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ON

THE MECHANISM OF INHERITANCE.

GIVEN TO THE DUNDEE BRANCH.

BY

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As the facts concerning inheritance, secured by observation, accumulated, it came to be noted that in them could be recognized an orderliness, an interrelationship. It was then inevitable that the human mind, in its inherent desire to trace and describe order in nature, should seek some mechanism that in its working could account for these facts. So the idea of an "idioplasm" (Nägeli and others), a special substance the function of which was to transmit and control the hereditary characters, details of form and of function, in the developing individual came into being. This idioplasm remained a purely theoretical conception until Wilhelm Roux (1883), out of his work on cell division, was able to point out that many of the functions of this hypothetical substance could be performed efficiently by the nuclear chromatin. Upon this suggestion Weismann (1886, 1894) modelled his theory of the germ-plasm; but inspiring as his hypothesis was, it was constructed at a time when knowledge of the essential organization of the cell was still incomplete and insufficient. Since that time, however, a considerable body of knowledge concerning the cell has emerged from investigations in cytology, microdissection, and tissue culture, and to-day there exists a very clear picture of the living cell which allows the statement to be made with a certain degree of confidence that the chromosomes, because they most nearly satisfy the demands made upon the mechanism of inheritance by the accumulated facts of experimental breeding, are to be regarded as this idioplasm. It can be shown that the only identifiable cell organs that can satisfy these demands are the chromosomes; in their behaviour is realized the precise conditions of hereditary transmission demanded by the results of countless breeding experiments. The theory relating to the functions of the chromatin in inheritance is known as the chromosome theory of heredity.

Of the characters of the living organism known to be hereditary there are two classes—those in which the mode of inheritance has been amply demonstrated, and those as to which sufficient knowledge is as yet not available. Critically controlled experimentation soon demonstrated that the inheritance of characters was not haphazard, but subject to definite rules or laws. It also quickly became apparent that the most striking fact which emerged from a survey of these laws of inheritance was that they applied with equal force to all sorts of living things, that laws established from a study of one organism applied with minor, often readily interpretable, exceptions to all the rest. It can be stated that the principles established by a study of experimentally convenient animals may be applied with success to forms with which, because of various practical difficulties, there has been as yet insufficient experimentation. Man, exceptional in many ways, is essentially similar to those forms of life with which the geneticist has worked; in fact, investigation has already shown that many of his characters—morphological, physiological, psychological—are subject to the universal laws of inheritance. Knowledge of inheritance in the human is essential for accurate diagnosis and prognosis in medicine, and must become the basis for any sound and scientific effort in racial improvement. Problems of human inheritance must be studied by somewhat different methods from those employed in the case of the ordinary experimental stocks. Direct experimentation is impracticable, and the only method now available is that of collecting and analysing sufficient data gleaned from family histories. For examples that clearly illustrate the fundamental orderliness and precision in the transmission of hereditary characters it is desirable to turn to the usual experimental

materials of the geneticist. Examples of similar modes of inheritance in the case of human characters are abundant.

It is most convenient to call upon the Dipteran, *Drosophila melanogaster*, the fruit-fly, for illustrations of the different modes of inheritance of characters, for the reason that to its study we owe most of our knowledge of the hereditary mechanism.

(A) If as a parental generation (P_1) a fly with the wild type "long" wings is mated to one with vestigial wings (this character, "vestigial wing form," appeared as a sport or mutation in a long-winged stock) the first filial generation (F_1) are all long-winged. The character "long-winged" is dominant and in relation to it vestigial is recessive. If these F_1 long-winged flies are interbred they will produce a second filial generation (F_2) which includes two classes of flies in respect of wing form—long-winged and vestigial—and in every four on the average there will be three of the former to one of the latter.

(B) If a vestigial-winged fly with the wild-type body coloration grey is mated with a long-winged ebony-coloured fly (the ebony coloration appeared as a mutation in a grey stock) the F_1 flies will all be long-winged greys (grey is dominant to ebony). They will exhibit the two dominant members of the two contrasted pairs of characters. If these F_1 flies are interbred they will produce four classes of offspring in F_2 —long-winged greys, long-winged ebones, vestigial greys, and vestigial ebones—and in every sixteen, on the average, these four classes will appear in the relative proportions of 9 : 3 : 3 : 1. It is to be noted that the two characters of respective parents, vestigial grey and long-winged ebony, have become dissociated and recombined.

(C) If a long-winged grey F_1 male out of the mating vestigial grey and long-winged ebony is mated with a vestigial ebony female, there will be produced four classes of offspring in equal numbers—long-winged greys, long-winged ebones, vestigial greys, and vestigial ebones.

(D) If a vestigial black fly (not ebony, but another mutant character very similar on inspection) is mated with a long-winged grey, all the individuals of the F_1 generation will exhibit the two dominant characters—long-winged and grey. If a male of this generation is mated to a vestigial black female (that is, one exhibiting the two recessive characters), only two classes of offspring will appear—vestigial blacks and long-winged greys—and these will be produced in equal numbers. It will be noticed that the character associations in this generation are exactly those that were exhibited by the two flies with which the experiment started.

(E) If instead of the F_1 male (as in D) an F_1 long-winged grey female is mated to a vestigial black male, then four classes of offspring will be produced, not two as in (D), and not in equal numbers as in (C), but in the following relative proportions: long-winged greys 41.5 per cent.; vestigial blacks 41.5; long-winged blacks 8.5; and vestigial greys 8.5. It is to be noted that this result differs from that in (D) in that there is a dissociation and recombination of characters, but only to a certain limited extent.

(F) If a white-eyed male is mated to a (wild type) red-eyed female, all the F_1 males and females alike, will be red-eyed, and if these F_1 individuals are interbred the F_2 will consist of three reds to one white in every four on the average (see A); but all the white-eyed individuals will be males. The recessive character of a grandfather is exhibited by none of his children, by none of his granddaughters, and by only 50 per cent. of his grandsons.

(G) If, on the other hand, a red-eyed male is mated to a white-eyed female, then all the males of F_1 will exhibit the white-eye character of their mother, whereas all the F_1 females will exhibit the red-eye character of their father. There will be criss-cross inheritance, sons "taking after" their mother, daughters after their father.

These are the main modes of inheritance that have to be accommodated by the hereditary mechanism. It is now to be shown how the chromosome mechanism can accommodate them. From a consideration of these facts there can emerge an appreciation of the exact demands that must be made upon the hereditary mechanism. The chromosomes in their architecture and behaviour must be examined in the light of these demands.

In medical practice the questions that are asked and have to be answered are these: If an individual with a certain characterization marries and has children, will these be normal? How is it that to perfectly normal parents a child with a peculiar characterization is born?

The geneticist is not concerned with the nature of a character, whether it is helpful or harmful; he is concerned solely with the mode of its inheritance. If accurate pedigrees are available, it is usually a simple matter to answer these questions. Most of the human characters so far investigated belong either to type (A) or (F) or (G) above. If it is established that a certain character, such as brachydactyly or diabetes insipidus, is a simple dominant, or that it is sex-linked as in (F) and (G)—for example, haemophilia or colour-blindness—reference to the interpretations given in this paper will enable the practitioner to predict and to explain.

It is to be stated that even yet there exists but little definite knowledge concerning the chemical nature of chromatin; it is known, however, that it is intimately related to the activities of the cell as a whole; that it has a definite architecture and disposition within the nucleus; that it is a semifluid colloid which undergoes gelations and liquefactions of a limited and definite order, and is continuous with the nuclear matrix and thence with the cytoplasm. It is known that during mitosis the chromatin becomes condensed and homogeneous and then displays most clearly the nature of its organization into units, the chromosomes. It is established that the number, size, form, and behaviour of the chromosomes are constant in a species and are characteristic of that species (Fig. 1). It

FIG. 1.—The chromosomes of man. (After Painter.)

is known that even when the chromatin is thus condensed in the form of chromosomes it still retains its organic contact with the non-chromatic part of the cell of which it is but a part, though an essential part. It is to be understood that the modern theory of inheritance does not require a special idioplasm concerned solely with hereditary transmission. Reproduction is a function of the cell as a whole, dependent, however, like all its other properties, upon the presence of nuclear chromatin. However, it can be stated that all the evidence there is points to the fact that in the gamete the chromatin alone possesses those attributes of constancy of proportion and behaviour which would appear to be necessary to satisfy the theoretical requirements of an idioplasm. It will be noted that among the bisexual species reproduction is effected by the combined activities of two sexually differentiated parents, each of which contributes to the new individual but a single cell. Yet these gametes, which in their union form the zygote in which the new individual has its being, constitute the only material link between the generations, the narrow bridge across which all the organic inheritance must pass. The fertilized ovum is a new individual, specific to the highest degree, embodying all the possibilities of individual development and racial perpetuation. In certain favourable cases (such as that of *Ascaris megalocephala*, Boveri) it has been possible to trace back in a continuous series to the fertilized ovum in which all the cells of the body have their origin the gametes elaborated by that particular individual. There is a definite cellular continuity through all cell generations.

There are four pairs of homologous chromosomes in the body cells and immature gametes of *Drosophila melanogaster*, the members of any one pair being identical in size and shape (with the exception about to be stated). In the ripe gamete, egg or sperm, there are four single chromosomes, and because the chromosomes of the different homologous pairs differ one from the other in their size, shape, and relative position, it can be demonstrated that in the ripe gamete there is present one member of each pair, and that in the fertilized egg the diploid (double) number

is restored, and that of each reconstructed pair one member has been brought into the zygote by the sperm, the other by the egg. In respect of its chromosomes, the new individual receives from each of its parents one member of each homologous pair.

The chromosome picture differs in the two sexes. In the tissues of the female the members of each pair of chromosomes are identical. In the case of the male tissues one member of one pair is exactly similar in form, size, and disposition to the two members of the corresponding pair in the female, but its mate is unequal, is dissimilar. Since in respect of this pair the sexes differ, these chromosomes in the two sexes are referred to as the sex-chromosomes. The three chromosomes that are alike, two in the female and one in the male, are referred to, for descriptive purposes, as the X-chromosomes; the unequal mate of the X in the male is known as the Y-chromosome. Since of each pair of chromosomes only one can be present in the ripe gamete, then in respect of the sex-chromosomes all eggs must be alike, each containing an X, whereas there will be two sorts of sperm—the X-chromosome-bearing and the Y-chromosome-bearing. If an X-bearing egg is fertilized by an X-bearing sperm, an XX-bearing zygote will result. The male is digametic, the female monogametic in *Drosophila*, as also in man. The XX type of chromosome content is the female. If an X-bearing egg is fertilized by a Y-bearing sperm an XY type of individual will result, and this constitution is typical of the male. Here, then, is a simple and satisfactory self-perpetuating sex-determining mechanism.

FIG. 2.—Conventional diagram of the chromosomes of *Drosophila*. (After Morgan.)

The 3:1 ratio in the F_2 of an experiment such as that dealt with in (A) above can be explained if the following assumptions are made. The chromosomes are the idioplasm. In them are resident the agents or factors or genes which in their action determine the future characterization of the individual, controlling the differentiation of the organs and tissues during ontogeny. There is a gene for long-winged and another gene for vestigial, but only one of these can be present at any one time in the particular chromosome that carries them. In each of the chromosomes of a particular pair in the long-winged race there is a gene corresponding to the character long-winged; in the case of the vestigial race there is instead a gene for vestigial. In respect of this same pair of chromosomes the F_1 individual will have received one from each parent; each will carry the factor for long-winged in one chromosome of a pair, the factor for vestigial in the other. Why one gene in its action dominates the other we do not know; the observed fact is that in their relationship to vestigial and long-winged the latter is dominant. When these F_1 individuals elaborate their gametes, into each passes either the chromosome bearing the gene for long-winged or else the chromosomes bearing the gene for vestigial. If there are equal numbers of the two sorts of eggs and equal numbers of the two sorts of sperm, and if fertilization is at random, the following chromosome associations will result, and the four sorts will be equally frequent:—long-winged : long-winged; long-winged : vestigial; vestigial : long-winged; and vestigial : vestigial. Since the character long-winged is dominant to vestigial, there will be on the average in every four three long-winged flies to each vestigial in F_2 .

The 9:3:3:1 ratio in (B) above can be explained if it is assumed that the genes for the body colour characters, grey and ebony, are not resident in the same chromosome pair as are those for vestigial and long-winged (E=the gene for grey; e that for ebony). Grey and ebony

FIG. 3.—The chromosome interpretation of a monohybrid experiment.

When these F_1 individuals elaborate their gametes, into each passes either the chromosome bearing the gene for long-winged or else the chromosomes bearing the gene for vestigial. If there are equal numbers of the two sorts of eggs and equal numbers of the two sorts of sperm, and if fertilization is at random, the following chromosome associations will result, and the four sorts will be equally frequent:—long-winged : long-winged; long-winged : vestigial; vestigial : long-winged; and vestigial : vestigial. Since the character long-winged is dominant to vestigial, there will be on the average in every four three long-winged flies to each vestigial in F_2 .

The 9:3:3:1 ratio in (B) above can be explained if it is assumed that the genes for the body colour characters, grey and ebony, are not resident in the same chromosome pair as are those for vestigial and long-winged (E=the gene for grey; e that for ebony). Grey and ebony

in their relations to each other are exactly similar to long-winged and vestigial. Grey is dominant, and in the F_2 of a grey by ebony mating there are three greys to each ebony on the average in every four.

FIG. 4.—The chromosome interpretation of a dihybrid experiment.

Any zygote with the genes—

- V and E will be long-winged grey — 9
- V but not E will be long-winged ebony — 3
- E but not v will be vestigial grey — 3
- Without E and V will be vestigial ebony — 1

The results obtained in (C) can be explained just as simply as seen in Fig. 5. The sperms of the male will be

FIG. 5.—The chromosome interpretation of a back cross, showing free assortment.

of four sorts (as above) and they will be produced in equal numbers. All the gametes of the female will be alike in respect of the genes for vestigial and ebony. It follows, then, that since vestigial ebony are recessive characters, the number and proportion of the classes in the resulting generation are predetermined by the number and proportion of the different sorts of sperm elaborated by the male.

- VvEe ... Long-winged greys ... 25 per cent.
- Vvee ... Long-winged ebones ... 25 per cent.
- vvEe ... Vestigial greys ... 25 per cent.
- vvee ... Vestigial ebones ... 25 per cent.

It will be recognized that so long as there are as many chromosomes as there are independently heritable characters there is no difficulty in accounting for the mode

of their transmission, as will be seen from the following table.

No. of chromosomes in the gamete (the haploid number).	No. of possible combinations of maternal and paternal chromosomes in the zygote.
1	4
2	16
3	64
4	256
5	1,024
6	4,096
7	16,384
8	65,536
9	262,144
10	1,048,576

In the case of the human there are twenty-four chromosomes in the gamete, so that it can be seen that infinite variety in the zygote is possible, even though only one gene were borne on one chromosome.

In *Drosophila* there are many hundreds of characters that can be paired off in the same way as vestigial and long-winged, grey body colour and ebony, yet in each gamete there are four chromosomes to bear their genes. It follows that either the chromosome hypothesis fails to satisfy the demands made upon it, or else more than one gene is resident in one and the same chromosome. If the genes for several different characters are resident in one and the same chromosome, then if that chromosome preserves its integrity during its transference from cell to cell the characters corresponding to the genes resident therein should be transmitted together and should remain linked in inheritance.

FIG. 6.—The chromosome interpretation of a back cross, showing linkage.

If the genes for black and vestigial are resident in one and the same chromosome, then the results obtained in (D) above can be interpreted. FR_1 is a symbol indicating that an F_1 individual is backcrossed to a recessive. FR_2 represents the resulting generation.

It has been found that all the characters so far examined in *Drosophila* fall into four groups. The members of any one group give this 50 per cent. : 50 per cent. ratio when any pair of them are involved in a breeding test similar to that above; but when any one of them is associated with a member of any other group the result is a 25:25:25:25 ratio, similar to that in the vestigial-ebony experiment described above. There are four linkage groups, and four chromosomes. It is reasonable to argue that upon a particular chromosome are resident the genes of a particular group of characters. More will be said of this conception later.

In (E) it is seen that this 50:50 ratio is not obtained when an F_1 female is mated with the double recessive. It will be agreed that the reason for the production of four classes of offspring instead of two must be that the F_1 female elaborated four sorts of eggs instead of two, for the sperm of the double recessive male are all alike, and since the characters vestigial and black are recessive, they will not disguise the results. The classes and the proportion of these can be explained if the F_1 female elaborated the following kinds of eggs in the proportions suggested.

B	V	b	v	B	v	b	v
41.5	41.5	8.5	8.5				

In order that these four sorts shall be elaborated in these proportions, it is necessary that in the maturation of 17 per cent. of the eggs there shall be an interchange of chromatin between the chromosome B-V and b-v in such a way that the part of the one chromosome carrying the gene B shall be detached from the rest carrying V; that the parts of the other chromosome shall be similarly separated; and

that these chromosomes shall then reunite in such a way that part of one unites with part of the other, as in D of Fig. 7. It will be noted that interchange leads to

FIG. 7.—Crossing-over.

significant results only when the chromosomes concerned are dissimilar in their genetic constitution. It is in the case of the "heterozygous" female that crossing-over leads to the production of recombination classes. For reasons at present unknown crossing-over does not occur in the case of the digametic sex of *Drosophila*, though it does in other forms.

The two new combinations after the interchange has taken place show again the same linkage relations to each other as did the former associations, showing that the linkage relation is independent of the characters that form the combination. Linkage between black and vestigial is exactly similar to that between grey and vestigial, and between black and long-winged. Such an interchange of chromatin between the two members of a pair of homologous chromosomes is known as crossing-over, and the percentage of the recombination or cross-over classes is referred to as the crossing-over value (C.O.V.), whilst the linkage between two genes is expressed by the percentage of cases in which they remain together. If the linkage in a particular case is 50 per cent. and the C.O.V. 50 per cent., the result would exactly simulate the effects of free assortment giving a 25:25:25:25 per cent. ratio. As a matter of fact, this situation has not arisen in the case of *Drosophila*, being prevented by the occurrence of double crossing-over, fracture and reunion at two points in the chromosome some distance one from the other.

It will have been recognized that this theory of inheritance, like many of its predecessors, postulates the existence of a number of individual particles of substance each of which controls the development of some particular tissue or character in the developing organism. Like the gemmules of Darwin, the biophors of Weismann, the physiological units of Spencer, the pangens of de Vries, the genes of Morgan are required to be minute yet distinct units of, or areas in, the chromatin. It is, therefore, of profound interest to know that the chromosomes are indeed made up of small aggregates, the chromomeres. It has been established in favourable cases that a particular chromosome always exhibits the same series of chromomeres in any stage when they can be identified. Wenrich (1916) in the grasshopper (*Phrynotettix magnus*) has shown that any particular chromosome, to be recognized by its distinctive shape, size, and behaviour, is built up of a definite number of chromomeres, and that these are to be individually recognized by constant differences in form and relative position. The chromosome has a definite and constant organization.

The fact that the chromomeres are arranged in the chromosome in a linear series and that each chromomere has its own particular place or locus in this series is of prime importance in the interpretation of linkage and crossing-over.

FIG. 8.—Chromomeres in linear series. Conjugating chromosomes of the marsupial *Petauroides*. (After Agar.)

During the maturation divisions in the production of the gametes the segregation of homologous chromosomes is complicated by the fact that the members of each pair, prior to their separation, become most intimately intertwined. This apparently single but really double chromosome then splits longitudinally. This conjugation of homologous chromosomes provides the opportunity for

crossing-over. It cannot be shown to have occurred, but if during this conjugation the two chromosomes stick, fracture, and rejoin before separation, then interchange of chromatin will have occurred. It is not without significance that conjugation occurs when the chromosomes are drawn out to their greatest attenuation so that the homologous chromomeres derived from the two parents achieve the maximum degree of association in a linear series. It is seen that the equivalent chromosome contributions of the two parents and their random assortment in maturation and chance recombination in fertilization, together with the possibility of an inner reorganization of each chromosome through its most intimate association with another of identical structure but different content, provide an infinite range of new combinations of characters which can be tested out by environmental agencies. The chromosome mechanism can supply the variations upon which the forces of selection can operate. It becomes apparent also that this conjugation of chromosomes in synapsis excludes the possibility of fruitful crosses between species widely different in chromosome constitution.

If the conjugation of homologous chromosomes is accepted as evidence in support of the conception of crossing-over, and if the genes are strung like beads upon a string, each particular gene having its own particular locus upon a particular chromosome, then it follows that the percentage of crossing-over between any two loci can be regarded as an indication of the distance between them. If the members of a pair of homologous chromosomes during their conjugation are as likely to fracture and reunite at one point as at any other point along their length, it follows that the further apart any two genes lie in the chromosome, the greater is the chance of crossing-over occurring; and conversely, the nearer together the genes lie, the smaller is the chance of crossing-over occurring. If this is so, then it is possible to construct a map of the chromosomes, showing the relative positions of the different genes resident in each. If A, B, and C form a linear series, and if B lies between A and C, then the crossing-over percentage occurring between A and C should equal the sum of the C.O.V.'s between A and B, B and C. The conception of the localization of the genes in linear alignment is due to the peculiar differences between the C.O.V. between genes of the same character linkage group. The relation of three or more points to each other is a relation of linear order and cannot be represented in space in any other manner than by a series of points arranged in a line. The linear order of the chromomeres is established beyond question. Linearity is the expression of a system in which there is a fixed succession of elements. The distance between any two elements is constant, but is variable throughout the series. In the case of the more simply organized forms of life it is possible to conceive the idioplasm having the form of a congeries of chromatin units, the members of which can exist separately within the nucleus and become associated by chance. In the more complex forms, however, the precision exhibited in the inheritance of a most complicated characterization demands a very precise and more complex hereditary mechanism, such as is supplied by the chromosomes in their constitution and behaviour.

In order to learn how the chromosome map is made, let us assume, for example, that the character Dachs (short legs) appears as a mutation in a stock of *Drosophila*. Breeding experiments show that it is an hereditary character, for when mated with the wild type it gives a 3:1 ratio in F_2 . We then, let us say, mate a black normal-legged individual with the new form, grey Dachs, to get an F_1 . The F_1 male is then back-crossed with a double recessive female, and we get a 50:50 ratio. We then know that Dachs belongs to the same linkage group as does black. The F_1 female then back-crossed with a double recessive male gives black normal-legged 41.25, grey Dachs 41.25, black Dachs 8.75, grey normal-legged 8.75 per cent. The C.O.V. between Dachs and black is 17.5 per cent. We already know that the C.O.V. between black and vestigial is 17 per cent. We can, therefore, anticipate that the C.O.V. between Dachs and vestigial will be either 0.5 or 34.5 per cent., the actual figure being decided by the relative positions of the three genes. If a Dachs long-winged

fly is mated with a normal-legged vestigial, and the F_1 male mated to the double recessive female, a 50:50 ratio will be obtained. Dachs is in the same linkage group as vestigial. If the F_1 female is mated with the double recessive, it is found that the C.O.V. between Dachs and vestigial is 34.5 per cent. It can now be stated that the relative positions of Dachs, black, and vestigial are in the order given, black coming between the other two almost exactly midway.

FIG. 9.—Chromosome interpretation of sex-linked inheritance.

FIG. 9A.—The reciprocal cross giving "criss-cross" inheritance.

One per cent. of crossing-over is taken as the unit for expressing linkage relations. This unit can be represented in a diagrammatic map of the chromosomes as 1 cm. or any other convenient size. A line is drawn to represent a chromosome. A horizontal mark across it is made to represent the position of the gene for black. Seventeen units of distance to one side of it another mark is made for the gene for vestigial, and 17.5 units to the other side of it the mark for the gene for Dachs is made. The making of the map is begun. Some 107 genes require to be placed in this chromosome. Their characters all show linkage with black and vestigial and Dachs, and with each other, and the C.O.V. between any two of them is characteristic. Out of crossing-over work with them it is soon possible to arrange them all in their proper order. In the other linkage groups of *Drosophila* there are 70, 106, and 3 characters respectively. This map gives to the breeder those powers which are possessed by the synthetic chemist in the manipulation of his materials. It can be compared to a railway time-table which shows the sequence of the stations and the distance between them.

All that remains is to show which particular chromosome carries the genes for a certain character linkage group.

A consideration of the facts related in (F) and (G) will lead to the conclusion that the characters red and white eye are being transmitted from generation to generation by some mechanism which is also concerned in the determination of the sex of an individual, and that the simplest interpretation of the facts can be made if it is assumed that the male, in respect of the elements of the sex-determining mechanism, elaborates two sorts of sperm—one, the X-chromosome-bearing, the other the Y-chromosome-bearing. If it is assumed that in the X-chromosome are resident the genes for those characters that in their inheritance behave as does white-eye, being sex-linked, and that in the Y-chromosome there are no genes, the facts can be accommodated. In Diagram 9 the solid chromosome is the X carrying the gene for red-eye, the open one the X carrying the gene for white-eye; XX is a female, XY a male; red is dominant to white.

Other evidence exists which demonstrates that the X-chromosome is concerned in the transmission of the sex-linked characters. It has been shown that when a white-eyed female is mated with a red-eyed male, criss-cross inheritance is observed, the daughters being red-eyed like their father, the sons white-eyed like their mother; and it has been shown further that this type of inheritance can

be explained perfectly satisfactorily on the assumption that in the single X-chromosome of the father there is resident the gene for red-eye, and that in each of the X-chromosomes of the mother there is a gene for white-eye, that red is dominant to white, and that the male is digametic, the female monogametic. (Fig. 9A.) It so happened that Bridges found in his stocks exceptions to this rule, and it was not until the chromosome constitution of the individuals concerned was examined that the exceptional cases could be explained.

During the maturation of the egg the two X-chromosomes, like the members of every other pair of homologous chromosomes, disjoin, one passing into the polar body, the other remaining in the ovum. If the X-chromosomes of a white-eyed female failed to disjoin two sorts of egg would result, one containing two X-chromosomes and the other without an X-chromosome. If the XX egg is fertilized by a Y-bearing sperm, an individual with an XXY sex-chromosome constitution would result. This has been shown to be the case, and the individual looks like and functions as a female. If this non-disjunctional XXY white-eyed female is used, instead of the ordinary XX female, exceptional results will ensue.

Bridges was able to explain all his exceptions to the rule of criss-cross inheritance by reference to the sex-chromosome constitutions of the individuals. The exceptional white-eyed daughters are white-eyed because they do not get one of their X-chromosomes from their red-eyed father; the exceptional red-eyed sons are red-eyed because they get their X-chromosome from their father, whereas normally the son gets his Y-chromosome from this source.

It can be accepted that the X-chromosome (chromosome I) bears the genes of the sex-linked group of characters. It can be shown that the small, round, centrally placed chromosome (chromosome IV) carries the genes for another group of linked characters. Individuals with but a single IVth chromosome (Haplo-IVs) and others with three instead of two (Triplo-IVs) have been identified, and these abnormalities in chromosome number are associated with definite abnormalities in general characterization. On chromosome II, one of the larger boomerang-shaped chromosomes, are placed the genes of the characters linked with black; on the other large curved chromosome, chromosome III, those linked with Star.

FIG. 10.—Non-disjunction. Chromosome interpretation of exceptional sex-linked results. (After Morgan.)

The story that I have endeavoured to tell is but a brief outline. I have told it because I know of its interest and am convinced of its usefulness. It is desirable, in my opinion, that the medical man should be well acquainted with the principles of the science of genetics, which will give to him a better understanding of his many and varied problems. If I have aroused your interest, I may hope that you will seek further information from the masters at whose feet I am so proud to sit.

For further information consult:

Gates, R. R.: *Heredity and Eugenics*, Constable, London.
Morgan, Sturtevant, Müller, and Bridges: *The Mechanism of Mendelian Heredity*, Henry Holt and Co.
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