Chromosomes, Heredity and Sex: A Review of the Present State of the Evidence with regard to the Material Basis of Hereditary Transmission and Sex-Determination.

By

L. Doncaster, Sc.D.,
Fellow of King's College, Cambridge.

With 4 Text-figures.

It is now rather over ten years since the hypothesis was first put forward that the segregation of Mendelian allelomorphic characters is caused by the pairing in "synapsis" of chromosomes of paternal and maternal origin, and their subsequent separation into different gametes (**58**, **59**, **64**). At about the same time, the discovery of an "accessory chromosome" in the spermatocytes of several Orthopterous and Hemipterous insects, which passes undivided into half the spermatids, led to the suggestion that this body was a sex-determiner (**31**), and shortly afterwards Castle (**13**) put forward the hypothesis that sex-determination is due to a pair of Mendelian factors, which segregate in gametogenesis in such a way that every germ-cell bears one or other. In this paper it is not proposed to review the earlier work, nor to give an account of all the papers which have added to our knowledge of the subject, but to summarise some of the more important lines of evidence which have become available in the last few years, so as to show as far as possible the present state of our knowledge.[1] Further, it is not proposed to deal at all completely with the various theoretical speculations to which the matter has given rise, except in so far as is necessary for the

[1] References are given on p. 517 to papers which may be regarded as typical.

understanding of the way in which the facts referred to are related to the general question of the material basis of hereditary transmission and of sex-determination.

The argument falls naturally into the two divisions of the relation of the chromosomes to Mendelian heredity on the one hand and to sex on the other, but these two are intimately connected hy the phenomena of sex-limited inheritance, from cases of which some of the most important evidence with regard to both branches has been obtained. It will, therefore, be most convenient to consider in their relation to chromosome behaviour, first, heredity alone, then sex, and finally the phenomena of sex-limited inheritance.

(1) Chromosomes and Mendelian "Factors."

The opinion that the chromosomes are the "bearers" of characters which show Mendelian inheritance has been supported on several quite distinct grounds, some of which are inferential, others depending on direct observation. The earlier arguments in favour of this idea were founded entirely on observations which suggested that the behaviour of the chromosomes in the maturation of the gametes is of exactly the kind which would give rise to Mendelian segregation. The facts are so familiar that no detailed account is needed. It has been maintained by many observers, especially in cases in which the chromosomes differ conspicuously among themselves in size, that the nuclei of the somatic cells and spermatogonia or oögonia contain a double complement, composed of sets of maternal and paternal origin respectively, and that in "synapsis" each maternal chromosome first pairs with a corresponding paternal one, and then separates from it at one of the maturation divisions into a different daughter-cell. If, then, each chromosome corresponded with a Mendelian character, and if chromosomes bearing allelomorphic characters always paired together, the segregation of the members of an allelomorphic pair into different gametes would be accounted for. And since it is a matter of chance with regard to any pair whether the paternal or maternal

element goes to a particular daughter-cell, the independence of different allelomorphic pairs in the formation of gametes is also explained. The mechanism for producing Mendelian segregation appears so perfect that it is difficult to believe that the two phenomena are unrelated, but there are serious difficulties which have first to be explained. The first of these is that there may be more pairs of allelomorphic characters than there are pairs of chromosomes, and yet the characters of different pairs show no constant association with one another. Several theoretical suggestions have been made to meet this objection, most of which assume that the chromosomes are not indivisible units, but are made up of smaller parts, each of which is the bearer of one Mendelian character. By some it is supposed that the units may be interchanged during synapsis; by others, that they become separate in the "resting" nucleus, and that it is a matter of chance whether they return into one or other of the homologous chromosomes to which they belong. The evidence for the compound nature of chromosomes is now so strong[1] that the difficulty cannot be regarded as very serious, but the exact manner in which the units are arranged in the chromosomes is far from being settled. One hypothesis with regard to this part of the question will be discussed more fully later, in connection with gametic coupling.

The second objection to the hypothesis that the pairing and separation of chromosomes in gametogenesis gives rise to Mendelian segregation is more serious, since it is based on the denial that the chromosomes behave as described. Some observers refuse to credit the chromosomes with individuality of any kind (**33**), and without some sort of individuality,

[1] Compound chromosomes have been described in Ascaris (T. Boveri, 'Ergebnisse über die Konstitution der chromatischen Substanz des Zellkerns,' Jena, 1904, p. 27); in the bee (H. Nachtsheim, 'Arch. Zellforsch.,' xi, 1913, p. 169) and in other cases. The writer finds that in the nearly related moths, Nyssia zonaria and Biston hirtaria, the chromosomes of the former are exactly four times as numerous as in the latter, and much smaller, so suggesting that those of B. hirtaria may be compound.

leading to constancy of behaviour of the hypothetical units which "bear" the Mendelian factors, the whole hypothesis would fall to the ground. Others, while admitting the conjugation of chromosomes in synapsis, maintain that it is not a mere coming together in pairs, followed by complete separation, but that the two chromosomes which pair fuse so intimately as to make separation of the parts almost or quite impossible (**10**, **10a**). Others, again, deny the existence of a "reduction division" in Weismann's sense, and maintain that parts of both the paternal and maternal chromosomes go into all the gametes (**32**). If any of these conditions were general it would completely destroy the basis of the hypothesis under consideration. When, however, the various objections are critically examined, they begin to appear less fatal to the hypothesis. In the first place, the three classes of objection mentioned are mutually exclusive; if the supposed facts on which any one of them is founded are genuine, the others must of necessity be mistaken. Secondly, they are largely founded on negative evidence, and if an observer, however competent, fails to find certain phenomena in the material on which he is working, this not only does not prove that the phenomena do not occur in other cases, but it may not even prove that they do not occur in his own material. The ease with which the alleged phenomena are observed varies greatly in different species, and they may quite possibly occur in cases in which the nature of the material makes proof or disproof of their occurrence impossible. In the opinion of the writer the wide-spread agreement among workers on chromosomes in favour of the existence of some kind of individuality, and of a genuine reduction division, makes the first and third of the objections mentioned of small importance. With regard to the complete separation of chromosomes which have paired in synapsis there is much less unanimity, and the question must be regarded as still open.[1]

[1] In this connection, the discussion by W. E. Agar, 'Quart. Journ. Micr. Sci.,' 57, 1911, p. 1, based on peculiarly favourable material (Lepidosiren), is of importance.

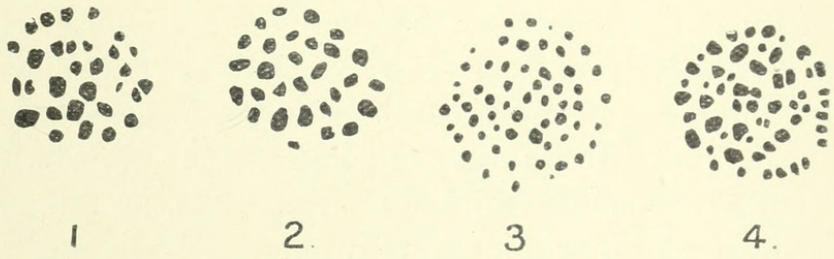
Apart from the fact that, according to many observers, the pairing and separation of the chromosomes in the maturation divisions provide just the mechanism required to bring about Mendelian segregation, there are two other lines of argument which point in the same direction. One of these is again inferential only, the other depends on direct observation. The former is concerned with the phenomenon of gametic coupling—the fact that in a number of cases two separate Mendelian units tend to be more or less closely associated in their inheritance. Gametic coupling was first discovered by Bateson and Punnett (**6**, **7**) in plants. In animals it has been worked out rather fully by Morgan in Drosophila (**41**, etc.), and is now known to be widely distributed. The facts, put shortly, are that if a form possessing characters A and B is mated with one from which these factors are absent (represented a, b), the crossed individual produces gametes, most of which bear either both A and B, or neither of them, the combinations A b and a B being relatively rare. The fact that there is this association in transmission between distinct Mendelian factors is strong evidence that they are borne in some body which behaves in gametogenesis as a unit, and the only bodies known to behave in the way required are the chromosomes. This argument is strengthened by the behaviour of such characters in cases of sex-limited inheritance, which it will be convenient to discuss at a later stage. It is also strongly supported by the fact that in Drosophila there are three groups of such coupled characters; each of the characters included in any one group shows coupling with the others of the same group, but characters belonging to different groups are inherited independently of one another. Morgan has put forward a hypothesis which it must be admitted is rather speculative, to account for these facts (**42–44**). He suggests that the factors for the coupled characters are all borne in one chromosome, the chromosome being regarded as consisting of a series of units arranged along its length like beads on a string, each unit bearing one "factor." In synapsis two such chromosomes pair side by

side, corresponding units being opposite one another. Several observers (**10a**, **28**, **29**) have described chromosomes as twisted round each other in pairing, and Morgan suggests that if, when they are so twisted, the split which separates the chromosomes is straight, as Jannsens has maintained (**26**), the resulting daughter-chromosomes will not be identical with those which paired, but will consist of parts of each. When the split occurs, units which are arranged next to each other will usually go into the same half, but units which are widely separated will often go into different halves. In this way he accounts for the different degrees of coupling which are found between different characters in the same species. The twisting of the chromosomes round each other in synapsis appears undoubtedly to occur in certain cases, but until the splitting across the twist postulated by Morgan has been shown with certainty to occur, his hypothesis must be regarded as almost entirely speculative.

The last class of evidence with regard to the relation of chromosomes to Mendelian factors depends on direct observation. At present few cases are known which bear directly on the question, and only two will be mentioned at this point. First may be mentioned the work of Federley (**20**). He found that hybrids between moths of the genus Pygæra showed that certain features of one species were dominant, while in other respects the hybrids were intermediate. When the hybrid was mated with one of the parent species, in most respects the offspring were all again hybrid in character; in one or two features, however, segregation took place. On investigating the behaviour of the chromosomes, he found that in the spermatogenesis of the hybrid nearly all the chromosomes failed to pair; the spermatocyte chromosomes were almost of the somatic number, and divided equationally in both divisions. One or two chromosomes, however, paired and segregated normally. When the hybrid P. *curtula* ♂ × P. anachoreta ♀ was paired back with pure anachoreta ♀ the offspring contained almost a complete triple set of chromosomes, for the hybrid provided almost complete

curtula and anachoreta sets, and the anachoreta parent a (haploid) set of anachoreta. The secondary hybrid therefore contained a double (diploid) set of anachoreta, and a haploid set of curtula chromosomes. In this case, in spermatogenesis of the secondary hybrid, normal pairing took place between the anachoreta chromosomes, while, as in the primary hybrid, the curtula chromosomes divided equationally, with the result that the gametes of the secondary hybrid contained a haploid curtula + a haploid anachoreta set. If, now, the chromosomes are the bearers of Mendelian factors, the fact is explained that the primary hybrid, when paired back with curtula, shows in

TEXT-FIG. 1.



1. First spermatocyte equatorial plate of Pygæra anachoreta, 30 chromosomes. 2. Similar equatorial plate of P. curtula, 29 chromosomes. 3. First spermatocyte equatorial plate of hybrid P. anachoreta ♀ × P. curtula ♂; 58 chromosomes, so that only two chromosomes have united to form a pair. All the others are about half the size of the spermatocyte chromosomes of the pure species. 4. First spermatocyte equatorial plate of secondary hybrid, P. anachoreta ♀ × (P. anachoreta ♀ × P. curtula ♂); 56 chromosomes, of which about 30 are large, and consist of two units paired together (presumably anachoreta chromosomes) and about 26 are small, unpaired, presumably curtula chromosomes. (After Federley.)

general no segregation, since in each generation nearly complete haploid sets of chromosomes of both species are present in the gametes. One or two chromosomes, however, pair and separate, and correspondingly one character at least was observed which showed Mendelian segregation.[1]

[1] The present writer has confirmed Federley's results as to the behaviour of the chromosomes, in reciprocal crosses between Biston

The second piece of direct evidence connecting chromosomes with inherited characters is due to Baltzer (**5**). Previous investigators had found that the cross between the sea-urchins Sphærechinus granularis ♀ and Strongylocentrotus lividus ♂ produces plutei intermediate in character between those of the parent forms, while the converse cross, in the rare cases when the larvæ survive, gives plutei in which the skeleton is of the pure maternal form. Baltzer has examined the behaviour of the chromosomes in the two crosses. He finds no peculiarity in the cross with Sphærechinus ♀, but when Strongylocentrotus is used as the female parent, he finds that about 16 chromosomes are constantly omitted from the daughter-nuclei at the first and second segmentation division of the egg. He infers by three distinct methods that the eliminated chromosomes are paternal, i.e. derived from Sphærechinus, and since the haploid number of Sphærechinus is 20, there remain only about four Sphærechinus chromosomes in the hybrid plutei, which are maternal in character, while the full number remains in the intermediate plutei produced by the converse cross. That the eliminated chromosomes are paternal is inferred (1) from the shapes and sizes of the chromosomes; (2) from a study of a tetraster, in which the number corresponds with the expectation if two spermatozoa had entered the egg and only eight of the sperm-chromosomes behaved normally; (3) by the fertilisation of non-nucleated Strongylocentrotus egg-fragments with Sphærechinus sperm, in which again only about four chromosomes divide normally.

Tennent (**60**) similarly finds elimination of chromosomes in the cross Hipponoë ♀ × Toxopneustes ♂, but none in the converse cross. In this case the Hipponoë characters dominate in the pluteus whichever way the cross is made, but since the Hipponoë chromosomes are presumably present

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hirtaria and Nyssia zonaria. In this case the hybrids are sterile, so the later generations are not available. The work is to be published in the next number of the 'Journal of Genetics.'

in both the reciprocal crosses, this result would be expected if the Hipponoë characters were dominant.[1]

Indications of the same sort, but somewhat less direct, have been given by Herbst (**25**). He has found in occasional hybrids between Sphærechinus ♀ and Strongylocentrotus ♂, individuals with purely Sphærechinus skeleton on one side, and intermediate skeleton on the other. On the side with Sphærechinus skeleton the nuclei have half the volume of those on the other side, indicating that they contain fewer chromosomes, and he supposes that the spermatozoon has conjugated with one of the nuclei of the first two blastomeres, so that half the larva has purely maternal, the other half hybrid nuclei.

Evidence of this kind, while not proving that the chromosomes are directly concerned in the transmission of inherited characters, makes such a hypothesis very plausible.[2] Much unnecessary confusion, however, has arisen, from stating the hypothesis in the form—"the chromosomes are probably the bearers of inherited characters." Evidence has been adduced that the cytoplasm plays some part in determining these characters, and it has therefore been maintained that the statement is disproved. No one, however, would suppose that the chromosomes could act alone; they must act in and by their relation with the cytoplasm, and if the cytoplasm is that of a different species, the total effect must necessarily be different. A simple chemical analogy will make this clear. The substance represented CH_3H is a hydrocarbon; exchange

[1] The writer and J. Gray ('Quart. Journ. Micr. Sci.,' 58, 1913, p. 483) found elimination of one or two chromosomes in the cross Echinus miliaris ♀ × E. acutus ♂, but none in the converse cross. In the case of the cross E. acutus ♀ × E. esculentus ♂, in which some chromosomes are lost by becoming vesicular and failing to divide, there is evidence that the vesicular chromosomes are maternal (J. Gray, 'Quart. Journ. Micr. Sci.,' 58, 1913, p. 447). In these cases it was not found possible to correlate the chromosome behaviour with the inherited characters of the plutei.

[2] The evidence adduced by Goldschmidt ('Arch. Zellforsch.,' ix, 1912, p. 331) has not been mentioned, since its correctness has been disputed (O. Renner, 'Berichte d. deutsch. Botan. Gesellsch.,' xxxi, 1913, p. 334).

the hydrogen atom for chlorine and the substance CH_3Cl has different properties, while those of CH_3OH are different again. An exactly corresponding series, in composition and properties, is provided by the substances C_2H_5H, C_2H_5Cl, C_2H_5OH, and it would not be regarded as exaggeration to say that the change from a hydrocarbon to a chloride or an alcohol is produced by replacing the hydrogen atom by another atom or radicle. But the various atoms which may replace the hydrogen do not have exactly the same effects when attached to C_2H_5- as when attached to CH_3-; their effects are similar, but not identical. So when a chromosome of species A is replaced by one of species B, the effects of B in A cytoplasm cannot be expected to be identical with those produced in its natural environment. And when, as in Godlewski's famous experiment, it was found that Antedon chromosomes appeared to have no effect in Echinus eggs, it may well be that the environment was too strange for any interaction to be possible, just as the replacement of hydrogen by chlorine in some compounds is easy, in others difficult or impossible.

Further evidence with regard to the functions of the chromosomes in heredity will be given when dealing with sex-limited inheritance, after the general question of sex-determination has been considered.

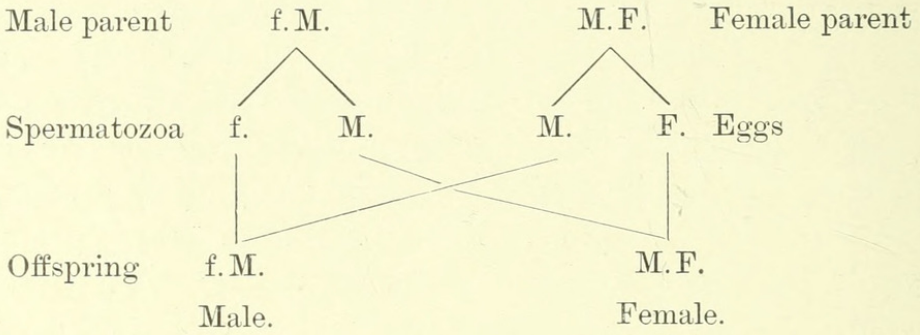
(2) Sex.

The evidence of connection between chromosomes and sex-determination is on the whole more complete than that which connects chromosomes with Mendelian factors. Here again the bulk of the evidence is indirect rather than direct, but since there are only two sexes it is much easier to associate a particular chromosome with sex-determination than to show that any one is connected with the transmission of a particular Mendelian unit. The evidence that a particular chromosome in many cases invariably accompanies one sex is so clear that it may almost be regarded as direct evidence for sex-determination by that chromosome, and some of the facts

are of such a nature that it would hardly be exaggeration to claim them as proving that hypothesis.

Very early in the present century cases were observed in insects in which one chromosome differed conspicuously from the rest in spermatogenesis, especially in taking no part in the spireme stage, but behaving as a "chromatin-nucleolus." It was then found that these species had an odd number of chromosomes in the male, an even number in the female, and that the difference was due to the presence of a pair of such "accessory" chromosomes in the female, and only one in the male. The "accessory" in the male has no mate, and goes over undivided in one (usually the first) spermatocyte division, but divides equationally in the other, with the result that of the four spermatids derived from each spermatogonium, two possess it and two are without it. In the female the two accessories pair and separate, so that one is present in every egg-nucleus. If all the spermatozoa are equally functional, half the zygotes will have one accessory, the other half two, and the natural inference was drawn that the former become males, the latter females. Such cases were at first known only in Orthoptera and Hemiptera; they have now been observed in most orders of insects except Lepidoptera and Hymenoptera, and in many other groups, a list of which is given later. Not all species of these groups, however, show this difference between the sexes, and doubt was cast on the sex-determining function of the accessory chromosome on the ground that its existence should be expected in every species which has two sexes. The next step was made by Wilson (**65**). He found that in certain Hemiptera the spermatogonia contained two "accessories," one of which was noticeably larger than the other, and that in consequence half the spermatids contained a large one, half a small, but that the females of these species had two large ones, so that each mature egg contains one. To avoid confusion he named these unequally paired bodies "idiochromosomes," and the unpaired body of the species previously described, a "heterotropic" chromosome. He further dis-

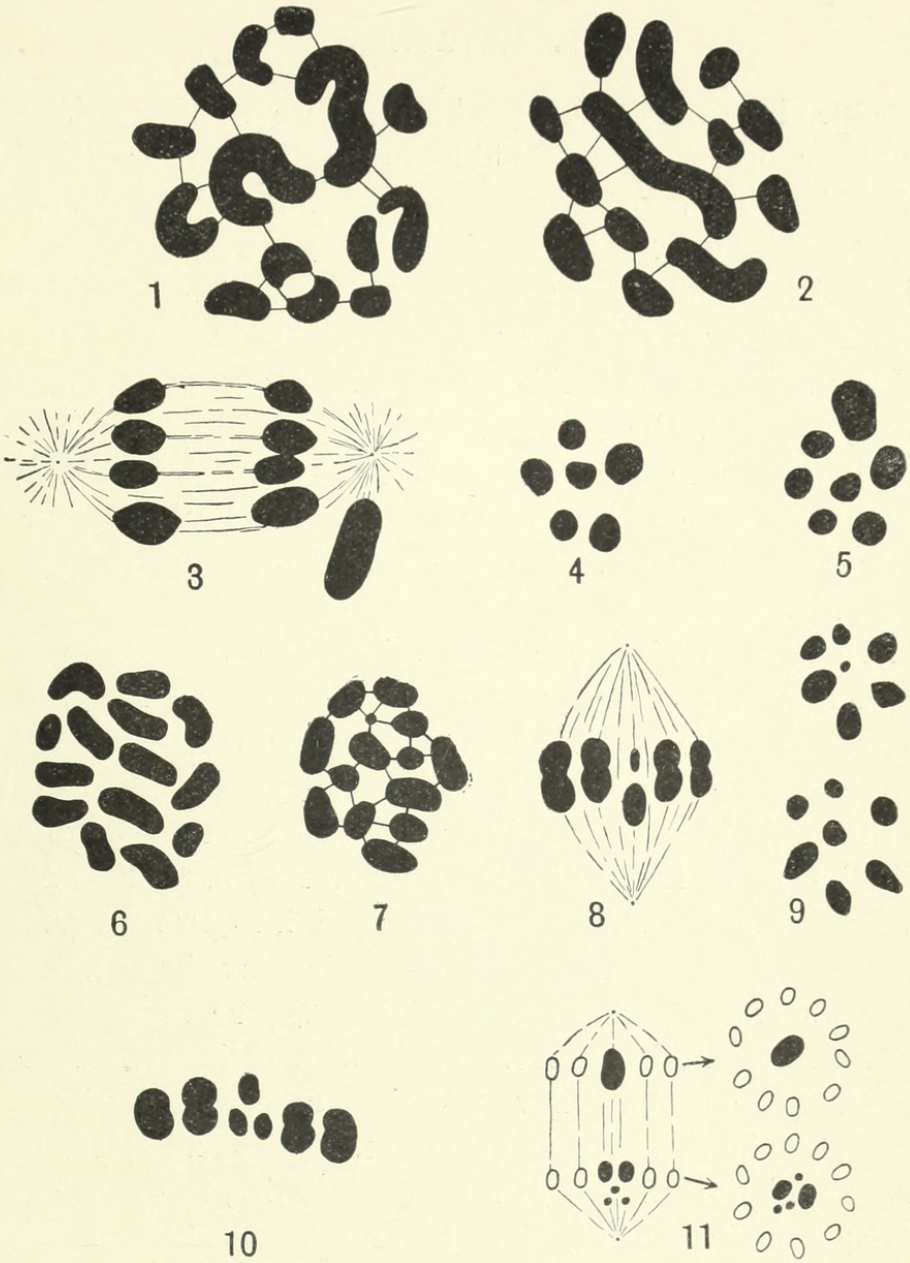
covered that in a series of species all stages could be found between cases in which both sexes had equally paired idiochromosomes, through the condition in which they are unequally paired in the male, to the extreme case of total absence of the smaller one in the male. It therefore seemed natural to conclude that whether they were in appearance alike or unlike in the male, they were different in function, and that, since one of them showed all stages of disappearance in related species, this one is probably not functional as a sex-determiner, even when it is present. Two main hypotheses have been suggested to explain their action. Wilson first suggested[1] that the two similar idiochromosomes of the female bear respectively male and female determiners, that the single functional one of the male bears a male determiner, and that selective fertilisation occurs in such a way that male-bearing spermatozoa fertilise female-bearing eggs, and spermatozoa without sex-factor fertilise male-bearing eggs, thus :



Femaleness is supposed to be dominant over maleness, and therefore the zygote MF is a female, Mf a male (f representing absence of sex-determiner). A second hypothesis, now more generally adopted, is due to Wilson and Castle (**67**, **14**), and is accepted by Morgan, who seems to have arrived at it independently : it is that sex is not due to specific male and female factors, but to the presence of one factor in greater or less amount. In the cases described, a " single dose " of this

[1] E. B. Wilson, ' Journ. Exp. Zool.,' iii, 1906, p. 29. The same suggestion was made on independent grounds by the writer (' Proc. Zool. Soc.,' 1906, p. 132, and ' Proc. Roy. Soc.,' B, lxxxii, 1910, p. 106).

TEXT-FIG. 2.



Forms of heterochromosomes in various Hemiptera. 1–5. Protenor belfragei (from Wilson). (1) Oögonial equatorial plate; two large heterochromosomes. (2) Spermatogonial equatorial plate; one large heterochromosome. (3) Anaphase, second spermatocyte division, side view; large heterochromosome below the right pole. (4, 5) Second spermatocyte division, polar view of two daughter-plates; heterochromosome in group 5. 6–9. Euschistus variolarius (from Wilson). (6) Oögonial equatorial plate; no conspicuously small chromosome. (7) Spermatogonial equatorial plate; one very small idiochromosome. (8) Second spermatocyte metaphase; large and small idiochromosomes in centre. (9) Sister groups, second spermatocyte division; small idiochromosome in upper, large in lower. 10 (from Wilson). Rocconota annulicornis, metaphase of second spermatocyte, showing large idiochromosome paired with two small. 11 (from Wilson, after Payne). Acholla multispinosa, second spermatocyte anaphase, showing large idiochromosome paired with five small.

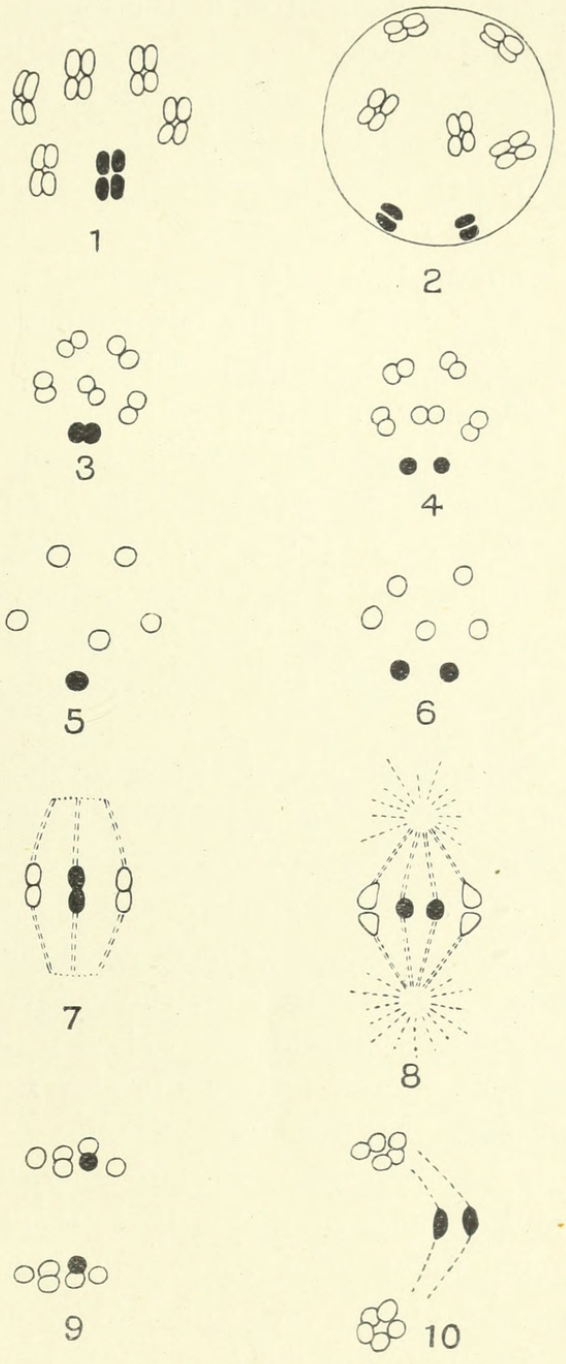
factor produces maleness, a double dose femaleness. The second hypothesis is preferable in not involving selective fertilisation, but involves certain other difficulties from which the former escapes.

Essentially similar phenomena with regard to sex-chromosomes have now been described not only in insects, but also in Myriapods (**9**), Arachnids (**8, 62**), Molluscs (**70**), Nematodes (**11, 23, 45, 51**), Birds (**24, 24a**), and Mammals (**27, 56, 68, 69**). In all these cases the male is described as having a deficiency of one (or sometimes two) chromosomes, or as having a small one in place of a corresponding large one in the female.

There are also a number of complications which have been observed in various cases, which will only be referred to shortly. In some species the male is described as having two or more chromosomes less than the female (**66, 47, 48**) ; in this case the two odd ones travel together into the same daughter-cell in the spermatocyte divisions, so that they may be regarded as behaving as one chromosome divided into two parts. In some cases both members of the pair may be compound. This class of facts is possibly of importance in connection with sex-limited inheritance. Cases of peculiar behaviour in hermaphrodite species have also been described, the true nature of which is at present obscure.[1] Two examples, however, must be given, one of a hermaphrodite, the other of a parthenogenetic species, since these have been worked out rather fully and add very important facts to our knowledge. The chromosome-cycle of the Nematode Rhabdonema (Rhabditis) nigrovenosum has been investigated independently by Boveri (**11**) and Schleip (**51**), from whose papers the following account is combined. The species, as is well known, has alternate generations which are hermaphrodite and bisexual. The hermaphrodites have as diploid number twelve chromosomes ; their primary oöcytes have six

[1] E. g. in Pteropoda, B. Zarnik, 'Verhandl. Deutsch. Zool. Gesellsch.,' 1911; summarised by Schleip, 'Ergebn. und Fortschritte der Zool.,' iii, 1912, p. 250.

TEXT-FIG. 3.



Oögenesis and spermatogenesis of the hermaphrodite generation of Rhabdonema nigrovenosum. (After Boveri.) Oögenesis on left, spermatogenesis on right. Heterochromosomes black. (1) and (2) Primary oöcyte and spermatocyte prophases; (3) and (4) daughter-groups of first maturation division; (5) and (6) equatorial plates of second maturation division; (7) and (8) diagrammatic side views of same stage; (9) and (10) anaphases of second maturation division. According to Schleip one of the heterochromosomes is included in one daughter-group, the second is left out entirely.

doubles, the mature egg six singles. The spermatogonia have twelve, the spermatocytes five doubles and two singles; the singles do not divide at the second spermatocyte division, and one of them gets left on the spindle, so that half the spermatids have six, half have five.[1] Half the fertilised eggs thus have twelve, and become females; half have eleven, and become males. In the gametogenesis of the free-living bisexual forms, all mature eggs contain six; in the males, the odd one does not divide at one spermatocyte division, so that half the spermatids have six and half five. Those with five appear to degenerate, so that all functional spermatozoa have six, and thus all fertilised eggs have twelve and become hermaphrodites. Why, in one generation, individuals with twelve become females, in the next, hermaphrodites, is not explained. It is noteworthy that the absence of one chromosome is not the cause of the production of spermatozoa rather than ova, since both oögonia and spermatogonia of the hermaphrodite have twelve.

The second special case is that of the Aphids and Phylloxerans described by Morgan (**35–37**) and von Baehr (**3**). Morgan's account of Phylloxera caryaecaulis may be taken as an example. The "stem-mother" has six chromosomes; her parthenogenetic eggs have no reduction and contain six. The parthenogenetic females produced from these eggs are of two kinds, which may be called female-producers and male-producers. Each form contains six chromosomes, but the male-producer has five large and one small, the female producer six large. Morgan suggests, without actually proving it, that the cause of this is that one of the chromosomes is compound, and part of it is extruded without division at the polar mitosis of the egg which gives rise to a male producer.[2] The male-producing female lays small eggs which

[1] This is Schleip's account of the second spermatocyte division; according to Boveri either both the "accessories" may be included in one spermatid or one may go into each, thus giving spermatids either with five and seven, or with six chromosomes.

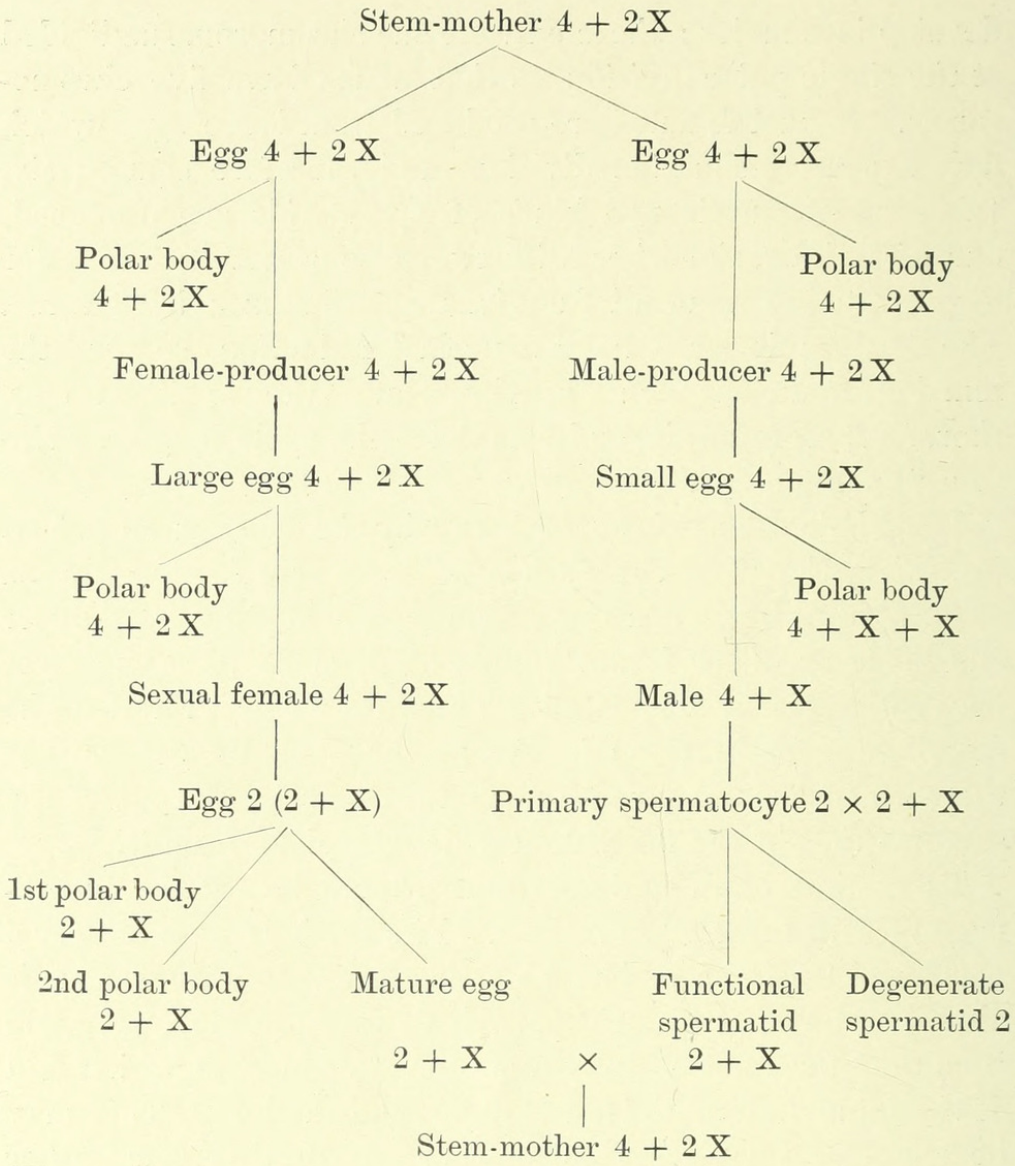
[2] In 'Heredity and Sex' (New York, 1913, p. 182), Morgan suggests that the difference between female-producer and male-producer may be

develop into males ; these extrude one chromosome undivided at the single polar division, so that males have five chromosomes. Sexual females are produced from large eggs which have a normal equation division, and therefore contain six. In spermatogenesis two kinds of spermatids are produced, one with three, the other with two chromosomes ; the latter degenerate, so that all functional spermatozoa have three. The fertilisable eggs have a normal reduction, so that the female pronucleus contains three, and the fertilised egg, therefore, contains six, and completes the cycle by giving rise to a "stem-mother."

The whole scheme is made clearer by the diagram on p. 504, in which the "sex-chromosomes" are represented by X. The difference between the chromosomes of female-producer and male-producer is not represented, since it has not yet been satisfactorily elucidated. The word "egg" refers to the egg before maturation ; in the parthenogenetic generations the chromosome group of the mature egg is, of course, the same as that of the individual which develops from it.

Two points of great importance should be noticed in connection with these observations. Firstly, it is possible for a polar division to occur in such a way that one chromosome is always thrown out with the polar body (male-producing eggs) ; it is, therefore, not entirely a matter of chance to which end of the spindle an undivided chromosome shall go. This may be a fact of very great moment in interpreting some other cases. Secondly, the absence of one X chromosome is not the ultimate cause of male-production, since it is predetermined in some way that some eggs shall extrude X (possibly by the loss of one portion of a compound chromosome in the previous generation), and that other eggs shall not. But this cannot logically be regarded as a proof that the presence or absence of X is not the cause of femaleness or maleness ; it only means that some factor is present which decides whether

referred back to the stem-mother ; there would be two kinds of stem-mothers, one of which produces female-producing offspring, the other male-producing.



X shall be extruded or not. So much emphasis has been laid on these facts by the opponents of the sex-chromosome hypothesis that a simple analogy may perhaps be forgiven. If in searching for the cause of a disease a pathologist found a bacterium, inoculation with which always produced the disease, he would be justified in assuming provisionally that this bacterium was its "cause." It would be no argument against his hypothesis to say that the "cause" was the injection-syringe, or the experimenter, both of which, however, may have to act before the cause can take effect.

In all the examples mentioned hitherto, the female has had

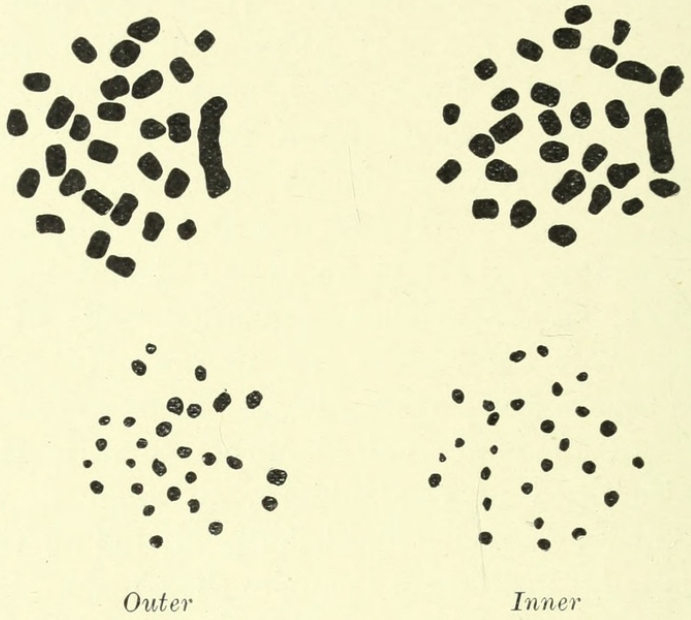
two similar "sex-chromosomes," the male one like those of the female and one smaller or absent. The facts of sex-limited inheritance make it probable that in some groups the converse arrangement should be found, and two cases of this have already been described, while the writer has a third at present under investigation. The first account of unequally paired chromosomes in the female was that of Baltzer in the sea-urchins Strongylocentrotus and Echinus (**4**), in which he describes a hook or horse-shoe-shaped element in half the eggs, replaced by a rod in the other half. Tennent (**60**), however, on similar evidence, concludes that in American species of Hipponoë and Toxopneustes it is the male in which there is an unpaired chromosome, and those who have had experience of detailed study of Echinoid chromosomes will regard the question as still open until further confirmation is forthcoming.

Recently an unequally paired chromosome in the female has been described in Lepidoptera, an order in which the probability of its existence had been predicted on the ground that sex-limited transmission occurs in the female. Seiler (**52**) describes in the eggs of the moth Phragmatobia fuliginosa a large chromosome which in one equatorial plate of the polar mitoses divides into two and in the other remains single. It may divide in either the inner or the outer plate. Since there are 27 ordinary chromosomes, the mature egg may contain either 28 or 29. All spermatocytes have 28. Since the equatorial plate of the first polar spindle has 28, there is no evidence to show whether the eggs which have the divided chromosome give rise to males or to females. Seiler inclines to the view that eggs with 29 give rise to females, but it is possible that both the large chromosomes of the male are really compound, and that only one is compound in the female.

The present writer has now under investigation a somewhat similar case in Abraxas grossulariata. In normal females of this species the oögonia have 56 chromosomes, but in a strain in which abnormal sex-ratios appear there are 55

(**17, 18**). In the eggs of females of the strain with 55 there are 28 in one equatorial plate of the second polar division, 27 in the other.[1] Since the females of this strain have 55 (diploid number),[2] and since all spermatozoa almost certainly

TEXT-FIG. 4.



Two upper chromosome groups, Phragmatobia fuliginosa, after Seiler: On the left, outer polar plate, 27 ordinary and one large chromosome (total 28). On the right, inner polar plate, which gives rise to egg nucleus, 27 ordinary and one large chromosome divided (total 29). Each figure was reconstructed from two sections. Two lower chromosome groups, Abraxas grossulariata: On the left, outer polar plate, 28 chromosomes; on the right, inner polar plate with 27. The two groups are separated by one section which contains no chromosomes; all the chromosomes of each group are in one section.

[1] There are certain points in connection with this case which still require further investigation, but that in eggs of this strain one polar plate has 27, the other 28, appears to be incontestible. In females not belonging to the strain referred to, both polar plates have 28, as would be expected from the oögonial number, 56.

[2] The exception in family 12·25, mentioned in the paper referred to, will be discussed in the full paper; no other exception to the number 55 was found in over forty larvæ of this strain in which oögonial figures could be counted.

have 28, it can hardly be doubted that eggs with 27 give rise to females, those with 28 to males. This case is thus exactly the converse of the typical examples of an "accessory" chromosome in the male, as seen in the Hemiptera, Orthoptera, etc. It is remarkable that in this case the male has one chromosome more than the female, although in forms in which the spermatozoa are dimorphic the male has one less. The bearing of this fact on theories of sex-determination will be referred to again later.

Finally, mention must be made of the conditions found in the Hymenoptera. In this order parthenogenesis is common, but differs from that of most parthenogentic animals in the existence of two polar divisions. Most commonly unfertilised eggs of Hymenoptera give rise to males; when females are produced parthenogenetically there is evidence that no reduction occurs, either because one or both polar divisions are suppressed,[1] or because both are equational. No case is known in which males are produced from eggs which are certainly fertilised, and in all which have been examined the male has half the number of chromosomes found in the female. The male has a haploid set, the female a diploid. Correspondingly, in all cases examined,[2] one maturation division of the spermatocytes is suppressed, so that the spermatocytes contain the same (haploid) number as the spermatogonia.[3] Nachtsheim (**46**) brings these phenomena into line with the facts known about sex-chromosomes by the suggestion that

[1] L. Doncaster, "Gametogenesis of the Gall-fly Neuroterus lenticularis," 'Proc. Roy. Soc.,' B, lxxxiii, 1911, p. 476. It should be noted that in Neuroterus, as in Morgan's case of Phylloxera, it is predetermined which eggs shall undergo reduction and become males, and which eggs shall suppress the maturation divisions and become females, since all the eggs laid by any one female behave in the same way.

[2] E.g. in the bee, F. Meves, 'Arch mikr. Anat.,' lxx, 1907, p. 414; H. Nachtsheim, 'Arch. f. Zellforsch.,' xi, 1913, p. 169; in Neuroterus, L. Doncaster, 'Proc. Roy. Soc.,' B, lxxxii, 1910, p. 88. Several other forms give concordant results.

[3] Armbruster, L., 'Arch. f. Zellforsch.,' xi, 1913, p. 242, interprets his observations on Osmia differently; his figures and discussion are not convincing.

two of the chromosomes of the female are sex-chromosomes. The male, with half the number, has only one, but since all spermatozoa bear it, all fertilised eggs have two, and so become females. Similar suggestions had previously been made by Wilson and others.

In this connection mention should be made of the conditions found in Rotifers, about which there has been some controversy, but the facts appear fairly clear. In Hydatina, Lenssen (**30**) has shown that in the parthenogenetic eggs which will become females one polar division is suppressed, while it takes place normally in male-producing eggs and in eggs which will be fertilised ("Dauereier"). He believed that female-producing parthenogenetic eggs produced no polar body, male-producing eggs and Dauereier, one. Whitney (**63**), however, has shown that female-producing eggs have one polar body, male-producing eggs two. The present writer has confirmed Lenssen's observations on the suppression of a polar division while the egg is in the oviduct,[1] but all the observations can be brought into line by assuming that in female-producing eggs the first polar division is suppressed, but that the second takes place normally after the egg is laid, and that in male-producing eggs the first takes place before, the second after laying. In Rotifers, therefore, as in Hymenoptera, the female probably has the diploid, the male the haploid number of chromosomes.

This completes the main lines of evidence connecting sex-determination with chromosome behaviour, apart from those derived from the facts of sex-limited transmission.

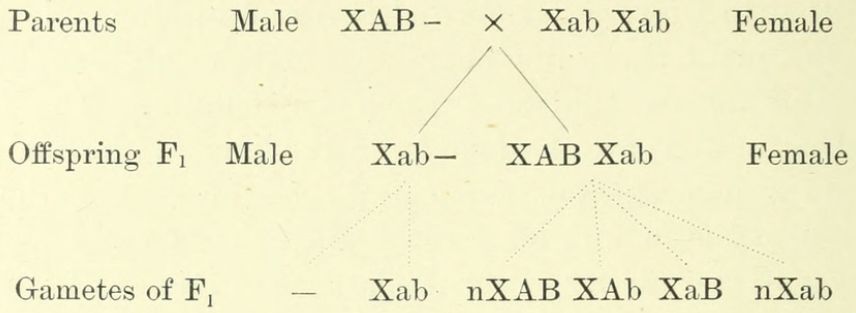
(3) Sex-limited Inheritance and Chromosomes.

Sex-limited inheritance may be defined as the transmission by individuals of one sex of a factor only or almost exclusively to offspring of the other sex. In different groups it occurs in different sexes. In the first cases to be discovered (Abraxas, canary, fowl) the female transmits certain

[1] Unpublished.

characters only to her sons, while the male transmits the same characters to both sons and daughters. Later it was found that in Diptera (Drosophila) and in Mammals (cat, man) the male transmits characters only to his daughters, while the female transmits them impartially. The facts show that in one case the female, in the second the male, is constantly heterozygous for certain features, and that in inheritance the factors for these features are closely coupled with a sex-determining factor. The case of Drosophila will be the most convenient to deal with first (**38–41**). Morgan finds that the male transmits certain of the normal features of the species (red eye, long wing, brown colour) only by his female-producing gametes, so that when mated with a female lacking any of these characters, the male offspring are without them. Now the male Drosophila has been shown by Miss Stevens (**55**) to have a pair of unequal chromosomes, and Morgan makes the not unnatural assumption that the larger of these chromosomes bears not only the sex-factor, but also the factors for the sex-limited characters. Since half the spermatozoa contain the larger chromosome, and half lack it, and since all the eggs contain it because it is equally paired in the female, half the zygotes have it in duplicate and become females, half receive it only from the mother and become males. And since, by hypothesis, the larger idiochromosome of the male bears both the sex-factor and the factors for the sex-limited characters, the latter are transmitted by the male to his female offspring only. Morgan has carried this conception further in connection with the phenomena of gametic coupling. When a male having two sex-limited characters is crossed with a female lacking both, the female offspring have both, the males neither. In the gametogenesis of the heterozygous female so produced, the two factors are, in some cases, not distributed evenly among the gametes, but tend to be associated, so that the gametes which bear either both or neither are much more numerous than those which bear one only. A diagram will make this clearer, in which the two characters concerned are represented as A

and B, their absence as a and b, the sex-factor as X, and the absence of sex-factor by a dash (—).



The number n, by which the combinations AB or ab outnumber aB and Ab, varies in the case of different characters from quite small numbers to 100 or more. Now Morgan supposes that in the synapsis stage of the first-cross female (F_1), the chromosomes XAB and Xab pair together, and become twisted round one another as was mentioned earlier, and that in subsequent separation it is possible for A to exchange places with a and B with b, and that the frequency of this interchange ("crossing over") will depend on the positions of the units representing A and B in the elongated chromosome.[1] In the male, no such "crossing over" is possible, since the chromosome XAB or Xab has no similar mate.

There is one difficulty, however, which makes this "crossing-over" hypothesis doubtful, in spite of its beautiful simplicity. It is that exceptions to sex-limited transmission occur in almost all the known cases. Morgan himself has recorded some in Drosophila, but prefers to regard them as due to experimental error. In other cases, however, they are indubitable. If sex-limited transmission were due to the existence in an unpaired chromosome of the units determining the characters, those characters must always without exception be transmitted from the male to the female, or, in the Lepidoptera-bird group, from the female to the male. Exceptions, however, always occur, with greater or less frequency

[1] This idea has been worked out in some detail in the case of Drosophila by A. H. Sturtevant, 'Journ. Exp. Zool.,' xiv, 1913, p. 43.

in different cases, and another explanation, equally concordant with the known facts of chromosome behaviour, is available. It has been shown by several observers (**66**, **47**) that the "sex-chromosome" is not infrequently compound, and in one case (**49**) the two parts are constantly separate, though they are reported always to go to the same pole of the spindle. If now one portion of the "sex-chromosome" bears the sex-factor, the other portion the sex-limited factors, failure of sex-limited transmission will arise whenever the components of the chromosome become separate, and go to different poles. The frequency with which this happens may be expected to vary in different cases. This suggestion, due originally to Wilson (**66**), really differs from Morgan's only in the supposition that the sex-chromosome is commonly coupled with a chromosome which bears the sex-limited factors, instead of assuming that these factors are borne in the sex-chromosome itself. The exceptions to the normal sex-limited transmission make this latter assumption untenable.[1]

The facts of sex-limited transmission thus support the hypothesis that both ordinary Mendelian factors and the sex-determining factor or factors are borne by chromosomes, although the details of their relations are still very far from being clear.[2] That there is some intimate relation, however, between a chromosome and the transmission of sex-limited characters is almost certain from the fact that sex-

[1] Since this was written Bridges (12a) has suggested a hypothesis to avoid this difficulty. He assumes that exceptions are caused by "non-disjunction" of the sex-chromosomes, so that both go into one germ-cell. This explanation, if substantiated, would account for most of the recorded exceptions, but not that of the tortoiseshell male cat, which contains both the colour-factors characteristic of the female, but must be supposed to have only one sex-chromosome.

[2] The recently published work of Miss K. Foot and Miss E. C. Strobell ('Biol. Bull.,' xxiv, 1913, p. 187) cannot be used as an argument against this proposition. They have shown (as was previously known in birds and moths) that a secondary sexual character in Hemiptera can be transmitted through the sex which does not show it, but the character was not sex-limited in transmission; their results, therefore, have no bearing in the present discussion.

limited transmission by the male is only known in groups (Diptera, mammals) in which unpaired or unequally paired chromosomes have been found in the male, while of the two groups (Lepidoptera, Birds) in which sex-limited transmission by the female occurs, in one (Lepidoptera) two cases have now been described of an odd element in the female. It can hardly be coincidence that the spermatozoa should be dimorphic in respect of a chromosome in the forms in which sex-limited transmission by the male takes place, and the eggs diamorphic in the same way in those in which sex-limited transmission is by the female. It should be noted also that the unpaired chromosome has been described as compound in mammals, and one of the unequal elements as compound in Phragmatobia (moth) and possibly so in Drosophila, so supporting the suggestion that sex-limited inheritance is related to the association of a chromosome with the sex-chromosome.

One anomalous observation, however, must be mentioned. Guyer (**24, 24a**) has described an unpaired accessory chromosome in the male of the fowl and guinea-fowl, although only sex-limited transmission by the female is known in birds (fowl, canary, pigeon). Either his observation is mistaken,[1] or the facts are less simple than other cases would suggest. On Wilson's earlier hypothesis that both sexes are heterozygous for sex-factors, with selective fertilisation, the case causes no difficulty, although it is fatal, if substantiated, to the later hypothesis of the presence or absence of one single sex-factor. In this connection it may be mentioned that there are some isolated instances which suggest that in cases which have normal sex-limited transmission by one sex, there may be partial coupling of the same characters with a sex-factor in the other sex. Such cases are so doubtful and irregular in their appearance that they cannot be regarded as evidential at present, but if they should be found to be genuine, they would also support the hypothesis that both sexes are heterozygous.

[1] As this goes to press, it has been contradicted by A. M. Boring and R. Pearl ('Journ. Exp. Zool.,' xiv, 1914, p. 53).

In general, therefore, the facts of sex-limited inheritance support the contention of a direct relation between chromosomes and the transmission of inherited characters, although they do not as yet enable us to choose between particular theories of sex-determination.

(4) Conclusion and Summary.

The various classes of facts which have been described in the last two sections, if considered by themselves, provide strong evidence for the existence of an intimate relation between the presence or absence of a particular chromosome and the determination of sex. The case for the relation of chromosomes to Mendelian factors is less conclusive, but if the connection between chromosomes and sex-determination be admitted, the facts of sex-limited inheritance make it almost impossible to reject the belief in a similar connection with Mendelian factors. There are, however, certain rather grave difficulties in the way of accepting the conclusion with regard to sex which demand a few words of explanation.

In the first place, if sex is constantly determined by the presence or absence of a particular chromosome, it is difficult to understand why, within one group of animals, species of one order or class give indications that such a chromosome exists only in the male, although species of another order give exactly similar evidence that it is present only in the female. This difficulty disappears if the hypothesis is adopted that both sexes are heterozygous for sex-factors (♀ = MF, ♂ = Mf), and that there is selective fertilisation in such a way that M-bearing eggs are only fertilised by f-bearing spermatozoa, F-bearing eggs by M-bearing spermatozoa. It must be admitted, however, that in the absence of any direct evidence for selective fertilisation, this hypothesis is very speculative. A suggestion which is perhaps more probable is that there are two independent sex-factors, M and F, and that when both factors are homozygous (MMFF), in some forms M is epistatic over F, giving a male; in others, F is

epistatic over M, giving a female, but that either, when homozygous, is always epistatic over the other when the latter is heterozygous. In this case, in the majority of insects and in mammals the male would be represented MMFf, the female MMFF, while in Lepidoptera and birds the male would be MMFF, the female MmFF. This hypothesis is in accord with the observed fact that in many insects and some mammals the male has one heterochromosome, the female two, while in the peculiar strain of Abraxas described, it is the female which has one chromosome less than the male.

A second problem, which is really more closely connected with this one than may appear at first sight, arises from the considerable number of cases in which sex is actually or apparently altered by conditions acting on the unfertilised egg or on the developing individual. In addition to such instances as that of the crab infected with Sacculina, in which Geoffrey Smith has shown that males may so far assume female characters as to produce ova in the testis, there are many cases in which such conditions as staleness of the eggs cause alterations in the sex-ratio (usually by increasing the proportion of males) which cannot be explained by selective mortality, nor, in fact, by any known cause except a change in the sex-determining power of the eggs.

Such cases would seem to offer an almost insuperable obstacle to the belief that sex is determined by the presence or absence of a particular chromosome, and yet the facts with regard to chromosomes are too clear and definite to be disregarded on this account. It is possible, however, that suggestions towards a reconciliation can be found by taking into consideration some of the facts which are known about the relations of sex to general metabolism. G. Smith (**53**) has shown that the change from male to female secondary sexual characters in the crab infected with Sacculina is accompanied by deep-seated metabolic changes which are induced by the parasite. Steche (**54**) has brought forward somewhat similar evidence in the case of Lepidopterous larvæ. He finds that there are important metabolic differences

between the sexes, and that, when estimated by precipitin tests, there is nearly as much difference between the blood of the male and female of one species as between the bloods of the same sex of related species. Such observations as these, taken together with the fact that the secondary sexual characters of each sex can be inherited through the other sex (**61**), suggest that possibly the fundamental difference between the sexes is not a factor which directly determines whether the individual shall possess testes or ovaries, but is really a difference of metabolism.

Where differences of metabolism are found in the two sexes it has usually been assumed that these are caused by the presence of testes or ovaries, by means of hormones or other internal secretions. It may, however, be worth while to consider whether the metabolic differences are not primary, and whether the primitive gonad may not develop into an ovary in one case and a testis in the other in consequence of a fundamental difference existing in all the cells. In vertebrates the secondary sexual differences are largely dependent on the presence of a functional ovary or testis, but in insects this is not the case, and if Steche's observations are substantiated they indicate that all the cells of the body are different in the two sexes. Further, the existence of occasional gynandromorphs in vertebrates, in which one side of the body has male characters, the other female, while the gonad contains both male and female elements, shows that there must be some difference in the tissues of the two sides of the body on which the secretion of the gonad can act.[1] If, then, there is any truth in the conception here outlined, the presence or absence of a chromosome does not affect the primary sexual organs directly, but, perhaps by its presence in every cell, alters the whole metabolism in such a way that the organism is caused to become of one sex rather than of the other, in consequence of its type of metabolism. There is no necessary reason, however, for supposing that other causes might not alter the metabolism in the same way. Geoffrey Smith has, in fact,

[1] This was pointed out by C. J. Bond at the British Association, 1913.

indicated the means by which it is affected in sacculinised crabs, and it is conceivable that other causes, such as "staleness" of the eggs before fertilisation, might from the beginning change the metabolism (perhaps by destroying the activity of a "sex-chromosome," as suggested by Pearl and Parshley (**50**)), in such a way as to cause an originally female-producing egg to develop into a male.[1]

The general conclusion must be that although the observations connecting a particular chromosome with the determination of one sex are in many cases indisputable, there is no evidence to show how this chromosome acts; and that, since the sex of the offspring is in some cases modifiable by environment, it is probable that the presence of the chromosome is associated with a particular kind of cell-metabolism, of which sex is to be regarded rather as a visible expression than as a cause.

Summary.

In the first section a summary is given of the main lines of argument leading to the conclusion that "Mendelian characters are determined by chromosomes." Some indication is given of the restrictions which must be placed on the meaning of this phrase in respect of the part played by the cytoplasm in heredity. It is concluded that the arguments in its favour, though very strong indirectly, are not supported by sufficient direct evidence to be regarded by themselves as indisputable.

In the second section the chief classes of facts are reviewed which suggest a relation between chromosomes and sex-determination, and a preliminary account is given of a new case of an unpaired "sex-chromosome" in the female, in a strain of the moth Abraxas. It is concluded that the arguments for a relation between chromosomes and sex are much

[1] The production of workers from female-producing eggs of the Hymenoptera is possibly a comparable instance. A change of metabolism induces fundamental differences in structure between individuals whose inherited constitution is identical, and these differences are of essentially the same nature as those which distinguish the two sexes.

stronger than those connecting chromosomes with Mendelian factors.

In the third section the facts of sex-limited inheritance are discussed; these are regarded as strongly reinforcing the arguments of the two preceding sections.

Lastly, certain difficulties are considered, and it is concluded that sex cannot be determined directly by the presence or absence of a factor which merely determines whether an ovary or a testis shall develop, but that the determining factor causes a certain type of metabolism, which in turn leads to the production of one sex or the other. If such a metabolism is induced by other causes, an individual of one sex may probably arise from gametes which, in the absence of disturbing causes, would have given rise to the other sex.

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