanisms of sex-determination, in which the Y or W chromosome is relatively unimportant. More likely the second mutation (say, that causing female-sterility) was of a "sex-limited" type, such that its effect could be produced only when the effect of the first mutant gene in question (say, that causing male-sterility) was not being produced. Thus the second mutant gene would tend to become homozygous throughout the population and yet the effects of the two mutant genes would remain alternative. The first mutant would come to be heterozygous in half of the individuals and homozygous in the rest; it would have to be regarded as the "sex-determiner" proper. But it would seem a long way even from this kind of dioeciousness to one in which the sexes are automatically almost completely alternative, as in some animals that have been studied, where the development of a set of characteristics of one sex, in any given part of the body at any given stage, whether owing mainly to genetic or environic influences, necessarily goes along with a corresponding inhibition of a whole set of characteristics of the other sex. Many adaptive "modifying" mutations would have had to become established by selection, to

make the process controlled by the sex-determiner so effective, in causing the development of the characters of each sex to occur to the exclusion of those of the other sex.

As shown first by the work of Goldschmidt on the gipsy moth, the same genetic configuration may lead to either full maleness or full femaleness, for a given part at a given stage, independently of other stages, the result at that point depending on the strength of a particular developmental influence or influences, and in special cases the strength of the influence may change gradually during development so as to cross the critical level separating the two sexes. As the crossing of this level seems to involve a cleanly alternative alteration in nearly all sexual characteristics at once, that are scheduled to undergo development at the stage in question, it seems likely that the determining influence in question is a single one, *i.e.,* that there is normally a single "focal" process of development, or a single kind of developmental material, that is sex-deciding. That the same is probably true in Drosophila may be deduced from the recent work on intersexes by Dobzhansky and Bridges, extending Goldschmidt's principles to this organism. Further evidence of the largely unitary character of this sex-deciding process is to be found in the fact that the mechanism of sex determination has time and again changed, and that when the change occurred it could scarcely have been by a series of small steps, as would have had to be the case if many independent processes had been involved.

It is reasonable to suppose that the present scheme of sex-determination in Drosophila, for instance, arose as the result of a mutation which affected the strength (*i.e.,* the intensity or concentration) of the process or substance in question. This mutation need not have represented the first origination of the dioecious condition or of the sex-deciding process in question. The pair of allelomorphs thereby established may merely have superseded another allelomorphic pair, or another set of alternative conditions, which previously had had the sex-

deciding rôle, just as must have happened when what I have designated (in "The Mechanism of Mendelian Heredity," 1915, p. 83) as the "WZ" method of sex determination of butterflies and of birds superseded the previous XY type more generally characteristic of insects and of vertebrates, respectively. We are not compelled to conclude that the new gene or pair of genes that had this deciding effect was the one that synthesized the "focal" substance, or that chiefly carried on the "focal" process in question. No doubt, as in the production of other characters, this substance or process too depended, and depends, on many genes, some more and some less important, some helping to determine its nature, others only influencing its "strength," or allowing it to exist (see Diagram 2). In the same way, whether or not a pistol shall be fired may depend upon various details of the nature of the mechanism, upon the powder or merely upon the pulling of the trigger. To which of these possible categories the newly deciding gene belonged can not now be ascertained. But this single mutation must by itself have been enough to allow the gene in question to become fully sex-determining, *i.e.,* to decide between a fully functional male and functional female, otherwise the mutant would not have been able to survive.

Altenburg (*op. cit.*) has pointed out that there is at first sight an apparent genetic difficulty encountered in accounting for the origination of the above mutation, inasmuch as the work on non-disjunction shows that the X is far more important than is the Y in sex determination and that therefore the male represents, in effect, a haploid condition of sex-deciding genes present in diploid in the female. We may account for such a situation in one of two ways. On one interpretation we take as our point of departure the genotype of a male or hermophroditic individual, not containing the present sex-determining gene or genes which I have designated as "S" ("Mech. Mend. Hered.," 1915, p. 78) which now exist in the X chromosome, but homozygous for an earlier allelo-

morph, which we may call "s," and which we must suppose to be indifferent in its effect on sex. By means of a "positive" mutation (*i.e.,* one different in its character from a loss, and similar to Hairy wing, Blond and Bar in Drosophila—see Muller, League and Offermann, 1931, *Anat. Rec.,* 5: 110), the indifferent gene "s" would have had to become changed to the sex-deciding gene "S," which had to be present in double dose (SS) before its effect of suppressing maleness (while allowing development of femaleness) could be produced. The indifferent allelomorph "s" in the "Y chromosome" remained equivalent to an "absence," so far as its effect on the sex characters was concerned, just as the normal allelomorphs of Hairy wing, Blond and Bar are equivalent in their effects on these characters to absences.

On the other interpretation, we start from the homozygous "SS" individual (female or hermaphrodite) as a base. We must now suppose that a mutation of S occurs which is similar in its effect to a loss, producing an indifferent gene, or an absence, "s." This lesser gene, or loss, s, may be said to dominate over S, in the sense that the one dose of S, in the combination Ss, has a different effect than the two doses, SS, this difference being sex-deciding. The peculiar feature of this situation is not that one dose has a different effect from two, but that the sex-determining mechanism should already have been so prepared in advance, as it were, that a mere loss was all that was necessary to produce the whole change-over. This becomes understandable, however, if we postulate in this case that the "focal" sex-deciding substance or process had been previously evolved, through a series of changes in other genes but that a different gene or other agent had hitherto been determining whether or not it should occur. Once having gone through this evolution, its strength would be influenceable by changes in various contributing factors. Of these, the sex gene "S" here in question was merely one.

In view of these considerations, we should also expect that in the future changes in still other genes might be able to exercise the deciding influence and so take over the function of sex determination, in which case, in all probability, other chromosomes would become sex-determining. Moreover, there is nothing in the mechanism projected which would, *a priori,* make it impossible for quite different kinds of influences, such as special external conditions, or the haploid-diploid difference, or the stimulus of fertilization, to take over the function of the pulling of the trigger of the already evolved sex-determining process. But it would be to the advantage of the organism if the sex-determining process were not easily influenced by ordinary environic differences, for then the sex ratio would be too easily upset, and so we should expect the process to have developed safeguards against being readily changed in such ways to the degree necessary to cause the change-over.

III. Singular or Plural "Sex Genes"?

The fact that originally there must have been just one gene that played the critical rôle in the sex-deciding process does not mean that, as time went on, and the X-chromosome became, by mutation pressure, increasingly differentiated from the Y, other genes did not finally come to be contained in the X which also, through the difference in the effect of their dosage in the one-X and two-X conditions, affected the process in question. Some of these may work in the direction of strengthening, others of weakening this process (when their dosage is increased), but the sum total of their activities, together with that of the original sex-determiner, must be about the same as the latter originally was by itself. So there is as much likelihood that the X-chromosome contains "minus" sex-genes—those working in the male direction—as "plus" ones, and if such exist there must be an intra-chromosomal balance between the two. Recent work of the author, League and Offermann (1931,

op. cit.; see also Muller, 1930, in *J. Gen.*, 23) indicates that in the X, owing no doubt to its peculiar history, the intra-chromosomal "genic balance" is peculiarly delicate and intricate, in regard to the determination of various traits, and sex should be no exception to this.

As I pointed out in 1928 (Muller and Altenburg, *Anat. Rec.*, 41: 100) breakage of the X-chromosome by x-rays will enable us to determine the approximate locus or loci of the present sex-deciding gene or genes in the X, along with the real map of other genes. Hence, if the sex genes are not too numerous, their number and their relative effects also can be determined in this way. My work on broken chromosomes had already showed at that time that not more than half of the X contained genes of consequence in this connection. Since then the work has progressed a good deal further, chiefly through genetic studies of Patterson on broken chromosomes in mosaic flies in which the normal half of the zygote allows the other half, having the broken chromosome, to live and have its sex ascertained. As I suggested in 1930 (Muller and Stone, *Anat. Rec.*, 47), the inviability of the individual having a large piece of the X broken or missing, which is our chief difficulty in such studies, should also be obviable, to some extent, by carrying out our studies on flies triploid for the autosomes, since here the genic disproportion would not be so great. Following this method, Dobzhansky and Schultz (*Proc. Nat. Acad.*, 1931) recently report finding that several parts of the X have some positive influence in sex determination. It is too early to make a digest of the whole matter, but we can at least say that some parts of the X of *Drosophila melanogaster,* including all genes to the right of forked, are practically without influence in sex-decision, other parts, in the extreme left end, are of little if any influence, and in the remainder the influences are at least unequal, and are being gradually traced down. For the further definite findings of importance along this line the reader may be referred to the very extensive work of Patterson

(abstracted, 1931, in *Anat. Rec.,* 51: 111), which he has summarized for us at the present meeting, in his address to the genetics sections.

In all the above discussion it has of course been taken for granted that it is not the absolute amount of the sex-deciding gene or genes which determine sex (still less the quantity of the X-chromosome material as a whole), but the amount relatively to that of other genes, with the products of which those of the sex-deciding genes react. There is no use detailing here the controversy into which my advocacy of this view brought me in the early days with other Drosophila workers, notably Sturtevant, who cited in opposition sex determination in Hymenoptera, which I maintained was controlled by a totally different type of trigger, but its final vindication came, as is well known, with Bridges' discovery of triploid females and intersexes in Drosophila and his more recent demonstration of haploid female tissue as well. You can not tell how sweet a cake is merely by knowing the amount of sugar used in making it, you must also know the amount of the other constituents and its total size: the same principle holds in sex determination. By the same token, too, we must conclude that the amounts of various specific autosomal genes are also important in sex-determination and, by means of breakage produced by radiation, we should eventually be able to trace down these genes also, and gain information concerning their rôles in the sex-deciding process.

We can not, in this short space, discuss or even pretend to outline the problems in the whole field of the genetics of sex, but it should not be forgotten that what I have called the "sex-deciding" process is but one process, and maybe a relatively small one, in the whole series of processes that interweave in the production of all the male and female primary and secondary sex characters and many so-called sex-limited characters (see Diagram 2). I have called it a "focal" process because, firstly, no doubt the reactions set up by various genes converge as

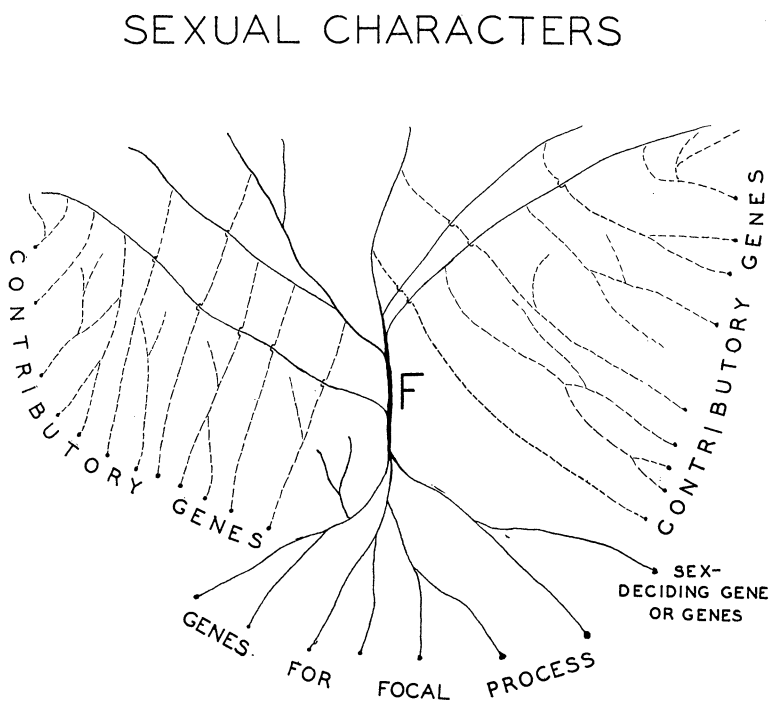

DIAGRAM 2. Schematic representation indicating the kinds of interrelationships existing between the final sex characters and the genes which determine them. Processes (physical and chemical, leading to morphogenetic effects) are indicated by lines, lines convergent from below upwards indicating interactions, lines divergent from below upwards indicating plural effects. The processes are represented as commencing with the genes below, and progressing upwards to the visible characters, above. Environic influences are not represented. Only one sex is shown. The "focal" or "sex-deciding" process, F, has the rôle not only of leading to the production of the characteristics of the one sex, but at the same time of inhibiting those of the other sex. This inhibition is not indicated here. Moreover, no distinction is made here between the direct production of a process and the "inhibition of an inhibition" of it, since the final effects are the same and a practical distinction can not usually be made. The diagram is admittedly vastly over-simplified, and is not intended to show the concrete relations of the processes, but only the kinds of relations existing among them.

to a focus, to make it what it is, to determine its nature and its intensity, and secondly, this process in its turn has multitudinous effects, lines of action diverging from it, as from the thither side of a focus, since the process

is necessary for the setting into action of all the various other processes which result in the production of all the different sex characteristics. But this multiplicity of effect also requires the cooperation of innumerable other genes, which, though not sex-deciding in the above sense, are certainly concerned with sex and are thus in a sense sex-genes. It may even be true that, to a slight extent, the majority of genes are influenced in the amount of their effects by the concentration of the sex-deciding genes, and are in this sense partially sex-genes, inasmuch as they tend to add to the sexual dimorphism.

IV. Rôle of the Y Chromosome

I have neglected the Y-chromosome in the above account, because the Y has neglected itself. According to the hypothesis of the origin of the Y which I published in 1914 (*J. Exp. Zool.*, 17: p. 326–328; see also *Gen.* 3, 1918, p. 479–484) the genes of the Y have gradually undergone inactivating and loss mutations, from the effects of which the organism has been largely protected, through the continual presence of an X having normal (or "hypermorphic") allelomorphs. In other words, the Y has paid the penalty always exacted by the protection of continual heterozygosis, and the consequent absence of natural selection. The largely inert Y may subsequently undergo changes in size and shape without detriment to the organism, and so tends to become visibly different from the X, luckily for cytologists and geneticists.[5] But it must

[5] Recent evidence (see Muller, League and Offermann, *op. cit.*) suggests that, although the individual "loss mutations" or "hypomorphic mutations" of the Y were not detrimental enough to prevent them from finally becoming established by mutation pressure throughout the population, nevertheless in the case of some of them, the ensuing one-dose condition of the genes of the X in the male may have exerted some sensible detrimental effect. If so, this effect was later compensated for by the selection of modifiers, which made the males with one dose about equal, in degree of expression of these X-chromosomal genes, to females with the two doses. If this interpretation is correct, loss of a whole section of the Y would have been detrimental, at a time before this piecemeal loss, accompanied by piecemeal compensation, had taken place. Alternatively, we may sup-

retain enough genes to allow it to act as the homologue of the X in segregation, if it is to persist at all, and, if any dominant genes exist or arise in it, which are advantageous to the sex in which Y occurs exclusively, they may be retained by natural selection. With regard to these male-helping genes we may observe the following: as it is a rule of evolution that characters at first merely an asset will, if they are retained long enough, finally become, through correlative evolutionary changes, a necessity, we find that at present the Y of Drosophila, though relatively unimportant in sex determination, nevertheless contains genes or gene-complexes, "k_1" and "k_2" found by Stern, 1927 (*Die Naturwiss.* Jahrg. 15) that are essential for the complete functioning of the male.

The Y, having become nearly inert, may also now serve as a source of inert chromatin that may become translocated into other positions, and even serve as an anchorage for the formation, by translocation, of new autosomes chipped off the old ones. At least, on the basis of the studies which have recently been carried on by Stone, Painter and myself, I have reached the conclusion that, by translocation, a large part of the Y of Drosophila has become engrafted on to the original X, so that only about half the length of the present X consists of original X-chromosome material, the rest consisting of inert material derived from the Y, material in the main unable to mutate, to undergo crossing over, or to function in morphogenesis (Muller and Painter, 1932, *Z. ind. Abst. u. Vererb.*, in press). Its function, if any, still remains a mystery, but the possibility of its existence in unsuspected situations must be taken into account in future cytological studies. Here we have one little example of the numerous ramifications of the secondary effects which sexual differentiation has led to.

pose that these "compensated" genes of the X are "neomorphs," functionally unlike any that ever existed in the Y. But even in that case, *duplications* of the Y or of whole sections of it could not have been innocuous until it had become nearly "empty."

V. Significance of Sex Studies

The genetic study of sex is important not merely because, according to Freud, sex is instinctively our major interest, a proposition which is at least disputable, even for *Homo sapiens biologensis*. It is important also because, as we have seen, it lies at the root of Mendelian heredity itself and is one of the major factors in evolution, even though it is not, in an absolute sense, necessary. Thirdly, it is important because it provides such admirable material for the study of gene interaction, of phaenogenetics, that is, of *Entwicklungsmechanik* from a genetic standpoint, together (fourthly) with the associated study of the evolutionary processes whereby these developmental complications arose. Sex and sex characters are peculiarly adapted for this purpose because, while they constitute a highly complicated mechanism developed through a long evolutionary sequence, nevertheless they can be dissected apart, practically down to their very root, by a combination of mutational, embryological and physiological means, without necessarily killing the organism (as witnessed by the results cited in the other papers in this symposium). This possibility arises from the fact that the vegetative functions can go on without reproduction and that the organism, through its possession of two sexes, must be already adapted to carry on either one without the other. Most other complicated systems—circulatory, digestive, excretory, etc.,—if much tampered with, soon result in lethal effects, and thus largely foil the knife of the genetic and morphogenetic investigator. Within the life system as a whole, then, we have here a contained system, the sex system, sufficiently independent so that it can be vivisected down to the point of extirpation without death ensuing, and which can therefore be used as an object of research to illustrate the general principles of gene interaction, morphogenesis, physiology and evolution pertaining to the life system as a whole.

APPENDIX

The reader may wonder why the letter "S" has been used in the preceding article to represent the sex-deciding gene or group of genes, rather than the letter "F," for femaleness, and why "M," for maleness, has been omitted completely. He may also think that some references should have been made to the development of these F- and M-containing formulae for sex, and to the controversy concerning to whom the credit for these conceptions should be given. In view of the prominence which has been given to this topic even in some of the more recent literature, the author ventures to present here a portion of a paper entitled "Erroneous Assumptions regarding Genes," which he wrote while at the Cornell Medical College in the winter of 1911–12, and which he did not have opportunity at that time to publish. It will be evident from this paper that even at that time the "FM" formulation was no new one, but that the grounds for its rejection were already extant. As a result of the ideas of the author advanced therein, and others added by him later, the representation "SS, SO" was used in the "Mechanism of Mendelian Heredity," 1915, 1923, and the criticism "What are Sex Factors," was presented in the same volume (see especially pp. 90–97 and p. 107 of the 1915 edition, or pp. 90–94 of the 1923 edition, which it may be of interest to reread in the present connection).

. . . We may in conclusion undertake a criticism of certain needless assumptions that are sometimes made regarding sex itself, for this may furnish an illustration of the applicability of the above line of thought (that the processes through which the genes accomplish their outward effects may be extremely complex and interrelated) in other directions. When we find that the male, for instance, is heterozygous for sex, the female homozygous, then, in the absence of any cytological evidence, there is only one justifiable formula by which the sexes can be expressed, namely XX = ♀, XY = ♂; or, if there is evidence from cytology that the X chromosome has no mate, the Y may be changed to O. All other formulae are unwarranted modifications of these two. Thus, Morgan, in an attempt to account for maleness in Drosophila (where the Y is absent and the scheme is XX = ♀, XO = ♂[6]),

[6] Just at that time, the Y was erroneously thought to be absent from Drosophila. Nevertheless, as it has since been found to be nearly "empty" genetically, this formulation will hold approximately anyway.

introduces an M into the formula and changes X to F. His formula for the ♀ is then FMFM, that for the ♂ FMM, where F, femaleness, stands for X, and M, maleness, is not sex-linked. Both of these assumptions are unwarranted. It may well be that not only factors necessary for femaleness but also factors for maleness abide with the X chromosomes. This may be true not only of sex characters common to both male and female . . . but even of distinctively male characters, or generalized "maleness" itself, if that exist. . . . For, just as a gene in haploid amount need not produce an effect equal in quantity to that of the diploid amount . . . , so too its effect may differ also qualitatively, when haploid, from the diploid effect. It is not uncommon for the effect produced by an agent to vary in quality as the agent varies in quantity. Thus, to build upon an idea of G. H. Shull's, a certain amount of alkali added to an acid solution yellow with alizarin, may change the latter to an orange color, whereas twice as much may make it deep purple. Therefore it is quite possible that XO = male, XX = female, without any non-sex-limited M, and therefore too that X is not identical with a hypothetical F, femaleness.

It is not even necessary, however, to postulate here that a certain gene in haploid number produces an effect different from that in diploid. We may instead assume that certain dominant factors for maleness exist "in" the X chromosome, but that there also exists in that chromosome a recessive inhibitor for this factor or factors (either a simple inhibitor or a complex of several genes that may have other side actions as well). We say recessive, meaning that the haploid quantity is ineffective. In this case the composition of the X chromosome, if represented according to the scheme of the preceding formula, would be MI; this too would represent the male, one I not being active, and M thus producing maleness. The female would be MIMI, the two I's effectually inhibiting maleness. In this case we could consider femaleness to be a non-sex-linked character or aggregate of characters, thus partially reversing Morgan's formula of FFMM = ♀, FMM = ♂ by putting MIMIFF = ♀ MIFF = ♂; we could, however, as well consider that "femaleness" (meaning all or a part of the factors necessary for femaleness) also was sex-linked, but recessive, like I, not dominant, like M. Then we would have MIF = ♂; MIF MIF = ♀. If we chose, we could simplify the formula by the omission of I, regarding F (or even M) as possessing its properties, especially since by the letters we are not strictly denoting single genes, but possibly collections of them. Then we would have MF = ♂ MFMF = ♀, M dominant to its absence, F recessive to its absence and inhibiting M. If likewise in the previous case (MIMIFF = ♀, MIFF = ♂) we considered I as being merely a property of M, we would have MMFF = ♀; MFF = ♂.

In all the above cases, we have for purposes of comparison used the scheme of representation of the formula under criticism; we do not favor this method of representation in general. For, as we pointed out in another connection, a single letter is used in Mendelian notation to represent a single gene, but, in cases where the factor has never been actually isolated . . . , we have no means of telling whether the effect is not due to the combined action of a number of genes, any of which may in their

turn be responsible for other effects as well. Thus, if when using F a single gene is meant, the assumption is unwarranted; if a possible collection is meant, the notation is unwarranted. In case F or any other such "character" is sex-linked, however, (as F is in Morgan's formula), this representation is somewhat more defensible, for in this particular case the character always segregates completely as a unit in the heterozygous sex, and the integrity of the letter is destroyed only by mutation. It seems therefore permissible to use a single letter here, provided we call attention to the exceptional nature of the case. . . .

However, if the "character" may be made up of a collection of non-sex-linked genes, it should never be represented in this way, for then the various components need not all be coupled together as they are in sex-linked cases. The integrity of the letter is thus destroyable by their independent segregation, whereas the use of a single letter implies that in segregation its genic original acts as a unit. This objection applies to the M of the formula under discussion, even if we regard the formula as correct in intention.

To pursue the case to its conclusion, objection is to be raised to the insertion of MM into the formula also because it is provided in diploid quantity throughout (♀ = FFMM, ♂ = FMM). The representation of any factor or factors which appear in like quantity throughout any complete series of cases, is superfluous. It is not legitimate to answer to this that the gene does not manifest itself in all these cases. Thus, in the case of the fly with the abnormal abdomen, let us assume, as is usual, that abnormality, the dominant, is also the presence. Then the abnormal fly is represented by AA or Aa, and the normal by aa. Normal is represented as the absence of abnormality, and yet for the production of the normal abdomen many factors, which together might be called NN, normality, are surely necessary. However, as these factors are present in all cases, they are not represented, even though they are in evidence as such only when A is absent and work differently or not at all in its presence (*i.e.*, do not manifest themselves), just as is the case with the hypothetical MM. If a certain somatic effect is produced, its representation in the germ cells is presupposed, and essential likeness of genic composition is assumed except where difference is indicated in the formula.

We have laid stress upon method of notation because a clear agreement as to method of symbolization is important for clarity of thought regarding the objects of the symbols. And as regards these objects, the genes, we hope we have indicated that, in regard to presence and absence and some other questions, it is necessary to conjecture freely and fully as to all the possibilities involved, if one wishes to avoid the paradoxical criticism—consequent upon the missteps which come inevitably to those who try to reach "natural" conclusions but avoid "unbridled theorizing"—that one has actually indulged in wild speculations. . . .