CHAPTER XIX

THE PARTICULATE THEORY OF HEREDITY AND THE NATURE OF THE GENE

THE attempt to explain biological phenomena by means of representative particles has often been made in the past. The superficial resemblance of the theory of the gene to some of the older theories, long since abandoned, has furnished the opponents of the Mendelian theory of heredity an opportunity to injure the latter by pretending that the modern idea of the gene is the same as the older ideas of Herbert Spencer concerning physiological units, of Darwin relating to pangenes, and especially of Weismann about biophors. There is no need for such confusion, for even a little knowledge of the evidence on which the old and the new views rest ought to have sufficed to make evident some important and essential differences. It need not be denied, however, that there is an historical connection between the mediæval theory of preformation and the particulate theory of heredity. Bonnet, one of the best known adherents of preformation, believed at first in "whole" germs, but later admitted that pieces of germs might be stowed away in regions of the body likely to be injured. Weismann, also, the most prominent modern adherent of preformation, held that whole germs, ids, are present in the germ-plasm, each standing for a whole organism—each (or most or one?) becoming unravelled as the embryonic development proceeded. In fact, Weismann's entire theory was invented primarily to explain embryonic development rather than genetics. Its connection with the modern idea of the germ-plasm is little more than an analogy—for reduction in Weismann's original sense meant the sorting out of the wholes of ancestral germ-plasms with which he peopled the chromosomes.[1]

The danger of any appeal to a theory of representative particles obviously lies in the ease with which by its means any phenomenon might be accounted for, if the theorizer is allowed to endow the particles with any and all the attributes that he wishes to use in his explanation. It was because Bonnet, Spencer, and Weismann assigned arbitrarily attributes to the ultimate particles of living matter, that these views appear to-day highly speculative. The different kind of evidence to which the modern theory of the gene appeals is what I wish to emphasize here.

The Evidence for the Gene

The evidence that Mendelian inheritance rests on the distribution of separate elements has already been given. The numerical results obtained in the second generation from any Mendelian cross involving a pair of contrasted characters, find their explanation on the assumption that the two original germ-plasms (or some element in them) separate cleanly in the germ-cells of the F_1 hybrid. Tested by back-crossing the assumption is verified. Recombining the P_1, F_1, F_2 individuals in all possible ways also gives results consistent with the very simple assumption that whatever it is that causes one race to produce one character, and another race another character, the two separate in the hybrid in such a way that equal numbers of germ-cells of each kind are produced. Up to this point the results do not tell us whether the two germ-plasms separate as wholes—one from the other—or whether only some part or parts behave in this way. But when two or more

[1] The nominal adoption (1904) toward the end of his career of hereditary units in the Mendelian sense did not go deep. Weismann still adhered to his view of dissociation of the ids as their most characteristic feature—the only one in fact for which they were originally invented. The evidence on which Mendelian units rest has nothing whatever to do with this cardinal doctrine of Weismann's teaching.

pairs of contrasted characters are involved in the same cross, we get further information as to the situation.

For example, Mendel showed that when peas that are both yellow and round are crossed to peas that are both green and wrinkled, there appear in the F_2 generation not only the original combinations, but also recombinations of these, *viz.*, yellow and wrinkled; and green and round (Fig. 106). Here also the numerical results 9:3:3:1 can be explained on the theory that the representatives of each pair of characters separate in the germ-plasm, and that the separation of each pair is independent of what takes place in the other pair. Obviously it can no longer be whole germ-plasms that separate, but there must be different pairs of elements in the germ-plasm that assort independently of each other. It has been found that this principle of independent assortment may apply to a considerable number of pairs of characters segregating at the same time. The only restriction that is found is in the case of linked pairs of characters. This relation will be considered later.

The independent assortment of the pairs of characters proves that the elements that stand for the characters in the two original germ-plasms may separate from each other. If each such pair of characters represented one of the pairs of homologous chromosomes, the evidence, so far considered, would be in accord with the view that the chromosomes were the ultimate units involved in the processes of segregation and assortment. The chromosomes are, as has been shown, independent units in the germ-plasm. But as *Drosophila* shows, there are many more pairs of characters than there are pairs of chromosomes.

It is obvious that if the chromosomes are the ultimate units involved, and remain intact, there could be no more *independent pairs* of characters than there are pairs of chromosomes. In animals and in plants there are no cases known where there are more independent pairs than there are chromosomes, so that, as has been pointed out in another connection, this evidence may also be appealed to as favorable.

The behavior of linked pairs shows, however, that the analysis must be carried further, because, despite linkage, the elements that went in together may be separated. The evidence shows that while some linked genes separate almost as freely as do independent genes, so that their linkage to each other can only be safely determined by their relation to certain other genes, other linked genes may separate not once in a hundred times, or even less often. Between these extremes all intermediate linkage values are found. These results indicate that the chromosomes do not represent the ultimate elements that may be separated out of the original complex (germ-plasm).

We are led, then, to the conclusion that there are elements in the germ-plasm that are sorted out independently of one another. The *Drosophila* evidence shows at least several hundred independent elements, and as new ones still appear as frequently as at first, the indications are that there are many more such elements than those as yet identified.

These elements we call genes, and what I wish to insist on is that their presence is directly deducible from the genetic results, quite independently of any further attributes or localizations that we may assign to them. It is this evidence that justifies the theory of particulate inheritance.

So far as representative elements in the germ-plasm are concerned, we might be content to rest the case on the preceding analysis of the results; but recent work has now advanced far enough to tempt us to assign further attributes to the genes than those deducible from the preceding analysis alone. Some of these attributes may appear better established than others, but, all together, they give a consistent body of data, and have therefore a certain value and use.

It has been pointed out that the evidence shows not only that the genes are carried by the chromosomes, but that there may be interchanges between paternally-derived and maternally-derived chromosome pairs. The evidence shows that this interchange is a normal feature of the germ-cell, and not peculiar to hybrids, or to a heterozygous condition of the pairs.

This analysis leads then to the view that the gene is a certain amount of material in the chromosome that may separate from the chromosome in which it lies, and be replaced by a corresponding part (and by none other) of the homologous chromosome. It is of fundamental significance in this connection to recognize that the genes of the pair that interchange do not jump out of one chromosome into the other, so to speak, but are changed by the thread breaking as a piece in front of or else behind them, but not in both places at once, as would be the case if only a single pair of allelomorphs were involved each time.

That the gene does not stand for the whole length of the chromosome between two other known genes is shown by the fact that new genes arising by mutation in the intermediate region do not affect the character of the gene already known. This fact recurring continually in *Drosophila,* where new mutations frequently appear, reassures us that the idea of the gene as a very small part of the thread is a legitimate conclusion, even if we can not tell how large or how small that region is.

1. The Manifold Effects of Each Gene

If we examine almost any *mutant* race, such as the race of white-eyed *Drosophila,* we find that the white eye is only one of the characteristics that such a mutant race shows. The productivity of the individual is also much affected, and the viability is lower than in the wild fly. All of these peculiarities are found whenever the white eye emerges from a cross, and are not separable from the

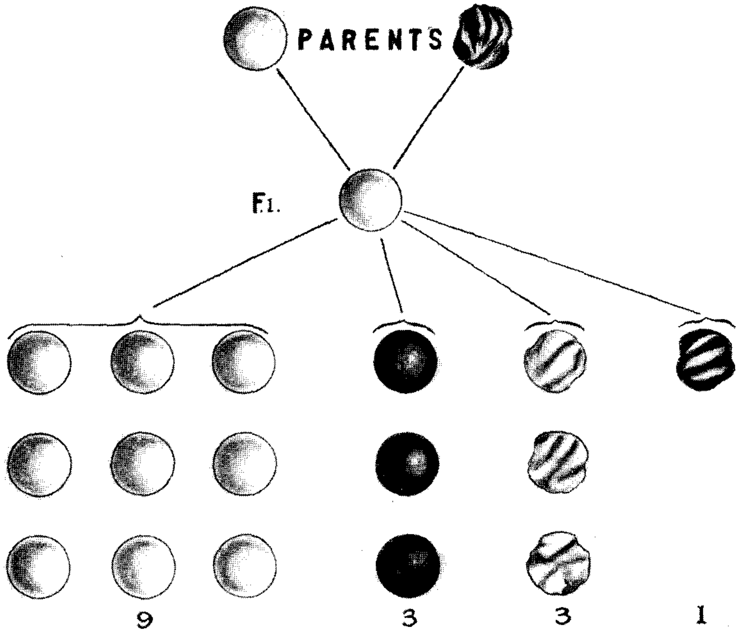


FIG. 106.—Diagram to show the inheritance of two pairs of Mendelian characters, viz. yellow versus green peas, and round versus wrinkled skin in garden peas.

white-eyed condition. It follows that whatever it is in the germ-plasm that produces white eyes, also produces other modifications as well, and modifies not only such "superficial" things as color, but also such "fundamental" things as productivity and viability. Many examples of this manifold effect are known to students of heredity.

It is perhaps not going too far to say that any change in the germ-plasm may produce many kinds of effects on the body. Clearly then the character that we choose to follow in any case is only the most conspicuous or (for purposes of identification) the most striking or convenient modification that is produced. *Since, however, these* effects always go together, and can be explained by the assumption of a single unit difference in the germ-plasm, *the particular difference in the germ-plasm is more significant than the character chosen as its index.*

2. The Variability of the Character is Not Due to the Corresponding Variability of the Gene

All characters are variable, but there is at present abundant evidence to show that much of this variability is due to external conditions that the embryo encounters during its development. Such differences as these are not transmitted in kind—they remain only so long as the environment that produces them remains. By inference *the gene itself is stable, although the character varies; yet* this point is very difficult to establish. The evidence is becoming stronger nevertheless that the germ-plasm is relatively constant, while the character is variable.

3. Characters That are Indistinguishable May be the Product of Different Genes

We find, in experience, that we cannot safely infer from the appearance of the character what gene is producing it. There are at least three white races of fowls, produced by different genes. We can synthesize white-eyed flies that are somatically indistinguishable from the ordinary white-eyed race, yet they are the combined product of several known color-producing genes. The purple eye color of *Drosophila* is practically indistinguishable from the eye colors maroon and garnet. In a word, we are led again to units in the germ-plasm in our final analysis rather than to the appearance of a character.

4. Inference That Each Character is the Product of Many Genes

We find that any one organ of the body (such as an eye, leg, wing) may appear under many forms in different mutant races as a result of changes of genes in the germ-plasm. It is a fair inference, I think, that the normal units—the allelomorphs of the mutant genes—also often affect the same part. We have found about 50 different factors that affect eye-color, 15 that affect body-color, and at least 10 factors for length of wing in *Drosophila.*

If, then, it is a fair inference that the units in the wild fly, that behave as Mendelian mates to the mutant genes, also affect the same organ that the mutant gene affects, it follows that many genes, and perhaps a very large number, are involved in the production of each organ of the body. It might perhaps not be a very great exaggeration to say that every gene in the germ-plasm affects several or many parts of the body; in other words, that the whole germ-plasm is instrumental in producing each and every part of the body.

Such a statement may seem at first hearing to amount almost to an abandonment of the particulate conception of heredity, but on the contrary, the statement conveys a very important idea in the modern conception of the nature of the genes and the way they act.

The essential point here is that even although each of the organs of the body may be largely a product of the entire germ-plasm, yet this germ-plasm is made up of units that are independent of each other in at least two *respects, viz., in that each one may change (mutate) without the others changing, and in segregation and in crossing over each pair is separable from the others.*

5. "The Organism as a Whole," or The Collective Action of the Genes

Several writers have stated their objections to the particulate theory of heredity on the grounds of their belief that the organism is a "whole." If this phrase is intended to mean that there is some sort of an entity or entelechy that directs all processes that go on in each living thing, there is little to be said here, except that this very old idea has not been found profitable as a working hypothesis. It is improbable, however, that many biologists mean to appeal to any such vitalistic agency when they speak of the "organism as a whole," but have rather some other idea in mind. I am inclined to think that certain phenomena of embryonic development are responsible for the slogan of the "organism as a whole." In the segmentation of the egg the entire chromosomal complex is distributed to every cell in the body. Each cell *inherits* the whole germ-plasm. How then it may be asked can the result depend on the particular make-up of its chromosomes rather than on the action of the whole material?

Granted that we know very little about the interactions between the cells that cause some of them to differentiate in one direction, others in other directions, yet if one fertilized egg should begin its development with one kind of material, and another egg with a different material, should we not expect the end products to be different, irrespective of the way in which the materials were present in the original egg? No matter where the differences may lie, *i.e.,* whether in the nucleus or in the cytoplasm, there is nothing here in any way inconsistent with this particulate theory of the composition of the germ-plasm. On the contrary, the only conclusion that seems at all reasonable is that if differences are present at the beginning, the end product is expected to be correspondingly different. So much is clear. But why, it may still be asked, are not two organisms that are different at the start, if only in some one difference, different later in every part, rather than in only some one small part such as in a red or in a white eye. The answer is, of course, that the first difference was such that it affected principally a particular process, *viz.*, the formation of the red pigment of the eye, and to a less degree, or not at all, other chemical processes. This seems to me an entirely consistent view.

Perhaps the difficulty in accepting the particulate theory lies in the erroneous idea that the specific effect comes into action only at the moment when the red pigment is about to form. But no one has, so far as I know, made such a claim. It may be true, but it has not been proven, and is moreover not in any way essential to the assumption of the particulate theory. On the contrary, as our knowledge of Mendelian heredity has increased many cases have been found where a special factor-difference affects not only one part of the body but many parts. It is true that the particulate theory as held at one time by Roux and for a long time by Weismann was used to explain the differentiating changes in the segmenting egg and embryo in the sense that development was looked upon as a process that resulted immediately in the sorting out of the inherited chromosomal particles to the different parts of the organism. Differentiation resulted in the sorting out of particular genes to particular groups of cells whose development they controlled. But the cytological evidence in regard to the chromosomes gave no evidence in support of the view, and the evidence from the experimental study of embryology seemed to entirely disprove any such basis for the developmental phenomena. In fact, Roux himself abandoned this view in the light of the brilliant experiments of Driesch and of other embryologists.

Our present conception of the relation of the germ-plasm to developmental phenomena has then only a most superficial resemblance to the older theories. The newer point of view may be summed up in a few words, and has in fact been stated already. First, that each gene may have *manifold effects on the organism, and second, that* every part of the body, and even each particular character, is the product of many genes. The evidence for these two conclusions has been so repeatedly referred to in the preceding pages that it is not necessary to go over it again. but it may be worth while to emphasize that these two conclusions are not pure speculations, but derived from the evidence itself. It may also be well to point out that even if the whole germ-plasm—the sum of all the genes—acts in the formation of every detail of the body, still the evidence from heredity shows that this same material becomes segregated into two parts during the maturation of the egg and sperm, and that at this time individual elements separate from each other largely independently of the separation of other pairs of elements. It is in this sense, and in this sense only, that we are justified in speaking of the particulate composition of the germ-plasm and of particulate inheritance.

There is a further idea deducible from well-known facts of physiology that may at first sight seem to give an *impression that the organism is a "whole."* This is the action of one part of the body on other parts by means of substances set free in the blood, called hormones. Many of them arise through the action of certain so-called endocrine glands. But the relation here is so obviously different from the problem dealt with as particulate inheritance that it calls for little more than passing notice. It may, however, not be without interest to refer to one case of the kind in which an endocrine secretion depends on a genetic factor inherited in the same way as are other genetic factors. There is a race of poultry known as Sebrights (Fig. 107, *a*) in which the males are always hen-feathered. This means that the feathers of the neck and back and the tail coverts of the Sebright cock are nearly like those of the hen of this breed, and not long and pointed as in the ordinary cock. When Sebrights are crossed to game bantams (which have ordinary males), the F_1 males are hen-feathered. When these are inbred the two types reappear in the F_2 males. One, or probably two, Mendelian factor differences account for the results.

It has been shown that when the testes are removed from the Sebright male, he then develops at the next moult (or at once if some feathers are plucked out) the long and highly colored feathers of the ordinary male (Fig. 107, *b*). It is probable, therefore, that the testes of the Sebright produce an internal secretion that inhibits in the male the full development of certain feathers. This makes him like the hen, and in this connection it is interesting to note that when the ovary of a hen of an ordinary breed is removed she also develops the full plumage of the cock, as Goodale has clearly demonstrated. Whether the testes of a male are of the sort to develop this inhibiting substance, depends on the presence in the cells of the testes of certain genetic factors. These factors are present, presumably, in all the cells of the body, but if they are, their activity is ineffective in the absence of secretions produced by the testes, as is shown by the castrated Sebright becoming cock-feathered. Whether this substance belongs in the heterogeneous group of substances called hormones—defined by the kind of action they produce rather than by any chemical peculiarity—or to the groups of enzymes that have a more or less specific action, cannot be stated.

The foregoing discussion touches upon the question as to whether there is any evidence that the genes themselves are to be regarded as enzymes.* In almost all of the

* Inadequate as is our knowledge of the physico-chemical processes that go on in development, it is enough to indicate that many processes are at work.

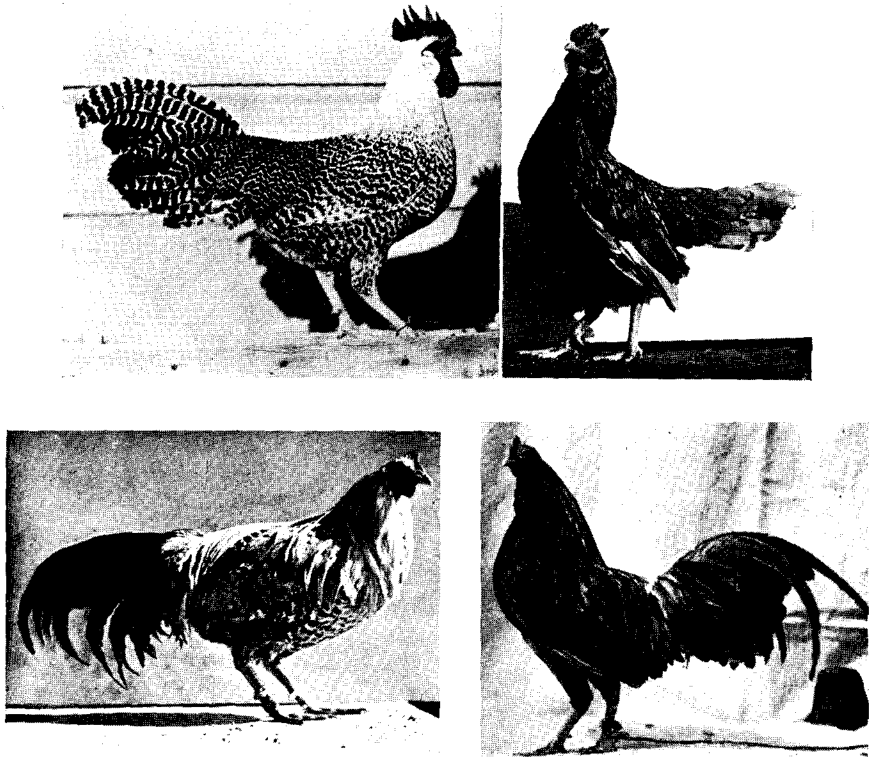
recent papers (Beijerinck, Riddle, Goldschmidt) that touch on this question it is argued, from the evidence of the specific enzymes supposed or demonstrably involved in the production of some final stage in the chemical reaction that leads to the character in question, that the gene itself is the same specific enzyme. The argument shifts back and forth from unit-character to unit-factor. The reasonable position to take in this matter is, in my opinion, that stated by Loeb and Chamberlain (1915), "The hereditary factor in this case must consist of material which determines the formation of a given mass of these enzymes, since the factors in the chromosomes are too small to carry the whole mass of the enzymes existing in the embryo or adult." It should not be forgotten, however, that the evidence in favor of enzyme action as the most important developmental process is by no means established, and even were the evidence for this view adequate, the stages between such action and the ultimate chemical nature of the gene may be too great to be cleared at a single bound. Some of the modern work on the chemical composition of the nucleus indicates that extremely complex protein compounds *may* be present in it—even though some of the split products obtainable from it may be relatively simple. It seems to me therefore that it is both premature and highly speculative at present to tie up the genetic evidence concerning the genes with hypotheses concerning their chemical composition. I urge this, but at the same time I realize of course that we should endeavor to obtain as soon as possible better knowledge as to the chemical nature of the chromatin.

Another question concerning the gene, that has been raised, is whether it is to be regarded as something having a definite molecular constitution, or whether the gene is to be regarded as a quantity of material fluctuating about a mode—its definiteness representing only a general tendency for the same frequency distribution to recur in each species. From the nature of the case such a question is speculative, and would have little importance were it not that, by imputing to the advocates of Mendelian heredity the assumption of absolute fixity to the gene, attempts have been made to throw the burden of proof that the genes are "constant" on the advocates of Mendelism.

So far as the genetic evidence is involved, I see at present no way of deciding whether the gene has a definite molecular constitution, or is only something that fluctuates under the condition of its occurrence about a mode. Interesting as it might be to speculate about these alternatives, it seems futile to do so at present, but there is one implication that I should like to examine. If the gene is a chemical molecule it is not evident how it could change except by altering its chemical constitution. Its influence, *i.e.*, the chemical effects it produces, might, however, be altered by changing other substances with which the material it produces reacts. This is the idea involved in the theory of "modifying genes."

But if the gene is a fluctuating amount of something it might seem that any "fluctuation" that is present at one time might be perpetuated by selection, and that a further fluctuation in the same direction might be utilized for a further advance, etc. It may be pointed out that this picture of the process is quite fanciful, and its success would depend largely on a denial of the premise as to the nature of the gene, *viz.*, that it is of a fluctuating amount. Johannsen's facts contradict an interpretation of the fluctuations of the character being due to a new modal position of the gene standing for that character. And his facts furnish the only crucial evidence we have at present.

A C



B D

FIG. 107.—A. Adult hen-feathered Campine male. B. Adult male of same race that had been castrated while still a young bird. When it became older it developed cock-feathering. *It resembles* the male of another race of Campines in which the male is normally cock-feathered. C. Adult hen-feathered Sebright male. D. Adult male Sebright, that had been castrated while still a young bird. It developed cock-feathering when it became older.