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# SOME POSSIBLE BEARINGS
# OF
# GENETICS ON PATHOLOGY

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Middleton Goldsmith Lecture delivered before the New York Pathological Society on February 3, 1922.

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# SOME POSSIBLE BEARINGS OF GENETICS ON PATHOLOGY

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It has been pointed out in derision that modern genetics deals, for the most part, with the inheritance of abnormalities and disorders of various kinds—albinos, brachydactyls, cretins, dwarfs, freaks, giants, hermaphrodites, imbeciles, Jukes, Kallikaks, lunatics, morons, polydactyls, runts, simpletons, twins, and Zeros: in a word, with pathological phenomena in a very broad sense. This statement, intended as a reflection on genetics, carries with it an implication that a study dealing with such material cannot be of first rate importance. Such condemnation will probably be received by pathologists with the kind of smile it deserves, and I feel that I am not likely to be called upon here to answer such an indictment. Nevertheless, I am going to ask your indulgence, for a moment, since this slightly malicious statement should not be allowed to pass unchallenged, both because it is inaccurate, and because, even were it true, the result of such work might still be of more importance than its critics seem to realize. The source of this criticism is not without significance. It comes almost always from those whose interests lie in the field of evolution —in the old-fashioned use of that word. Now the articles of all evolutionary platforms include a plank about heredity. This plank is for the most part an ancient article that has been worn pretty thin. It is difficult to replace it (or at least it is supposed to be difficult to replace it) with the new wood of Mendelian genetics. Hence, I think, originates the criticism referred to.

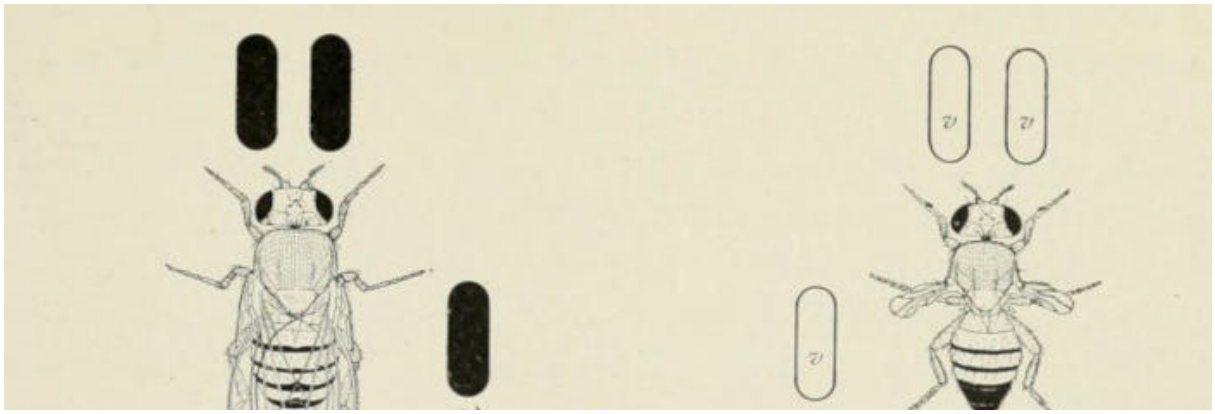
It is true that the student of Mendelian heredity does not often trouble himself about the nature of the character that he studies. He is concerned rather with its mode of inheritance. But the geneticist knows that opposed to each defect-producing element in the germ-plasm there is a normal partner of that element which we call its allelomorph. We can not study the inheritance of one member of such a pair of genes without at the same time studying the other. Hence whatever we learn about those hereditary

elements that stand for defects, we learn just as much about the behavior of the normal partners of those elements. In a word, heredity is not confined to a study of the shuffling of those genes that produce abnormal forms, but is equally concerned with what is going on when normal genes are redistributed. This method of pitting one gene against the other furnishes the only kind of information relating to heredity about which we have precise knowledge.

In man and in domesticated animals we find that individuals appear occasionally that are defective in one or another respect. Some of the defects are inherited. Rarely a new one appears that has not been seen before. But the majority of them are reappearances of characters that have been carried under the surface as recessive genes in the germ-plasm. Today we recognize that each of these modifications, if recessive, has first arisen as a mutational change in a single gene before it appeared on the surface as a character by the coming together of two such genes. Mendelism has furnished some information as to the way in which these hidden genes may get dispersed in the race. An example will serve to make this clear, Fig. 1.

If a fly with vestigial wings, a recessive character, is crossed to a wild fly with long wings, all the offspring ($F_1$'s) will have long wings. If these are bred to each other the offspring will be of two kinds, like their grandparents, in the ratio of three long winged to one vestigial fly. The extracted vestigials will breed true to vestigial. The fact that the gene for vestigial has been carried by long winged $F_1$ parents has not affected the gene in any way, for the second generation of vestigials has wings as short as those of their grandparents.

I have brought forward this case not so much to illustrate Mendel's law of segregation as to use the facts for another purpose.



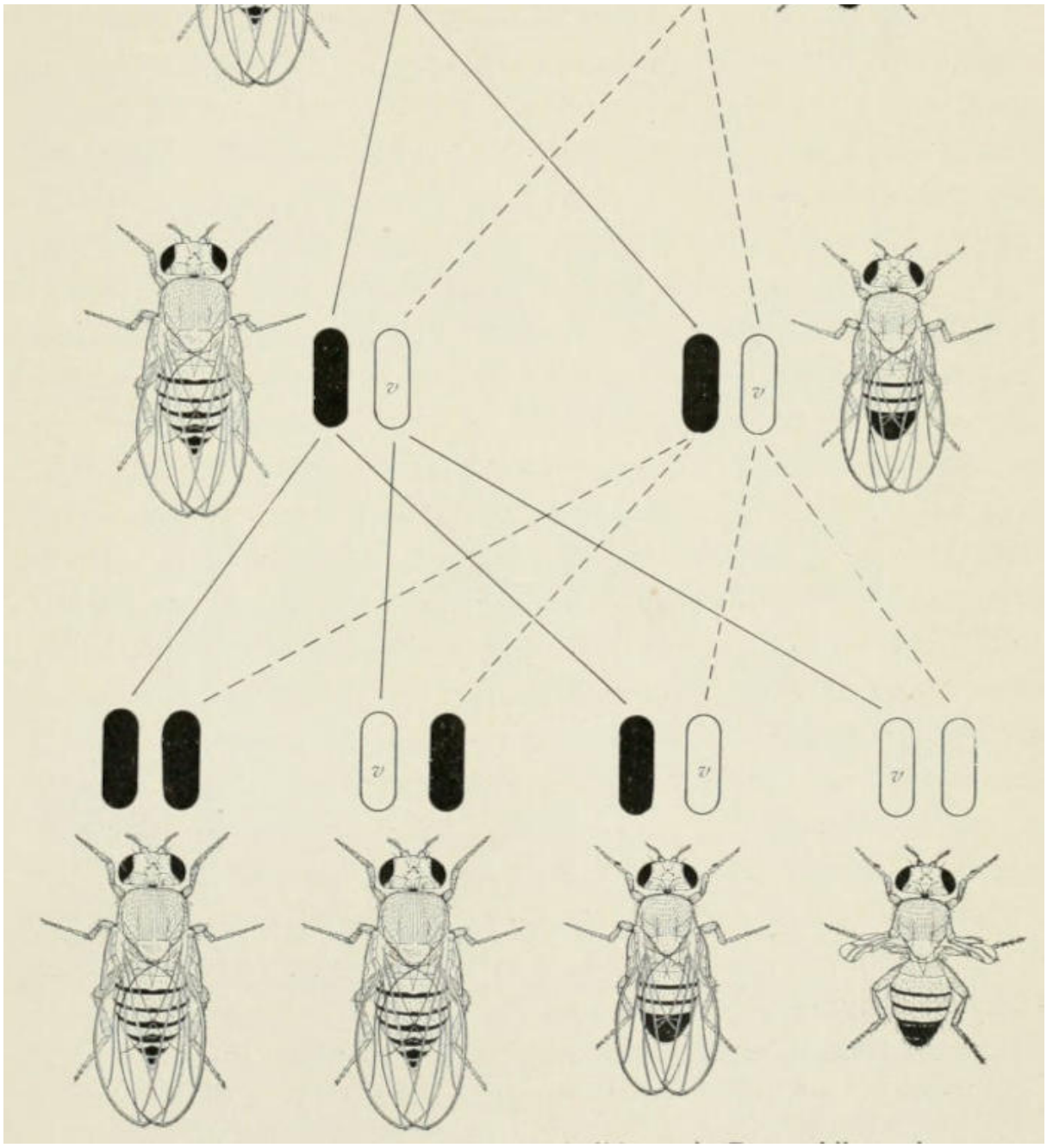


FIG. 1. Cross between long-winged (wild type) *Drosophila melanogaster* and vestigial-winged fly, producing long-winged offspring ($F_1$), which if bred to each other give in the next generation 3 long to 1 vestigial. In the middle of the diagram, the pair of chromosomes that are involved in this cross are represented. The chromosome with the factor (gene) for long wings is here black; that for vestigial is open (v).

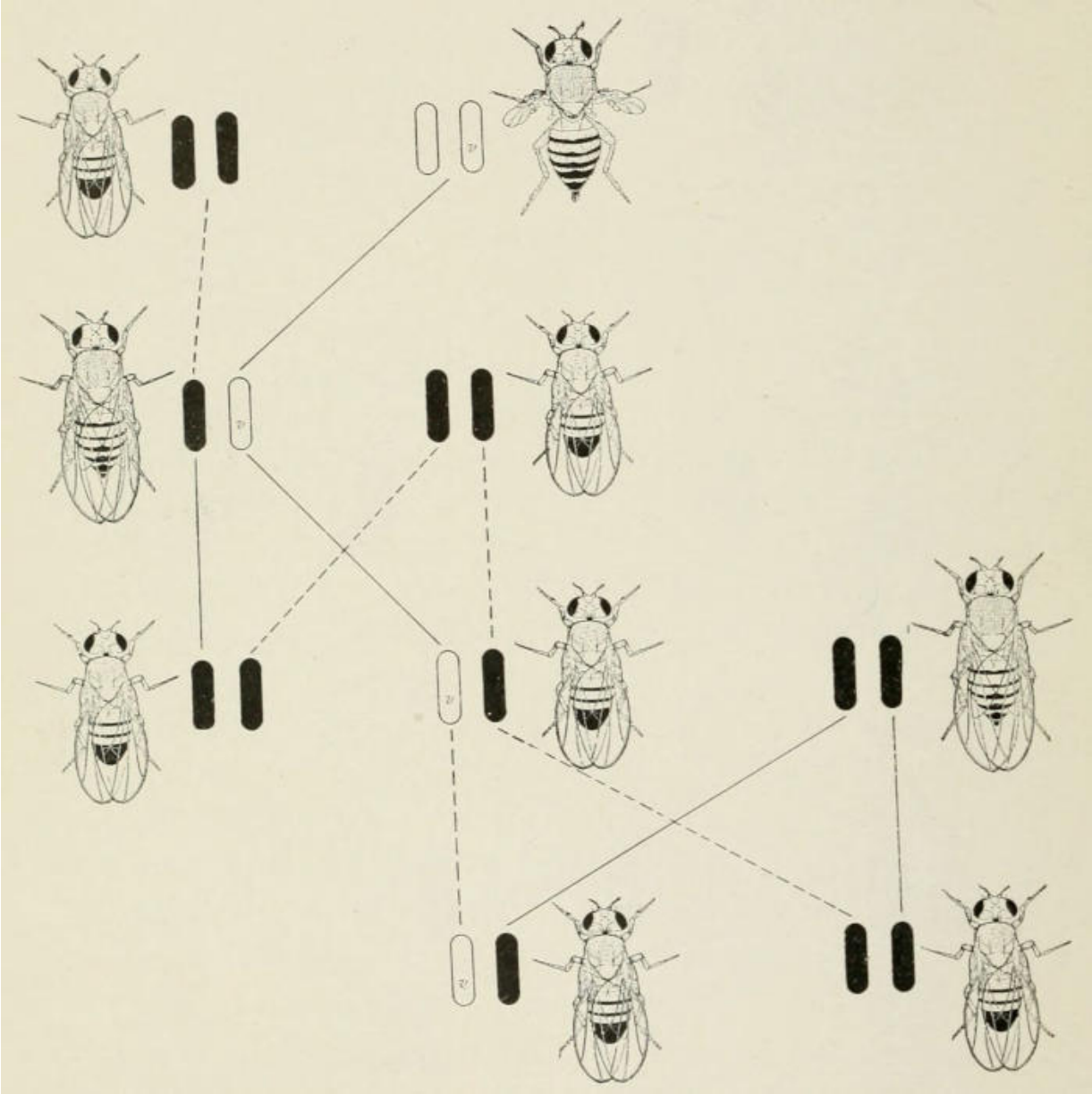


FIG. 2. Cross between long and vestigial wings, giving long in $F_1$. The long-winged hybrid $F_1$ female is then represented as out-bred to a wild-type male, giving long-winged offspring again—half pure-long and half hybrid-long. The last are represented as again out-bred to wild type, giving long-winged offspring again and of the same two genetic kinds as above.

When the vestigial fly was crossed to normal the mutant character disappeared in the hybrid. If such a hybrid is out-bred to normal all the offspring are again normal, but half of them carry the vestigial gene. If these are out-crossed again still only normal flies appear, Fig. 2. If such out-breeding is continued the vestigial gene will become widely distributed without ever showing itself at the surface, so to speak. If, however, at any

time two hybrid flies mate, then a quarter of the offspring will have vestigial wings. It might seem then that the character had appeared for the first time in the race, if one did not know its past. In reality its gene may have been there for some time. Probably many of the recessive defects and malformations that appear in the human race—at least those due to hereditary factors—have had representative genes in the germ-plasm for several generations before they have appeared on the surface.

We do not know how widespread recessive genes are in the human germ-plasm. The fact that defective individuals appear in certain communities may be safely interpreted to mean that individuals bearing the same gene have at last come together. On the other hand, the absence of such individuals from the community, at large, may only mean that the chance of suitable combinations is small, and does not mean necessarily that the gene in question is confined to the community within which the defects have been recorded.

My illustration may give, however, an entirely erroneous idea as to the chance of a recessive character contaminating the race. If one can control the matings, so that out-breeding takes place each time, the result would undoubtedly be like that in our diagram; but what chance is there for a recessive character, that is neither beneficial nor injurious, if left to itself, to contaminate widely the race with its gene? The answer is that for any one defect there is hardly any chance at all. On the other hand, there is always a possibility that a defect *may* become widespread despite the chances against each in turn. If a recessive *character* is selected against each time it appears on the surface, the chance is extraordinarily small that the gene for such a character could ever become widespread in a race. If the recessive character is advantageous, its chance is somewhat better, but still the chance that it may be lost is very great.

Let us turn for a moment to the inheritance of a Mendelian dominant character, and to simplify the situation let us first assume that the character itself is neither advantageous nor disadvantageous.

It is popularly supposed that if a trait is dominant it will be expected to spread more widely in the race than will a recessive character. This is owing largely to a verbal confusion. Colloquially we think of dominance as meaning spreading. A dominant nation, for example, is one that is spread

widely over the face of the earth. But a Mendelian dominant should carry no such implications. A dominant gene, if crossed into a race, will stand the same chances of being lost as a recessive gene, Fig. 3.

The situation is similar in many ways to the inheritance of surnames in any human population. A new surname introduced is likely to disappear after a few generations. There is a bare chance, however, that it may spread.

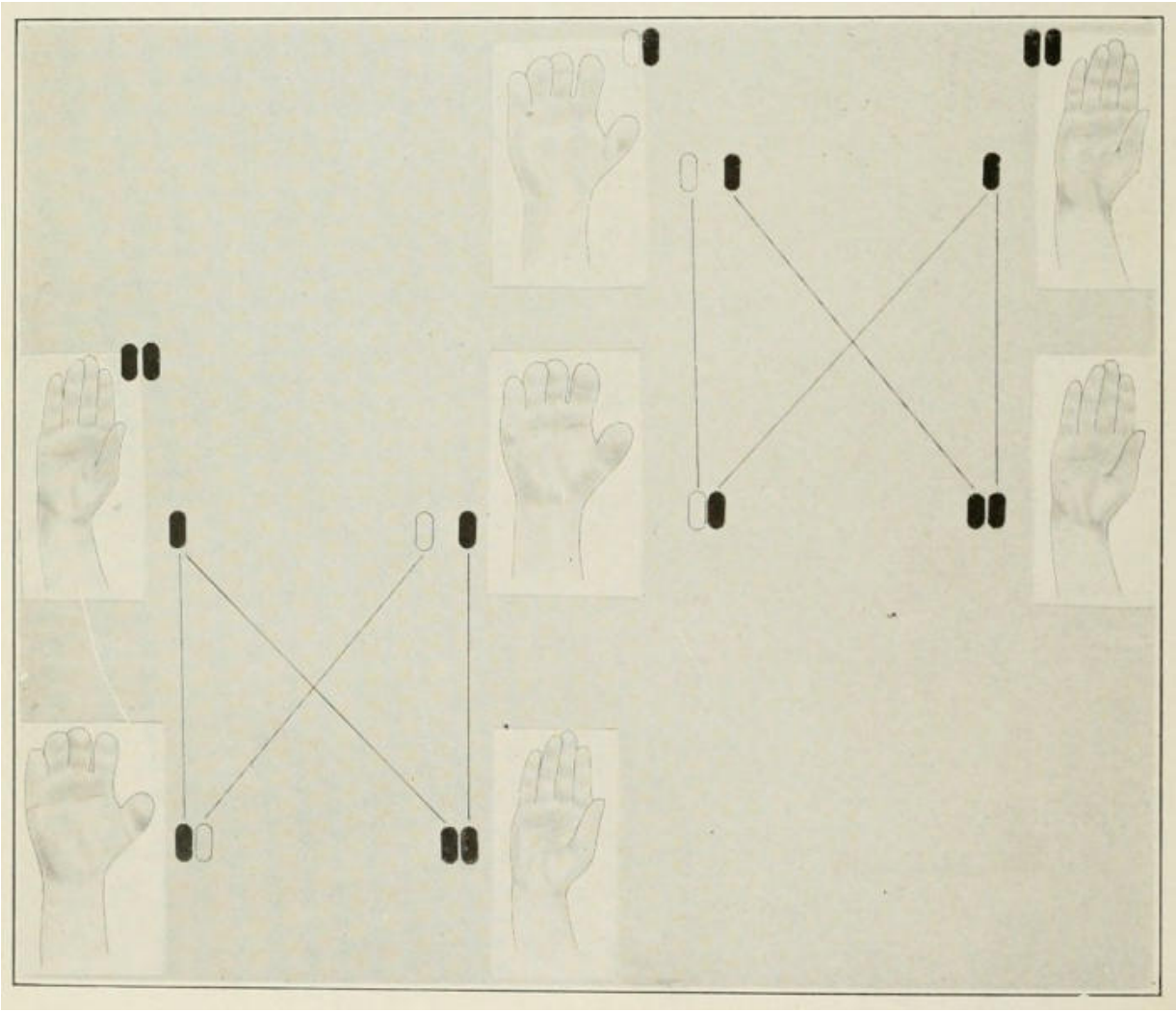


FIG. 3. Mating of short-fingered and normal individual (the short-fingered character is dominant), giving in $F_1$ normal and short-fingered individuals in equal numbers. If the latter is out-bred to normal again, half the next generation is normal and half short-fingered.

Of course if a dominant *character* is advantageous in itself, it will have a better chance of spreading through the race, than will an advantageous recessive character, because every hybrid that carries one dominant gene shows also the character, which increases the chance that it will propagate

and spread the genes. But, on the other hand, if a dominant character is injurious it will have a smaller chance of spreading than will an injurious recessive character; for, the recessive may be carried by the hybrid without showing itself, and therefore will not place the hybrid individual at a disadvantage.

An excellent illustration of dominance is that recently published by Mohr. He has traced, through five generations of a Norwegian family, the inheritance of a shortened first digit. In the history of this case there is one record that is extraordinarily interesting. A child was born that was so completely crippled that it died in infancy. One parent was short fingered; the other, a cousin, was probably also short fingered. It is possible that the child had a double inheritance of this character; it was a pure dominant. If this is true, then it appears that this character can survive to maturity only in the hybrid condition. As a matter of fact, in other animals there are some well-recognized cases of this sort. That of the yellow mouse is the best known. Yellow is a dominant and in double dose it kills; therefore when yellow is bred to yellow all the pure yellows die. The hybrid yellows and the pure blacks (in Fig. 4) survive. Here yellow is discriminated against in the embryo; but, being dominant, it still appears twice as frequently in each generation as does the alternate character (here black). In the fly, Drosophila, we have at least 25 dominant lethal characters, but as yet we have no knowledge as to why such a high percentage of dominant characters should be lethal when homozygous.

In man there are no certain cases known of lethal dominants unless some of the short-fingered types come under this heading.

Dominant and recessive characters have been so much discussed in modern Mendelian literature that it is popularly supposed that all Mendelian characters must be either dominant or recessive when bred to the type. This is not the case. The hybrid (or heterozygote) is frequently intermediate. In fact, it might be said, almost without exaggeration, that the heterozygote nearly always shows some traces of its double origin. Sometimes the hybrid character is nearly midway between the parent types, sometimes more like one, or like the other. The important fact, however, is that in the germ cell of such intermediate hybrids, there is the same clean separation of the parental genes. In consequence, we find in the second generation the two

grandparental types in pure form and an array of intermediates connecting them.

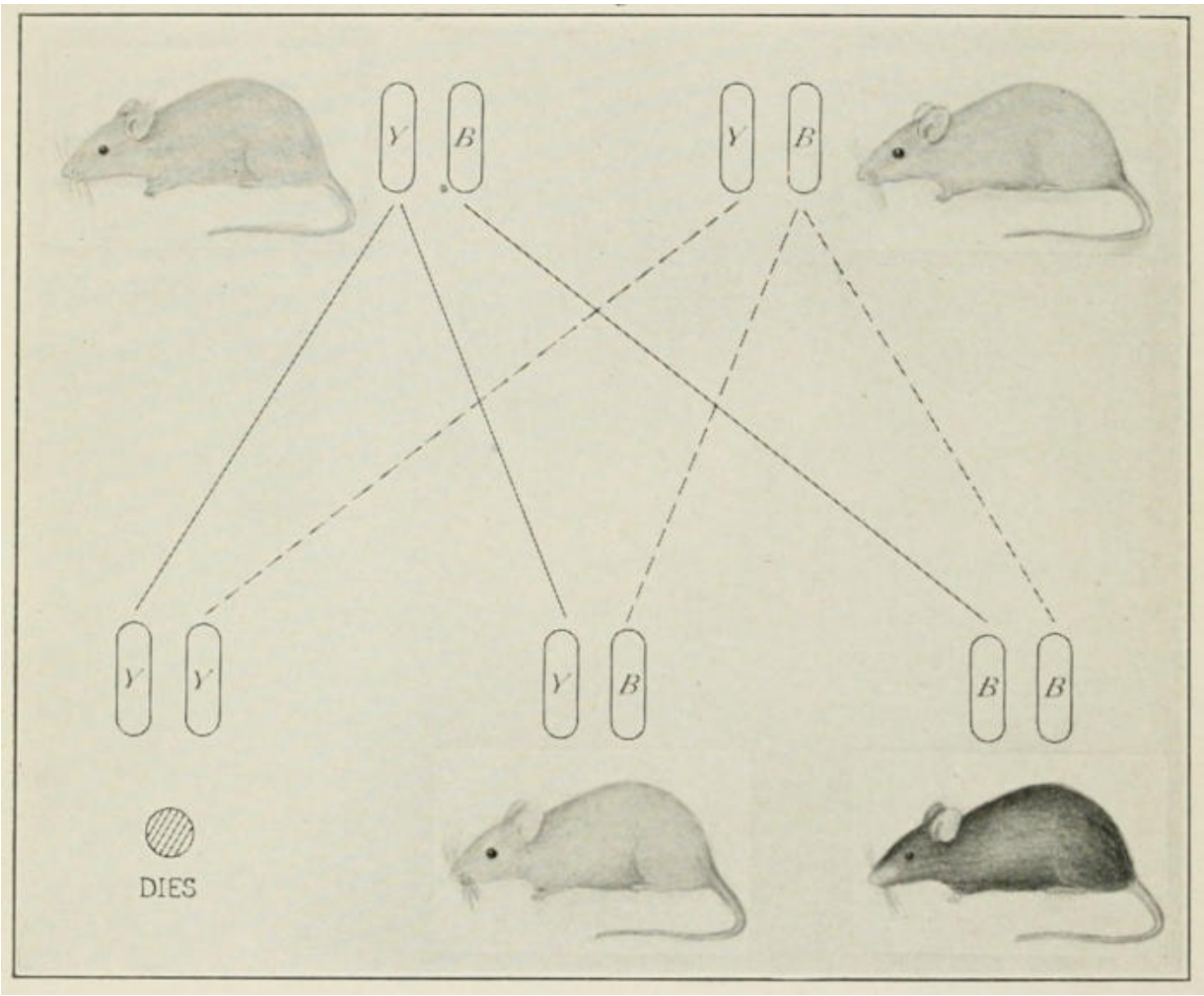



FIG. 4. Yellow mouse (YB) crossed to yellow mouse (YB) produces here black and yellow offspring, in the ratio of 2:1. These yellow are again hybrid, and if bred to each other give the same result again. Pure yellow (YY) offspring die at early stage. They constitute one quarter of all the offspring.

In connection with the question of spreading of mutant genes in the race there is another consideration, seldom referred to, that may occasionally have some weight in accounting for the dispersal of genes. In *some* combinations the hybrid may be more vigorous and more fertile than either parental race. Hence it may have a better chance of survival than an individual of either parent stock. It is a difficult question, that we cannot answer at present, whether a mixed strain has a better chance of survival than one or another of the strains of which it is made up. The possibility that some hybrid strains may be better than either pure strain is enough to

put one on his guard against the popular doctrine of racial purity so-called. Whatever advantages some kinds of pure races of mankind may have, from a political, religious or militaristic viewpoint, this should not blind us to the possibility of the biological advantages that certain mixtures may bring about. I emphasize the statement that *certain* mixtures of races *may* have a biological advantage. It is equally possible that other combinations may have a biological disadvantage. We are far from being able to state at present what combinations are beneficial and what are biologically injurious. It is an interesting problem, one of deep significance I think for the future of the human race, but mixed up as it is at present with difficult social and political questions it is a problem that only a light-hearted amateur or a politician is likely to be dogmatic about.

Before we take up the main questions before us this evening, I must speak of one other form of heredity. In many instances we have evidence that a character is the product of more than a single *mutant* gene. I say "mutant gene" because in fact every character is no doubt the product of the combined action of many genes, but in addition to this general relation there are many cases now known where there are several specific genes whose *chief* effect is on one character. Size differences furnish abundant data of this sort. One of the clearest cases is that of the size of the ear of corn. Some races of corn have short ears (and cobs), some long. If two such races are crossed, the hybrid is intermediate with a considerable range of variation. If the hybrid is self-fertilized, the progeny in the next generation shows a still wider range of variation, extending from that of the shorter grandparent to that of the longer. Both grandparental cobs have reappeared, but also many intermediate grades, Fig. 5.

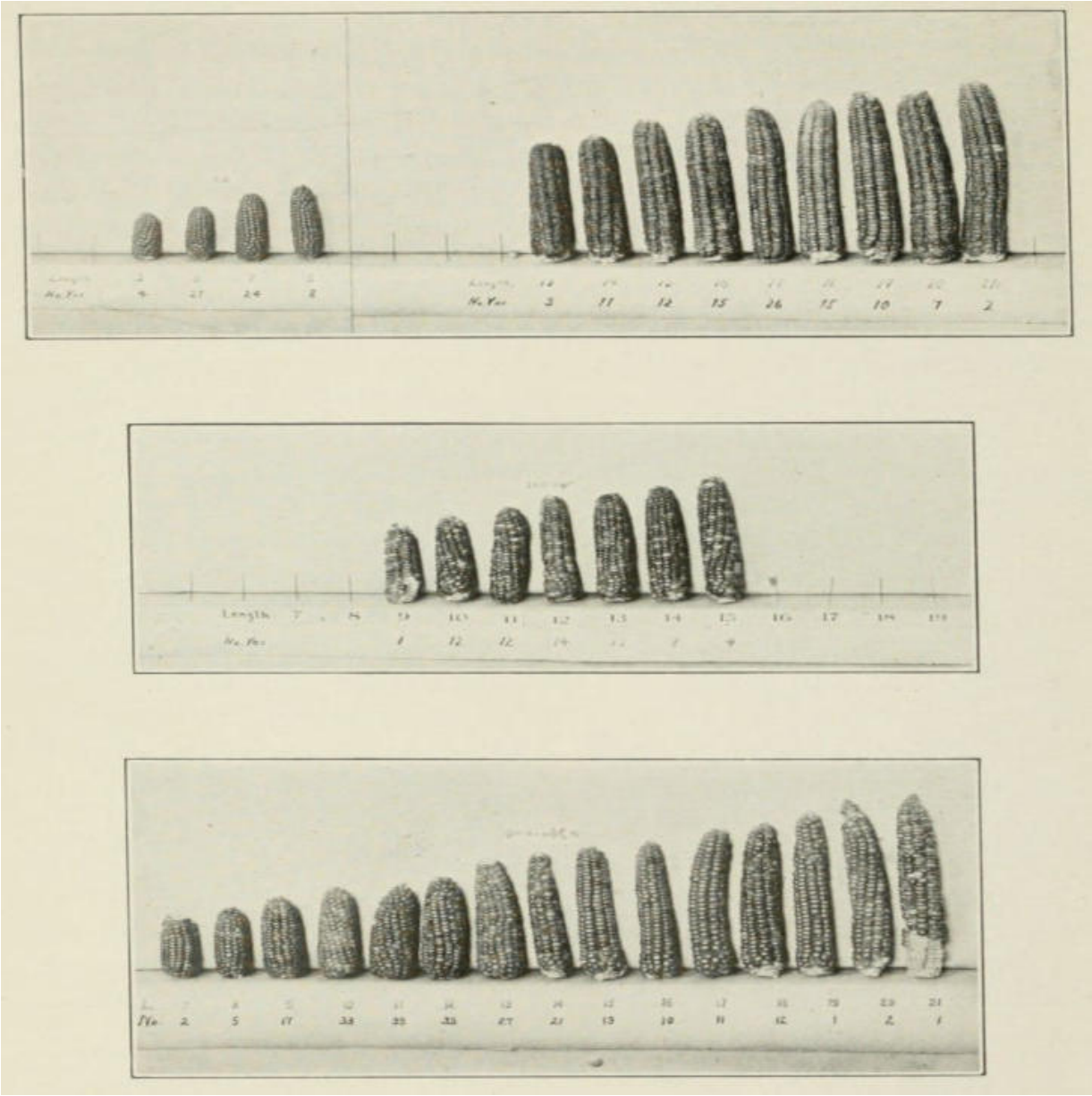


FIG. 5. Cross between long- and short-eared corn. Samples of two original types shown in upper part of figure, hybrid offspring in the middle of figure, and samples of 2d generation in the lower part. (After East and Hays.)

Such cases were formerly spoken of as blended inheritance. It was supposed that the materials of the two parents have, as it were, fused in the offspring and have remained fused. Today we have a better explanation. It is this. Besides two major factors that here determine cob length, there are other *minor* factors, some of which make the short cob longer, others that make the long cob shorter. These go over into the first generation hybrids, and are sorted out in the germ cells of the hybrid. Consequently, when the

$F_1$'s are inbred, there are all sorts of recombinations of the minor factors. This explains the greater variability of the second generation.

It is probable that in most of our domesticated animals, including man, much of the variability is due to multiple factors, which makes a study of inheritance in these groups extremely difficult, especially when, as in the case of man, the number of offspring from a pair is small, and critical combinations for study can not be made.

If then it is highly improbable that any particular defective trait could ever become widely spread in the human germ-plasm, how does it come about that such defects as feeblemindedness and insanity are so widespread in the racial inheritance? There are several possibilities here to keep in mind, but I think we ought not to pretend that we can give a completely satisfactory account of the situation.

First. While the chance is heavily against any one defect establishing itself, there is always the possibility that some one defect may establish itself. It must be remembered that while many defective strains may be lost, one would notice only those that had taken root. It is the presence of these that may give us an exaggerated idea of the generality of such occurrences.

Second. If the human germ-plasm is continually mutating to produce one or another kind of specific defect, this will increase the chance for any recurrent defect to finally establish itself. That particular mutations do recur in other animals is now abundantly established by evidence that comes from several sources.

Third. There is a growing impression that a good deal of feeblemindedness and insanity are environmental rather than hereditary traits; poverty, malnutrition, and especially syphilis are said to play a considerable rôle in their production. It is unsafe therefore to conclude that the human germ-plasm is as badly contaminated as some pessimists seem to think.

If we turn now more directly to special kinds of human inheritance we shall find a great deal of evidence showing that the same laws of inheritance that hold for animals and for plants apply to man. It would be surprising if this were not the case.

On the other hand, when we scrutinize the pedigrees that have been published to illustrate heredity in man, we shall find many of them very unsatisfactory in two main respects. (1) The number of offspring in a family is usually too small to serve as a sample of the germ-plasm of the parents. (2) Therefore, since recourse must be had to many families for sufficient data, it is essential that the diagnosis of the defects of the parents and of the children is correct. A single mistake may throw the result into confusion. In cases where the defect is structural, a correct classification may be possible, but in other cases, especially where psychological defects are involved, the diagnosis is difficult and the results, in consequence, less certain. Often the best that we can do in the case of man is to try to find the simplest Mendelian formula to which the evidence will fit. If one factor-difference will not suffice, then two must be tried; if two will not do, then three must be tried, etc. Now I need hardly point out that we can explain almost anything if we are allowed enough factors. It is, at best, a dangerous practice, one to be used only with great caution and the conclusion stated as provisional and checked in every possible way.

I propose now to pass in review some characters in man known to be inherited, choosing preferably those that come nearest to the field of pathology, or belonging to it. I shall begin with comparatively simple cases, about which there can be little doubt, and pass to more and more difficult situations. I am taking the risk of reaching an anticlimax, but nevertheless such a procedure will, I hope, serve our purpose this evening if I can point out where the evidence is satisfactory and where it is deficient.

My first illustration of inheritance in man may be said to be a physiological one, mainly because we do not know at present any structural or chemical basis for the reaction.

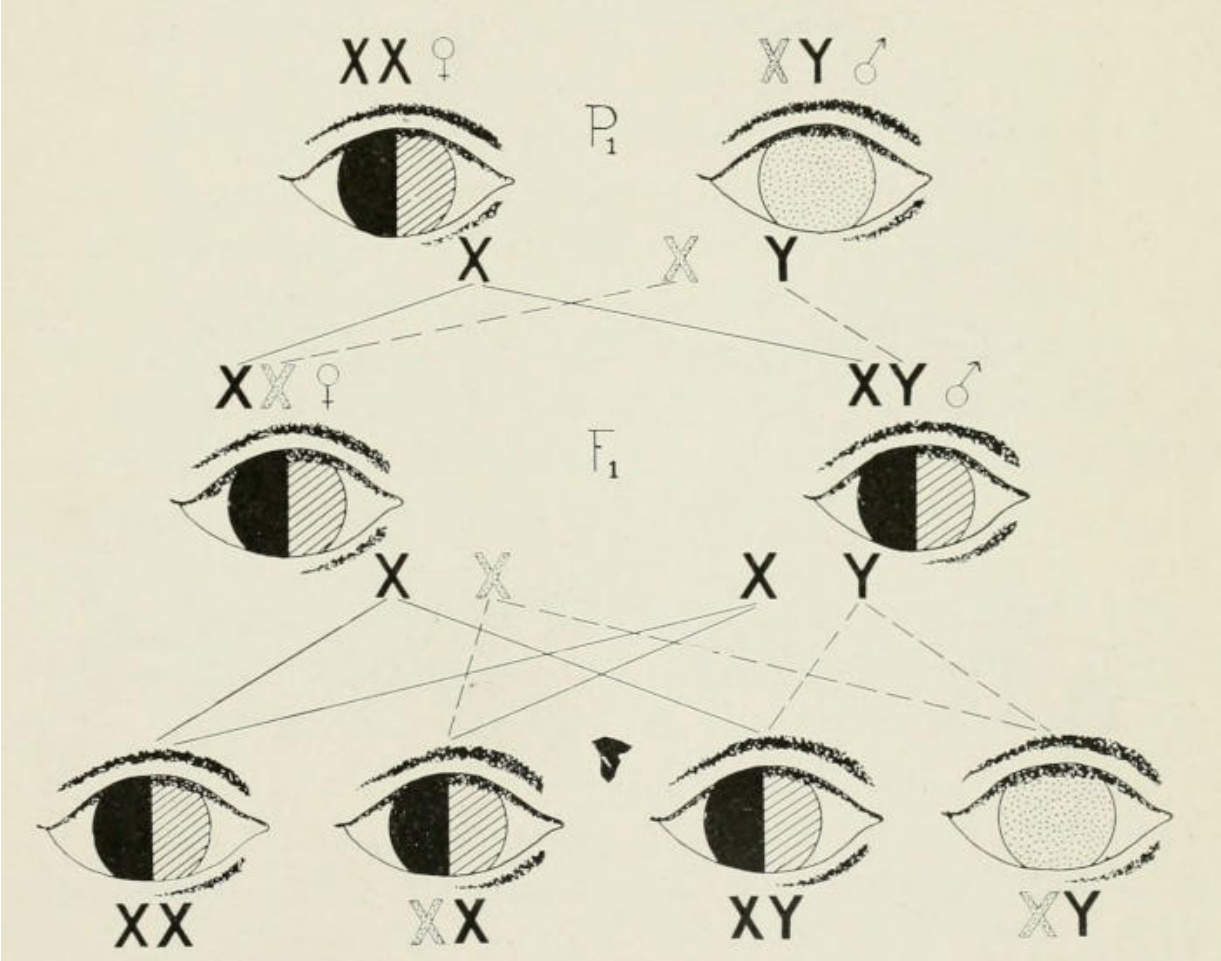



FIG. 6. Inheritance of color blindness of man which is sex-linked (i.e., the factor for color blindness is carried in the X-chromosome). This X-chromosome is stippled in the figure while the X-chromosomes for normal eyes are represented by black X's. The color-blind eye is also stippled, and the normal eye (which distinguishes between red and green) is here represented by an eye half black and half cross-lined. The 1st generation offspring ($F_1$) are normal eyed. In the 2d generation offspring, half the sons are color blind.

Color-blindness in man is clearly a case of sex-linked inheritance. It conforms to the general scheme of inheritance in other animals; in Drosophila, for example, we have about sixty mutant characters which show this form of inheritance.

A color-blind man married to a normal woman has only normal daughters and sons; all of the daughters, however, transmit color-blindness to half of their sons, Fig. 6.

Color-blind women are rare, because they can never arise unless a color-blind man marries a woman who is color-blind, or else marries a normal

woman who had a color-blind father, or had a mother heterozygous for color-blindness, Fig. 7.

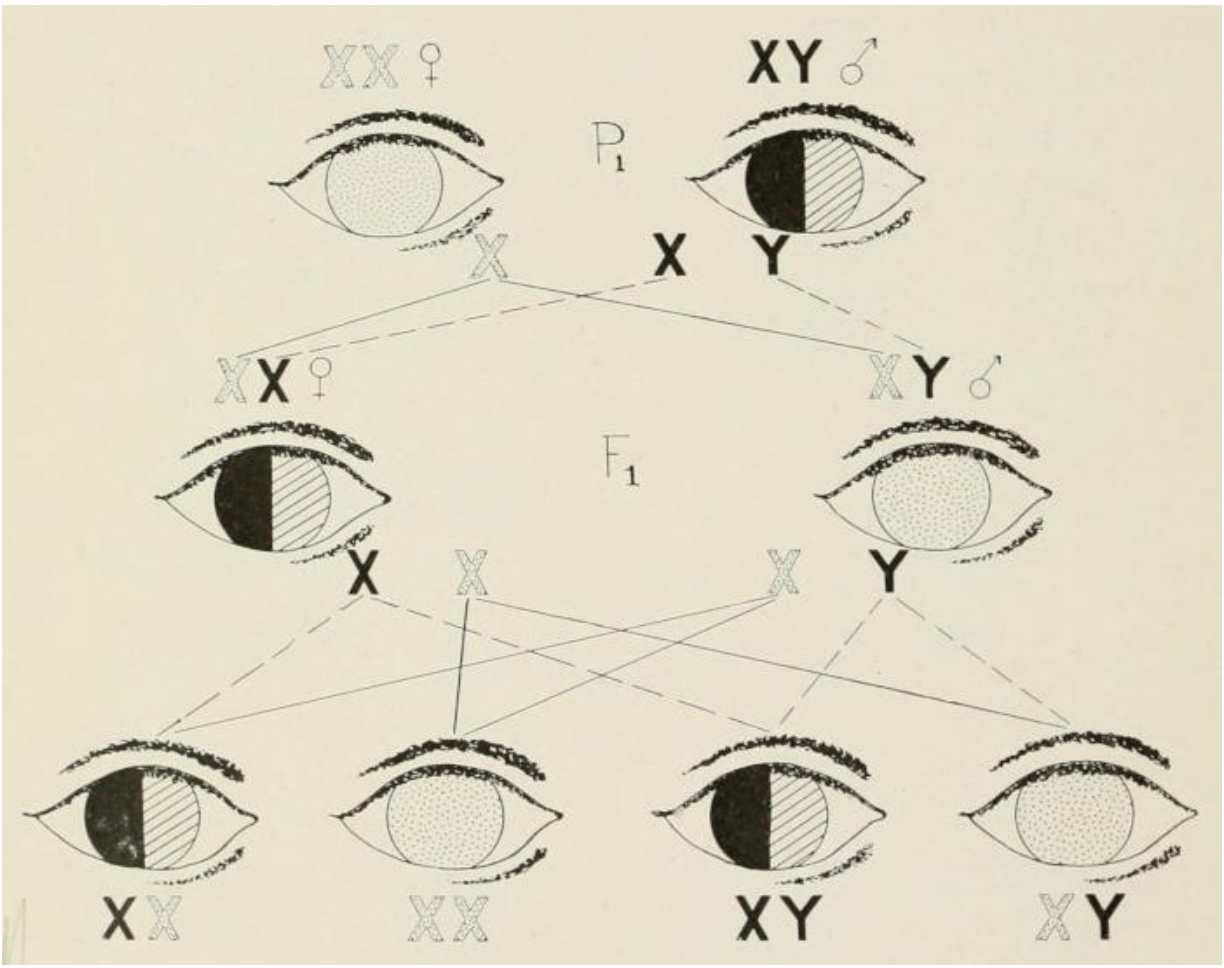



FIG. 7. Reciprocal of the cross shown in Fig. 6. Here a normal-eyed male marries a color-blind female, giving all color-blind sons and normal daughters. When two individuals like these marry, the expectation is for half of the daughters and half of the sons to be color blind, and half of the daughters and half of the sons to be normal eyed.

The pedigrees of color-blind families—and they are many—leave little doubt as to the mode of inheritance of this character.

Accepting this evidence as on the whole satisfactory, there is still something more to be said. As is well-known there are many grades of color-blindness. We do not know whether these grades are due to fluctuating (individual) variations—assuming it to be due to one gene: or whether there are several genes that differ in the degree to which they produce the defect. In fact we know now of a good many cases in other animals where there are several mutations of the same gene. For instance, in

Drosophila there is a series of ten such multiple allelomorphs for eye colors that range from pure white to deep wine-red. There is still another possible interpretation of the different kinds of color-blindness—one which *a priori* would seem to be the most probable—namely, that the differences are due to other modifying genes that affect the extent to which the character develops.

While in the great majority of cases, the scheme of color-blindness is that shown by the diagram, we know that occasionally the machinery may be changed to give a somewhat different result. It is possible, for example, that a color-blind man married to a perfectly normal woman may rarely produce a color-blind son. A few years ago such a result would have appeared to upset the entire scheme of sex-linked inheritance, today we understand how such cases may arise through a process that is called non-disjunction, which is best illustrated by numerous cases well worked out in Drosophila.

My second illustration has a more obvious chemical basis. Hemophilia is also sex-linked in inheritance. It is known to be much more common in men than in women, the explanation for this is the same as in the other case. In affected individuals the blood fails to coagulate quickly and the difference in chemical composition of the blood is, in contrast to normal, the inherited character.

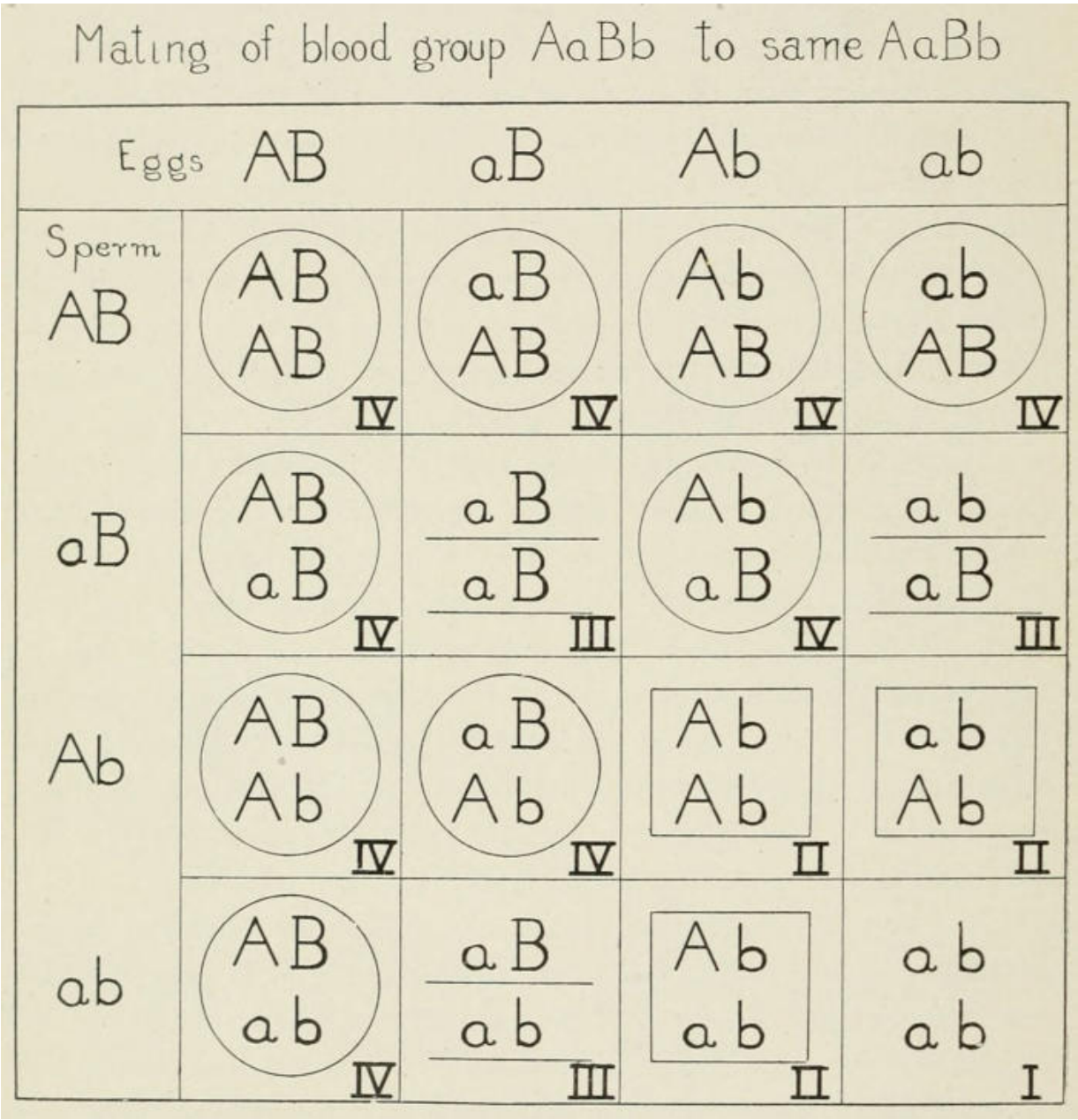



FIG. 8. Representing the kinds of individuals expected when an individual of the blood group type AaBb marries individual of the same blood type, namely AaBb. Sixteen kinds of individuals are possible in the ratio of 9:3:3:1. These belong to four blood types, namely, class IV that contains at least one A and one B; class II that contains at least one A but no B; class III that contains at least one B but no A; and class I that contains neither A nor B.

One of the most remarkable cases of heredity in man is found in the so-called blood groups. As first definitely shown by Von Dungern and Hirschfeld in 1910, the inheritance of the four blood groups conforms to Mendel's laws. So consistent is this relation that, as Ottenberg pointed out in 1921, the evidence might be used in certain cases to determine the

parentage of the child. Since this statement has recently been disputed by Buchanan, from an entirely wrong interpretation of Mendel's principles, I should like to point out that on the Mendelian assumption of two pairs of factors, all the known results are fully accounted for. If we represent one pair of genes by A and a and the other pair by B and b, and if we represent an individual with the genetic constitution AaBb mating with another individual of like constitution (AaBb), then each will contain four kinds of germ cells, viz., AB, Ab, Ba, and ab. The sixteen possible combinations formed if any sperm may fertilize any egg are shown in Fig. 8.

These sixteen individuals fall into four groups according to whether they have both A and B, or only A, or only B, or neither A nor B (*i.e.*, ab) in the proportion of 9AB:3A:3B:1ab. These four genetic classes correspond to the four recognized blood types IV, II, III, I, as indicated in the diagram. Now these sixteen kinds of individuals are found in all populations, so far studied, although in somewhat different proportions in different "races."

It is very simple to tell what the kinds of genetic offspring will be where any one of these sixteen individuals marries any other one. These possibilities are summarized in the following statement taken from Ottenberg:

| | | | | | |
|---|---|---|---|---|---|
| Unions of | I | and | I | give | I |
| | I | | II | } | I, II |
| | II | | II | } | |
| | I | | III | } | I, III |
| | III | | III | } | |
| Unions of | II | and | III | give | I, II, III, IV. |
| | IV | | I | | I, II, III, IV. |
| | IV | | II | | I, II, III, IV. |
| | IV | | III | | I, II, III, IV. |
| | IV | | IV | | I, II, III, IV. |

Two actual pedigrees, one of them carried through three generations, will serve to illustrate particular cases, Fig. 9.

From a knowledge of the blood group to which the child belongs it is possible to predict to what groups its parents may have belonged, and in

certain cases it is possible to state that an individual of a certain group could not have been the parent of a particular child.

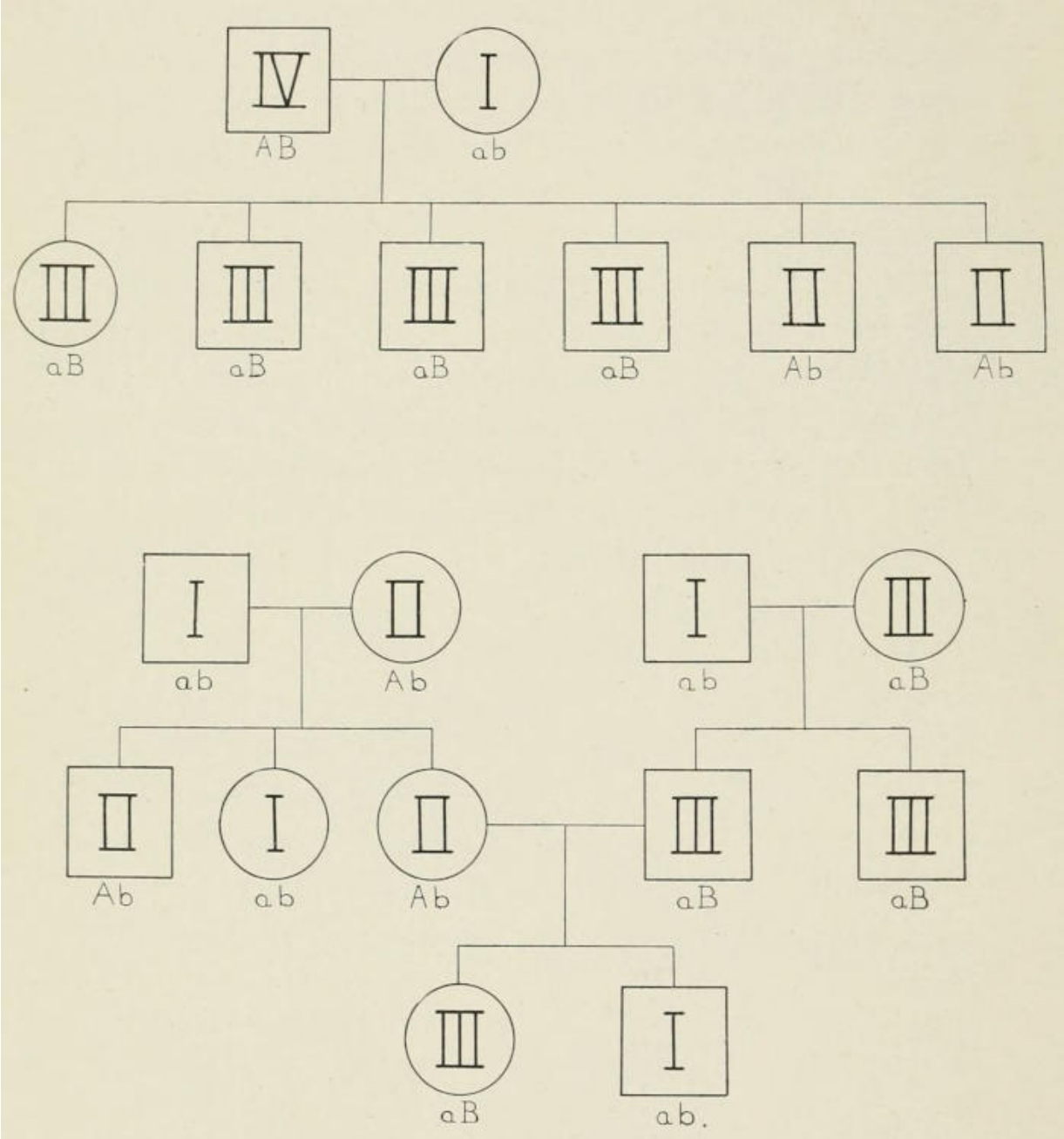



FIG. 9. The upper pedigree gives the children from the family in which types I and IV were the parents. The offspring belong to types II and III (two of the four possible kinds of offspring).

The lower pedigree represents three generations. The grandparents are I and II and I and III, respectively, while the parents are II and III.

In the transfusion of blood from one individual to another, that is sometimes necessary, it is essential that the blood corpuscles of the donor are not agglutinated by the serum of the recipient. Thus it is a matter of great importance to select a donor that does not bring about such a catastrophe. The simple rules are that individuals belonging to the same blood group (I, II, III, or IV) do not agglutinate each other's blood, but the blood corpuscles of an individual represented by AA or Aa will be precipitated if the donor contains the agglutinin represented by aa, and conversely the blood corpuscles of an individual represented by BB or Bb will be precipitated if the donor contains the agglutinin represented by bb. Inspection of the diagram will show that group II (with serum bb) precipitates III and IV, and group III (with serum aa) precipitates II and IV. Further the serum of group I (aa bb) precipitates all of the other groups; while the serum of group IV precipitates none of the others.

My fourth illustration has probably in some cases a glandular basis, and in this sense has probably also a quantitative chemical background. Height or stature in man is, in part, an hereditary trait. It is sometimes said that short is dominant to tall, because short parents may have both tall and short children, but tall parents produce only tall children. This is probably an overstatement, or at least a rather loose generalization. Height may be due to long legs, or to a long body, or to a long neck or to time of reaching maturity or to any combination of these; and these differences may themselves be due to independent factors in inheritance. The best that we can do with height at present is to refer it to a multiple factor basis, the actual factors being little understood.

In addition to these differences in stature, all of which we call normal differences, there are certain extreme conditions superimposed on these as a background, in which the endocrine glands probably play an important rôle. While it may well be that many of these cases are caused by tumors of one of the glands, more especially of the pituitary, thyroid, or testis, it is quite possible that there may be actual inherited differences in the size and activity of these glands.

So far as I know there are no thoroughly worked out cases of the inheritance of such differences in man or in mammals, but in the case of certain races of birds I have been able to show both by breeding tests and by

castration experiments that glandular differences are inherited according to the Mendelian scheme.

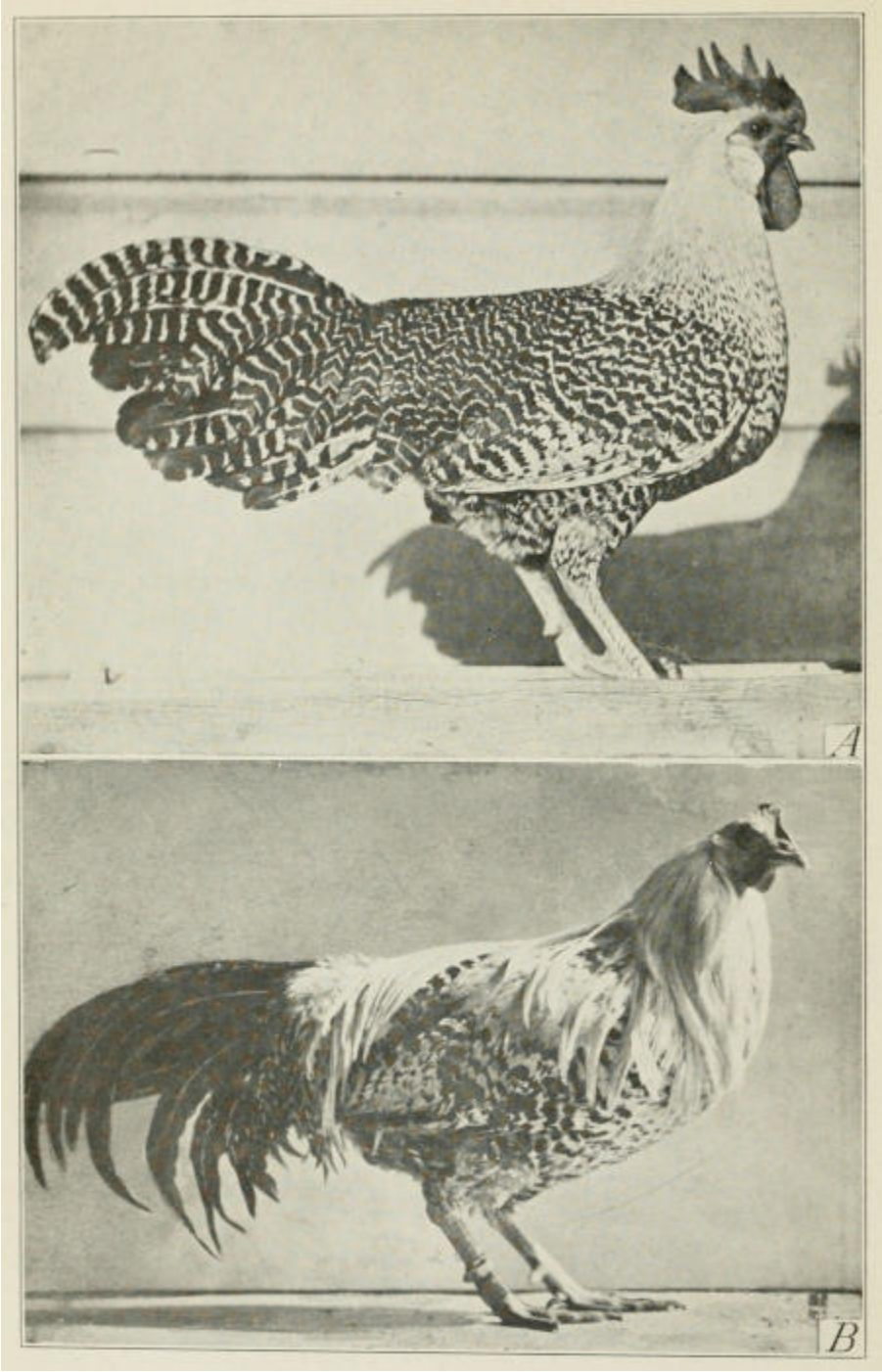



FIG. 10. Above (A) normal adult hen-feathered Campine cock. Below (B) castrated cock about one year after operation. The castrated bird has developed the secondary sexual characters of cock-feathering.

There is a race of fowls known as Campines in which there are two kinds of males, hen-feathered males and cock-feathered males. If the hen-feathered male is castrated, the new feathers that develop are the long feathers of the cock-feathered male, Fig. 10. In another race of fowls, Sebright bantams, only the hen-feathered males are known. If these are castrated, the new feathers that develop are the long feathers characteristic of all other races of poultry, Fig. 11.

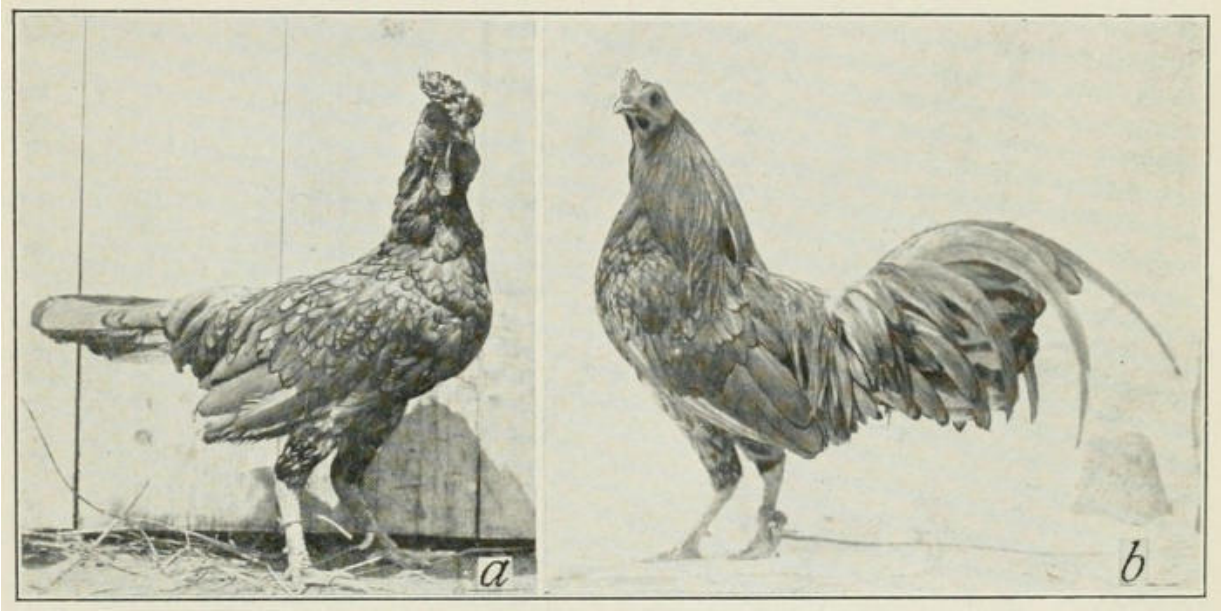



FIG. 11. To left (a) hen-feathered Sebright cock. To right (b) castrated Sebright cock that has developed characteristic cock-feathering.

If the Sebright male is out-crossed to a hen of another breed in which only cock-feathered males occur, it will be found that all the first generation males are hen-feathered. If these are now bred to their sisters there are produced, in the second generation, three hen-feathered males to one cock-feathered male, showing that the difference between the two races is inherited, Fig. 12.

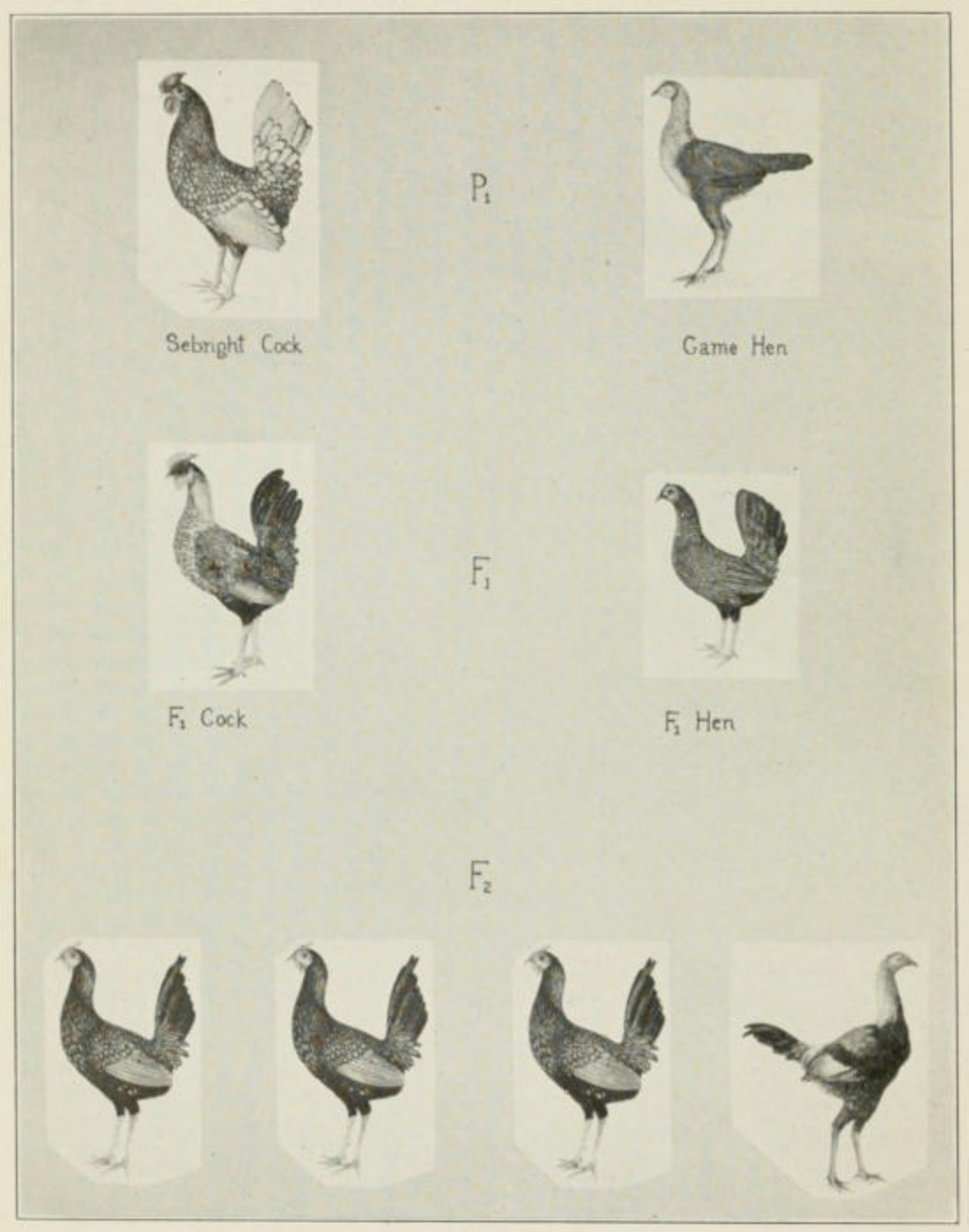



FIG. 12. Cross between hen-feathered Sebright cock and black-breasted game female belonging to a race with cock-feathered males. The offspring ($F_1$) are hen-feathered males and normal hens. These inbred give 3 hen-feathered to 1 cock-feathered son.

Now in this case we can perhaps go further. An examination of sections of the testes has shown that in the hen-feathered Sebright male there are certain kinds of cells, called luteal cells, while these are absent in the

sections of the testes of normal cocks. These same luteal cells are like those present in the stroma of the ovary of all female birds. If we assume that they make an internal secretion that prevents the development of cock-feathering, both in the normal hen and in hen-feathered cocks, we have a complete explanation of all the facts. This explanation is made more probable by the results of removing the ovary of the hen, when, as Goodale has shown, the spayed hen develops the full male plumage of her breed. Since the luteal cells are present in the hen and in the hen-feathered cock, and are absent in the adult cock-feathered male, it seems not a far-fetched hypothesis to assume that these cells (or their secretions) are those involved.

The next illustration carries its into a more debatable field. Many human defects are connected with the nervous system, and it is interesting to find that many of them are believed to be inherited; even when no corresponding structural basis in the brain can be made responsible for the defect.

Feeblemindedness, insanity, and even some types of criminality have been *said* to be inherited according to a simple one-factor Mendelian difference. Owing to the difficulty of diagnosis it is obvious that the student of genetics would be expected to approach these problems with the utmost caution. The data, on which some rather sweeping conclusions have been based, sometimes show, on closer scrutiny, obvious contradictions. Take, for example, the case of feeblemindedness which has been represented as though it differed from the normal (whatever that may be) by a single Mendelian factor difference. The evidence for this is far from convincing, and all that can be safely said, I think, is that there are types of imbecility that may possibly be due to multiple factors, but until the relation of imbecility to various disorders of the glands and to syphilis has been thoroughly studied, even my cautious statement may seem to go too far. Curiously enough no one has as yet had the temerity to suggest that some of the high-grade imbecile types—the moron, for example—might represent an ancestral stage of the human race. If this were true, intelligence would then be looked upon as an innovation in the race, that has not yet spread to all of its members. I am aware that a similar suggestion has been made with respect to the criminal. Lombroso’s “criminal type” is notorious. The criminal has been painted as the ancestral brute from which the more docile human animal has arisen through loss of “wild-type” genes. I need not state,

perhaps, that no one takes such speculations seriously today from a genetic standpoint.

Immunity and resistance to disease are subjects of great interest to geneticists as well as to pathologists.

Setting aside, of course, cases where the immunity is due to some *temporary* physiological state (little understood at present, I believe), and also setting aside immunity acquired by recovery from attack or inoculation, there still remain races that have, as we say, a constitutional resistance.

The best ascertained cases in this field are those worked out by Tyzzer and Tyzzer and Little. A carcinoma that originated in Japanese waltzing mice grew in practically every individual of the race when implanted. It failed to grow in "common" mice. The hybrid mice from these two races were also susceptible in nearly every case.

When the $F_1$'s were back-crossed to "common mice" the offspring were not susceptible. When the $F_1$'s were back-crossed to the Japanese waltzer all were susceptible. When the $F_1$'s were inbred only about 2.5 per cent. of the offspring were susceptible, Fig. 13.

These results show at least that there must be more than one, two or three factor differences between the two races that are concerned with tumor susceptibility.

Tyzzer and Little suggest in fact that 12 to 14 independently inherited factors are involved. Larger numbers of tests will be necessary before it is possible to state how many factors are needed. A curious feature of the case should not pass unnoticed. Many or all of the factors for *susceptibility* must be assumed to be dominant. It is not generally known, but there is some evidence that the so-called Japanese waltzer originated from Asiatic house mice, which according to some writers belong to a distinct species or at least a distinct variety. The results suggest that we may be dealing here with species or varietal differences, hence the large number of factor differences involved. It may be necessary to work with a simpler situation where fewer factors are involved; possibly such a case as that of the Jensen tumor will furnish proper material, but it will be necessary to work with pedigreed

material rather than with “Danish,” “French,” “German,” or even English breeds of mice.

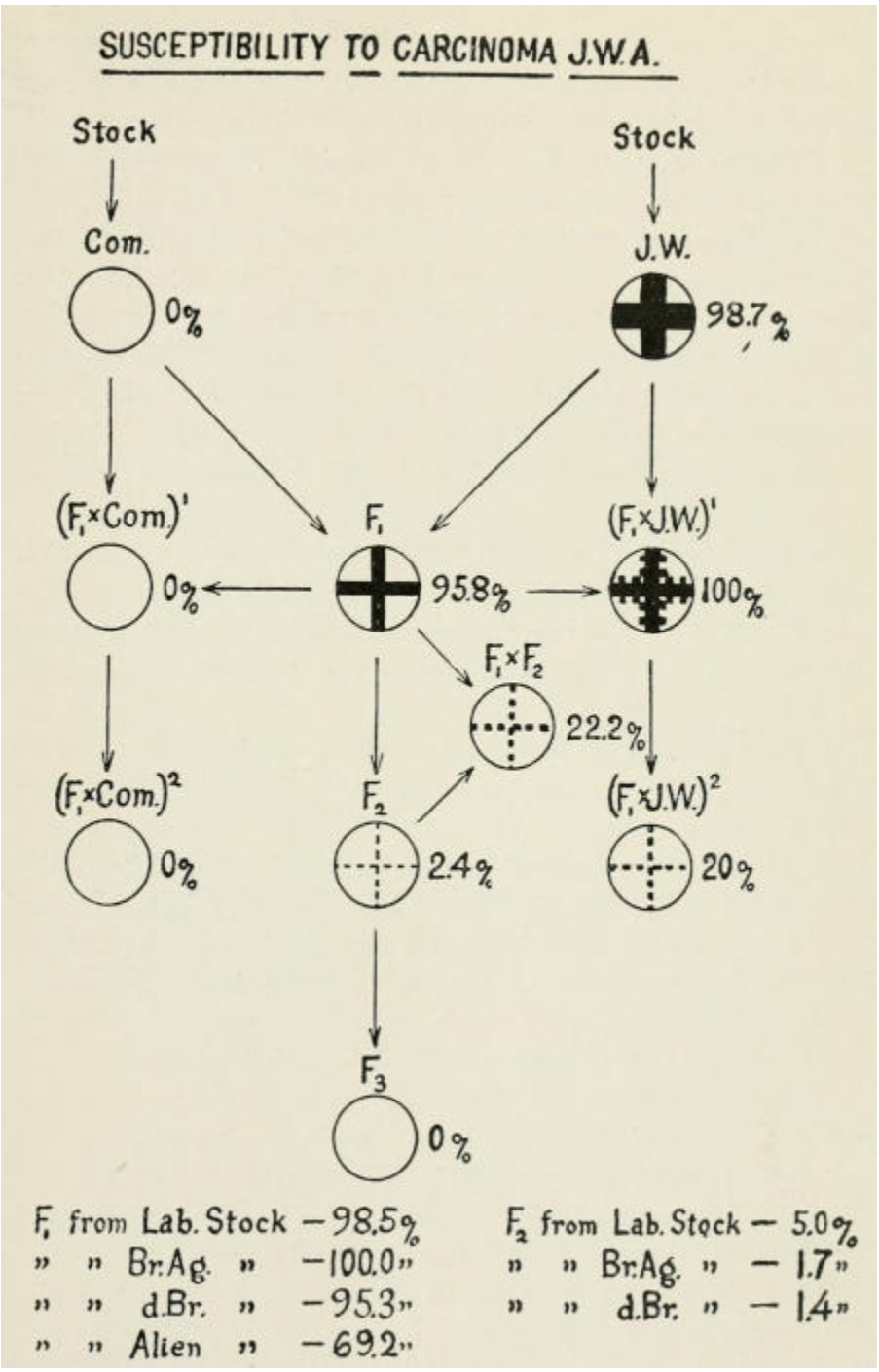



FIG. 13. Diagram showing inheritance of immunity to cancer. (From Tyzzer and Little.)

In plants also the inheritance of immunity of wheat to rust has been studied. Biffen’s results with wheat are those best known. An immune race

crossed to a susceptible race gave first generation plants that were attacked. This means that immunity is a recessive character. In the next generation there were 64 immune and 194 affected plants (a 1:3 ratio). If the immune plants are self-fertilized, they yield only immune plants in later generations.

Nilsson-Ehle and Vavilov think that such simple relations are rather the exception than the rule. Vavilov found that Persian wheat, immune to mildew, crossed to different susceptible species produced offspring that were immune in 13 combinations. In these cases immunity is dominant.

In the next generation several degrees of resistance were noted—and a few plants were even more susceptible than their grandparents.

It is interesting again to note that susceptibility and immunity are species and variety characters in these cases, but this does not mean that the differences are not Mendelian. It suggests however the possibility that several or many factor differences are often involved.

There is no more interesting field in which genetics and pathology meet than that of cancer. I realize how careful we on our side must be in discussing this question with you who are experts, nevertheless there are certain aspects of the problems of cancer from the genetic side that I may be allowed briefly to mention—not, however, without some misgivings.

Suppose all men over seventy-five died of arteriosclerosis. Could one say that hardening of the arteries is inherited? I think that it would be proper to use the word heredity to include such a case, but we would not know how it was inherited unless there existed another race of men who never died of the malady, and suitable matings were made between the two races.

Suppose again that all old men died of pneumonia. Could we say that susceptibility to pneumonia, after eighty, is inherited? Again, yes! But again we could get no information as to the way in which this susceptibility is inherited without crossing to an immune race.

Now suppose there are strains of mice all of which die of cancer after their first year. Could we say that in them cancer is inherited? The answer would depend in part on what connotations the word *inherit* carries with it, for, either susceptibility might be meant, or the “spontaneous” development of cancer might be meant. The latter interpretation is, I think, generally implied, which carries with it two further implications. First implication,

viz., that when a certain age is reached, a certain inherited complex leads to the development of cancer in one or more regions of the body. Here some such process as that of the hardening of the arteries seems to be vaguely implied. Second implication, viz., that a change in method of growth (a release from the ordinary restraining influences) suddenly occurs, beginning in a single cell of some particular tissue. Stated in this second way, the appearance of spontaneous cancer suggests at once a comparison with the mutation process that is known to occur in somatic cells as well as in germ cells.

Now if the first interpretation is to be placed on the word heredity, when applied to cancer, there is nothing more to be said, except that the only way such a situation can be studied as a genetic problem is to out-cross the strain of cancer mice in question to another that never develops spontaneous cancer. But if the second interpretation is implied, then the whole situation is put in a very different light. Let us examine this a little more closely.

Suppose, as a theoretical possibility, that spontaneous cancer is due to a recurrent somatic mutation of a specific gene to a dominant one that leads to cancer. Then the proportion of individuals that develop spontaneous cancer in such a strain will depend on the frequency of mutation of this specific gene. Consequently, if such a strain is out-crossed to another race (that introduces the allelomorph of the postulated gene), the number of $F_1$ offspring that develop the specific cancer would be half as numerous as in the original cancer strain (since the gene in question occurs only half as many times as in the original complex). In the $F_2$ generation the frequency for the extracted double dominant will be that of the original strain, that of the $F_2$ heterozygotes will be the same as that of the $F_1$, and the extracted double recessive class will not develop cancer at all. Now, if it is not possible to distinguish between these different $F_2$ classes by inspection, the difficulty of finding out how cancer is “inherited” would be very great. In such an imaginary situation, the ratio of cancer-developing mice may not appear to correspond to any of the known Mendelian ratios, because superimposed on the genetic situation there would be added results depending on the frequency of mutation when a specific gene is present.

Other complicating conditions will also suggest themselves to any one familiar with genetic and mutation processes; for, the possibility that the mutation itself is more or less likely to occur in one or another genetic

complex must be reckoned with, as well as the likelihood of the mutation showing itself or developing in any tissue or only in cells of specific tissues, etc.

I am far from wishing to suggest that spontaneous cancer is a mutational process, despite certain rather obvious resemblances to mutational effects in plants and animals, but I should like to insist that the appearance of spontaneous cancer is in its nature so peculiar that one can not afford to ignore such a possibility in any discussion as to whether spontaneous cancer is or is not “inherited.”

There are several cases of inheritance of tumors in our Drosophila material. Here I am on safer ground. One of them, discovered by Dr. Bridges, worked out by Dr. Stark, I should like to speak about, because it shows how linkage of characters can be used in the study of heredity of a character and conversely in its elimination. In a certain culture one fourth of the maggots develop one or more black masses of pigment in the body; such maggots always die. They are always males. Consequently there are twice as many daughters as sons in such a strain. The gene is carried by the X-chromosome and its inheritance is like that of all sex-linked characters as shown in Fig. 14.

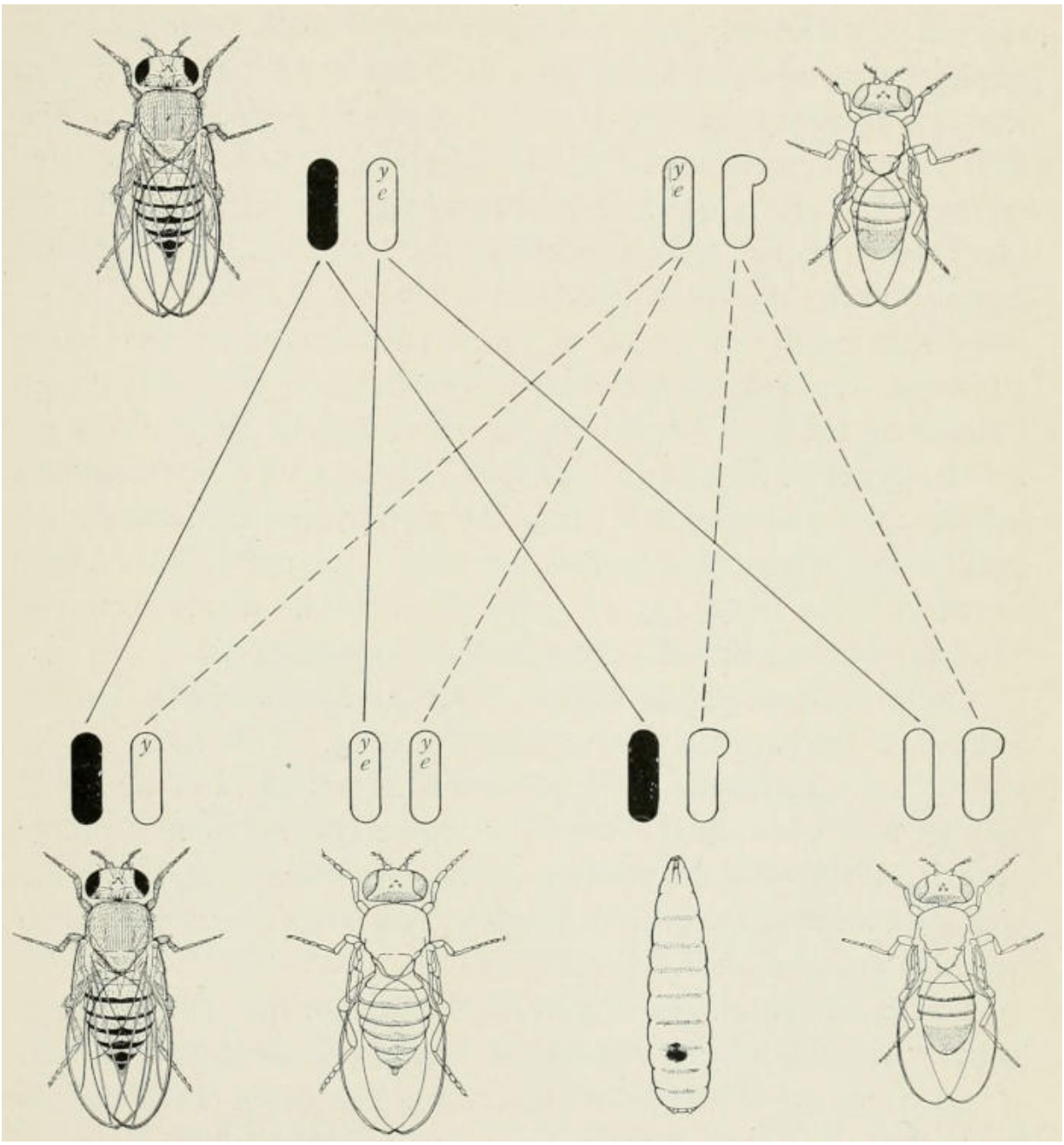



FIG. 14. Diagram showing inheritance of a sex-linked recessive lethal ("tumor") factor in *Drosophila melanogaster*. Here, in the center of the diagram, the sex-chromosome that carries the lethal factor is represented by the black rod. A female with the tumor-factor, normal wings and red eyes, in one of her sex-chromosomes and with the factors for yellow wings and eosin eyes in the other is bred in each generation to a male with yellow wings and eosin eyes. In the next generation there are twice as many daughters as sons, since all the sons that carry the black chromosome die. The half of the daughters (*i.e.*, those not yellow eosin) that carry the black chromosome repeat the same history. The linkage of yellow and eosin enables one to pick out in each generation those daughters that carry the tumor-factor.

All males that get their single X with this tumor-gene will die; therefore, since no adult males carry it, normal males must be used for mating in each generation. They are mated to females that are heterozygous for the chromosome carrying the tumor genes. Such matings as I have said always give two daughters to one son. But since half the daughters are normal and half carry the gene for tumor it is desirable to be able to pick out the latter from the stock. Therefore we have made use of a trick we call “marking the chromosome,” which means that we use a male whose sex chromosome carries a known gene near the tumor locus. By using this type of male in successive generations we get two types of daughters: one type like their surviving brothers in eye color that do not carry the tumor-gene and the other daughter with normal eyes that carries it. We use only the latter to continue the stock, but we could eliminate the tumor from the stock at once by using the other kind of daughters.

Curiously enough the tumor no longer appears in the inbred stock but reappears again on out-breeding. Nevertheless the sex-ratio in the inbred stock continues as before, and since the missing males are those with red eyes we know that the tumor-gene is still present and doing its deadly work —only now the young male larvæ die even before they reach the age at which the tumor is due to appear.

So far I have spoken of heredity as though that term had become synonymous with Mendelian heredity. Those of as who are at work on Mendelian inheritance are often criticized as too narrow. It is said that we do not recognize that any other kind of inheritance takes place. I do not think the criticism is quite fair, because, in the first place, the very great number of variations studied has been shown to conform to the Mendelian principles or at least to be capable of such interpretation. There are, however, a few exceptional cases. In certain albino plants it has been shown that the inheritance of albinism can be traced to the behavior of the chlorophyll bodies in the cytoplasm. The chlorophyll bodies are known to divide and to be distributed to the two daughter cells at each division independently of the nuclear division and of the maturation process in the egg.

Why, then, it is asked, may not there be present in the cytoplasm of the cell other self-perpetuating bodies that are responsible for certain kinds of inheritance? Why not go further and ask, why, since the cytoplasm appears

to be handed down from cell to cell, may it not furnish also a different medium for inheritance of characters? Theoretically such an argument is logical. No student of Mendelism would I think deny such a possibility. But, as a matter of fact, it is not going too far to say that, at present, there is little evidence that such inheritance takes place, except in a few special cases, like that of the chlorophyll bodies. It is safe, I think, to say that if cytoplasmic inheritance played any important rôle in heredity in the higher animals and plants, we should expect, by now, to have found many cases of it. None are known to us.

Whether Mendel's laws of heredity apply to unicellular animals, to bacteria and to similar types, in which the mechanism for this type of inheritance has not been shown to exist, can not be affirmed or denied from the evidence at hand.

There are at present three outstanding cases in the higher animals, in which an induced variation is said to be inherited afterwards. These cases are of great interest to pathology. We can not afford to pass them over. First, there is Brown-Sequard's claim that injuries to the nerve cord or to the cervical or sciatic nerves of guinea pigs produce effects that are transmitted.

Second, there are the cases of the inherited effects caused by alcohol in guinea pigs discovered by Stockard.

Third, there is Guyer's evidence that an effect on the eye, caused by foreign serum, is transmitted.

Brown-Sequard's experiments have been repeated several times; almost always with negative results. Today his claims are practically forgotten.

Stockard's results with guinea pigs, unlike those of Brown-Sequard, have been done under carefully controlled conditions. He has guarded against abnormalities in his stock by using pedigreed material. The malformations that reappear in successive generations are general rather than specific. Such organs as the eye are those hardest hit, but this is supposed to be rather a by-product of the general debility of the individual. Stockard points out that the alcohol has affected the germ cells, and it is through these that the effects are transmitted. Now if one or more genes had been permanently changed we should expect to have evidence of Mendelian inheritance. The results do not show convincingly that the inheritance is not Mendelian, but

it does not appear to be so. There is another possibility. Recent results have shown that rarely entire blocks of genes—pieces of the chromosomes—may be duplicated (owing to imperfect separation) or pieces may be lost. Here the effects on the organism are more far-reaching than when a single gene is changed. It remains to be discovered whether, in some such way as this, Stockard's remarkable results may be brought into line.

Guyer injected the crushed lens of rabbits into fowls. From the blood of the fowl he obtained serum that was injected into pregnant rabbits. The offspring of these rabbits whether male or female often had defective eyes and lenses. The defect was even transmitted to later generations. Here also the germ cells of the embryo may be changed by serum that at the same time affects the development of the eyes of the embryo in utero.

If this is the case we should expect, as Guyer pointed out, that the germ cells of the pregnant mother (into which the serum was injected) would also show effects. It should have been a simple matter to show this by a proper test. The test that Guyer made, namely by out-breeding the mother and finding no defective $F_1$ young, was quite inadequate if, as appears to be the case, the character is a recessive.

It is important to keep clearly in mind that there are two distinct questions involved in these three cases. Genetics has to deal with only one of them. There is first the question of the action of environment on the germ cells. Genetics has nothing to do with this question. There is then to be determined whether, if variations may be induced in these ways, they fall into one or another of the Mendelian moulds. This is for the geneticist to determine, but he finds himself in a curious predicament, for it can not be claimed that any of these three cases have been shown to give a direct Mendelian result—but neither can it be denied that they may possibly come under the scheme, or some modification of it. There we must leave the matter at present.

If I have appeared at times overcritical concerning the application of genetics to pathology, it is not because I do not sympathize with the attempts that have been made to apply genetics to pathology. I realize, of course, that from the nature of the case much of this work is pioneer work, where rough and ready methods have often to be resorted to. So long as this is kept in view, no harm can be done in attempting to find how far Mendel's

principles can apply to heredity in man. But I want to enter a protest against the danger of premature conclusions drawn from insufficient evidence. In our enthusiasm in applying Mendel’s laws, we should be careful not to compromise them.

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