Different Philosophies of Genetics*

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Prudens quaestio quasi dimidium scientiae.

IN the United States, a presidential address is usually scheduled for delivery after a banquet. Probably the underlying idea is that a well-fed audience is in a pleasant and mild mood, not too attentive, not too critical, and ready to submit quietly for an hour to whatever the old man is willing to produce. Unfortunately, I am not in this pleasant position today, having to face a hungry audience (at least mentally so), full of zeal, and with sharpened critical faculties. I might even quote here from Aristophanes (*The Clouds*):

> Phidippides: What do they call themselves?
> Strepsiades: I do not know exactly but they are deep thinkers and most admirable people.

Knowing this to be the case, I had to solve the difficult problem of deciding upon a topic worthy of my audience.

This means a topic which is not so special that it interests only a small group, but which nevertheless is on a sufficiently technical level; one which is general but not so general that it becomes commonplace; one which is to a certain extent controversial, at least sufficiently so to make an interesting discussion, yet at the same time is not so controversial that it is unsuitable for a discussion without the use of the gentle art of making enemies; one which is based upon the performance of the past without being of yesterday and retrospective, but also one which dares to look into the future and to risk a jump beyond the present without soaring into a flight of pure imagination; finally, it means a topic the discussion of which has a personal, subjective angle based upon the speaker's scientific past, but which does not end in dogmatism and opinionation.

Just as is the case with other sciences, for example, physics, so also genetics is based upon what a theoretical physicist (Sir E. Whittaker) has called "the unchangeable brute facts of experience which have the character of permanence." But, continuing the quotation, "The situation is different with an intellectual adventure such as theoretical physics; it is built around conceptions and the progress of the subject consists very largely in replacing these conceptions by other conceptions, which transcend or even contradict them."

There is no historically recognized science of theoretical genetics comparable to theoretical physics or natural philosophy, as it is called in England. But each thinking geneticist, in interpreting his factual data and in trying to fit his results into the total theoretical structure of his science, does it under the conscious or subconscious influence of his basic philosophy or *Weltanschauung* in regard to genetical thought. I mean to say by this that, when we interrupt our experiments to do some constructive thinking, we are likely to draw frequently widely divergent conclusions from the same facts. It is not that the facts are ambiguous or insufficiently established; is is the way we are looking at the facts that is different. But this difference does not necessarily mean that one is a better thinker than another. Rather it means, in many cases, that the general way of thinking, of analyzing facts and of putting them into categories, is different in different minds.

There is no objective way to decide which is the correct mental attitude and which is not. The decision lies with time, which as often as not will decide that both attitudes were wrong and will replace them by a third and a fourth, again subject to selection as further facts allow new evaluation of ideas in time. It is obvious, as was already hinted by the use of the word *selection*, that just this competition of divergent ideas, even basically, philosophically divergent ideas, is the method by which the theoretical level of a science develops.

Genetics is not any exception and, therefore, I should like to inquire into what I believe to be the two basic divergent philosophies of our science and to confront them with each other. Nobody would expect other than that in so doing I cannot help arguing in favor of my own way of looking at things. But this does not mean that I take less seriously the opposed points of view of some great geneticists and thinkers with whom I have to disagree. I realize well that another, in the same place, might argue quite differently. Although I am convinced of the correctness of my argument, otherwise I should not have a right to speak out, I realize that those who hold the ideas that I consider to be impossible are ready to turn the argument in their favor. I cannot help quoting here a beautiful and witty passage from *Through the Looking Glass*, which might be used by both sides in any disagreement on interpretation.

> "I can't believe that," said Alice. "Can't you?" the Queen said in a pitying tone. "Try again: draw a long breath, and shut your eyes."
> Alice laughed. "There's no use trying," she said, "one can't believe impossible things." "I dare say

* Presidential address to the 9th International Congress of Genetics, Bellaggio, Aug. 1953. Dedicated to his friend Otto Hahn on the occasion of his 75th birthday.

you haven't had much practice,'' said the Queen. ''When I was your age I did it for half-an-hour a day. Why, sometimes I've believed as many as six impossible things before breakfast.''

Now to the two philosophies of genetics to be contrasted. One is the statistical, or static, point of view; the other, the physiological, or dynamic, point of view. This antithesis does not mean that the two mental attitudes are mutually exclusive and could not be assumed simultaneously in their proper place. Nobody doubts that classical genetics is a statistical science and physiological genetics a dynamic one, each solving its own problems in its own way. What is meant is this. The statistical basic philosophy tries to interpret every generalized set of facts by the introduction of more and more units for statistical treatment. In the examples to be taken up subsequently, it will be seen that statistical thinking tries to explain all basic features of genetic phenomena by introducing more genes in the form of modifier systems built up by selection. In this way, a system is finally established, which is so conspicuous in much of present-day genetics, and which I must call hyperatomism and hyperselectionism. In my personal opinion, it will lead in the end to impossible consequences by requiring astronomical numbers of modifiers and a similar number of tiny but specific adaptations. This, I think, is an example of the "five or six impossible things" that the queen learned to believe before breakfast.

The physiological, or dynamic, approach, on the other hand, tries first to understand general phenomena in terms of genic action and developmental systems with all their consequences of interaction, embryonic regulation, and integration. Although this approach accepts, naturally, the basically statistical tenets of genetics, it tries, actually within the rule of parsimony, to avoid looking for explanations in terms of unproved, additional systems of units for more and more genic permutations. It prefers to find out how far explanations based upon the dynamics of the organism and its development under genic control will go. Let us illustrate the difference of mental attitude with a well-known example. In *Drosophila* populations, different inversions are found, differing in type and frequency in space and partly also in time. Without going into the details, this suggests that an adaptation brought about by selection is involved. Let us not discuss the merit of these facts but only the attitude toward their interpretation. The statistically minded investigator will look for systems of linked genes selected for a definite competition, which are protected from crossing over by the inversion and, thus, are kept in heterozygous condition. These blocks of genes are composed of such loci as are needed for adaptation to the particular environment. I am not discussing now whether this interpretation is correct but only the types of explanations for which different minds are looking. The geneticist who thinks in dynamic terms would look first for a possible function of the inversions. He would, for example, remember that inversions as such tend to change the time of development, and he would start experiments designed to find a physiological cause for the basic facts.

But let us get away from generalities and illustrate the alternative genetic philosophies with examples taken from the work of great geneticists whose philosophical outlook differs from mine. As the first example, I propose the theory of dosage compensation. The underlying facts are so clear that a detailed confrontation of the two basic types of interpretation is possible.

Sex-linked mutants in *Drosophila* are present in one dose in the male, in two doses in the female. Although normally this difference in dosage would lead to different quantitative expression of the trait, most sex-linked mutants appear identical in the two sexes. If the same mutations are made (by the use of duplications and deficiencies) to be present in one dose only in the female, they appear less extreme than in the male, and, vice versa, when put in two doses in the male, they are more highly expressed than in the female. This can be demonstrated, for example, for mutant eye colors and also for the normal type, which when checked photometrically shows the type of relationship just described. From these facts, the conclusion is drawn that the phenotypical identity of, in the present example, eye color in the two sexes is an adaptive trait and that this adaptation has come about by selection of dosage-compensating modifier systems for this sex-linked trait. The same reasoning will apply to all other X-chromosomal genes. All these modifiers must themselves be located within the X-chromosome, a conclusion that was first derived from dosage experiments with the bobbed alleles and later was studied in detail in eye colors. Thus the geneticist of statistical inclination turns first, if not exclusively, to an interpretation based upon extra genes and selection.

The geneticist of basically physiological persuasion would, from the beginning, look for an interpretation in terms of development. He would point out that male and female differentiation takes place in very different developmental systems laid down at the moment of fertilization by the different balance of the sex factors. He would point to the fact that developmental rates in the two sexes are different, that the relative rates for the individual and consecutive phases of growth are different, that times of determination as seen in temperature effective periods or in times for optimal production of phenocopies are different, and further, that the rhythm of differentiation of individual organs like the gonads differs in the two sexes. Thus, he would understand on the basis of different developmental systems why different dosages may fail to produce different phenotypes. He would also conclude that some developmental processes might be of such a kind that they would produce, in spite of the different development systems, different sexual phenotypes, as is known for a number of loci. This means that the loci in question act simply according to their dosage. The explanation that offers itself at once is that threshold phenomena are involved. The statistical geneticist would have to assume in this case that such sexually

dimorphic loci are of nonadaptational value and, therefore, are not in need of compensating modifier systems.

Let us go a little further into this interesting problem, not so much for the sake of proving that the dynamic type of explanation is the better one (although I cannot help but bring this out incidentally), but more with the intention of emphasizing further the contrast between the two basic ways of looking at genetical facts. The most recent student of the idea of dosage compensation does not fail to realize the possibility of an alternative interpretation. But he does not see this in terms of development—that is, genic action—but in terms of gene distribution. He says that the alternative is that the sex-determining genes themselves act as dosage modifiers. To disprove this, he points out some facts that are worth mentioning because they reveal so well the difference in basic outlook.

There is known a third chromosome recessive mutant, called "transformer," which in homozygous condition transforms 2X-females into what look to all purposes like males. If the eye color apricot is present, the transformed males have the same color as genuine males with apricot eyes. By introducing a duplication into a genuine male, it can be made to have two doses of apricot instead of one, with the result of a darker eye color. Therefore, the conclusion runs, the XX-males-by-transformation should have this darker color, if the sex determiners were also the dosage modifiers. Actually, the color is the same as in normal females and males, which means that not the sex determiners but the dosage compensators within the X-chromosomes are responsible.

This argumentation clearly assumes that the normal 1X-males and the transformed 2X-males are identical, which means that they have the same developmental system. If the problem had been looked at, not from the point of view of modifiers but from the point of view of development, it would have turned out that the males-by-transformation have a developmental system that is female in a number of basic features. Actually, the sex-reversal flies are not males but extreme female intersexes (= 2X-intersexes) in which some basic features of growth and differentiation (actually those of early determination) are still female. This is true for size and general growth, for time of development, for many proportions, and for the rhythm of gonad development. In addition, all sex-linked mutants that are sexually dimorphic—that is, without so-called compensation—show the female phenotype. Thus, the behavior of the eye color is just what is expected in the 2X-intersexes and the dosage-compensation explanation becomes superfluous.

It is remarkable that similar ideas have also been used to interpret the fact that autosomal mutants frequently have a somewhat different expression in the two sexes; for example, they express themselves less intensively in the males. To mention only one example, mutants that produce extra veins on the wings of *Drosophila* have, as a rule, a less extreme expression on the male wing. If one studies the development of this character, one realizes that such differences may, in a general way, be dependent upon time relationships between the general speed of development of the wing and the special rates of concrescence of the wing membranes between the future veins. Although the details are not clear, the general idea is obvious to the geneticist who thinks in terms of development. A well-known population geneticist, who met with this fact of different sexual expression of such mutants found in natural populations, offered the following explanation, assuming *a priori* that the presence of such mutants in the population is an adaptive feature, based on correlated physiological properties.

> The different expression in males and females is probably also a reflection of the adaptive nature of this variation. The mutations . . . are pleiotropic, producing, on the one hand, extra veins on the wing, and, on the other, some physiological peculiarities which determine high viability. . . . Since in these populations free crossing occurs, it is apparent that the complexes of genes of extra venation must be the same in females and males. The question arises then, how is it that with an equality of the mutation complex in the two sexes, and with a different degree of sensitivity to them in males and females, there is in both sexes the same level of physiological adaptation? If a given complex of mutants is adapted for females, it should be harmful for males. If, on the other hand, a weaker complex is adaptive in males, it should be inadequate for females. Equality of the physiological manifestation of the same set of mutations in females and males can occur under these circumstances only in the presence of an additional regulating genotypic mechanism, which, for instance, may partly inhibit the action of these genes in males.

This then is a good example of the basic cleft between the two philosophies of genetics: One considers all and everything the product of selection and adaptation and, therefore, explains all observations by introducing specific modifier systems produced by selection, necessarily reaching, in the end, astronomical numbers. I cannot help feeling that the argument, as quoted, is queer, even perverted. The other philosophy looks for simple facts of development of the type just mentioned, which might automatically produce the effect without recourse to additional special and selective genic systems. In the special case under scrutiny, the geneticist who subscribes to this philosophy would add in support of his argument that the same sexual dimorphism in the phenotype of a mutant that led to the complicated assumptions reported is also present when the same mutant appears anew under his eyes, without any previous or following selection.

These examples lead to another group of facts which, for a long time, have demonstrated the same basic difference in genetic thinking—facts in the field of sex determination. If we confine our discussion to standard zoological bisexual material with genetic sex determination, such as *Lymantria, Drosophila,* and some fishes, we know that genetic sex determination is based upon the balance between female and male sex

determiners, the two possible normal balances being produced by the 1X-2X-chromosome mechanism, while imbalance produces intersexuality. One type of determiners is located in the X-chromosome and, therefore, is present in either one or two doses. The other type is located outside the X-chromosome, which means in different cases in the Y-chromosome, or in the autosomes or in both. Thus, one or two doses of one group of determiners are always opposed to the same dose of determiners of the other sex, independent of whether we are dealing with male or female heterogamety. In each case, the action of the determiners within two X-chromosomes wins over the action of the constant determiners of the other sex; while one X-chromosome, meaning the action of only one dose of X-chromosomal determiners, loses against the action of the determiners of the other sex outside the X-chromosomes. This then is the primary sex-determining mechanism. Derived from the analysis of intersexuality in *Lymantria,* it is based upon the relative dosage or balance of the sex determiners and is, thus, the starting point for all ideas on genic dosage and genic balance.

What does the mechanism control? It is at this point that the two different philosophies become patent. Sex determination by the balance system of sex determiners means first the control of production of the sex cells of one or the other sex, then of the gonads; of the accessory sex organs, such as ducts, glands, and genital armature; further, of all sexual differences in morphology, physiology, and behavior which—in *Drosophila* or *Lymantria,* for example—amount to differences in practically every organ and structure as well as in developmenal speed, rhythms, and many reactions. Maximally, every single cell of the body may be considered different in the two sexes.

The geneticist of statistical persuasion who wants to explain such profound differences is bound to look for a system of genes in which separable determiners for every differential trait are represented. Now, the facts of diploid intersexuality prove that any fertilized egg, be it a 1X- or a 2X-zygote, is able to develop into either sex or anything in between (that is, the series of male or female intersexes). In addition, every single one of the traits mentioned will be affected. Therefore, the statistical mind concludes that in the genome there always must be present all the innumerable genes that control the development of all the female, as well as of the male, traits. In the extreme case of all-pervading sex differences, this means the presence of two complete sets of all the genes concerned in the formation of the type of the species—that is, of practically all genes in strongly sex-dimorphic organisms.

The terminology for this type of genetic setup varies. Sometimes, this double group of genes is termed sex-promoter genes, sometimes one speaks of A and G genes or also of alpha and gamma. The balance mechanism then becomes a trigger or realisator mechanism, which takes care that one or the other set of sex-promoter genes is stimulated, or one or the other is suppressed, or both of these actions occur simultaneously. In detail, this may mean either that the balance between male and female trigger genes exercises this controlling influence, or that the trigger genes within the sex chromosomes effect this stimulation or suppression according to their dosage, without being sex determiners at all.

I consider the latter assumption incompatible with the experimental facts of intersexuality, but this point is not relevant for the present discussion. The decisive fact is that this point of view requires the assumption of special genes for every possible developmental feature in both sexes, with, in the end, two different complete sets for the sexual alternatives for each dimorphic trait, which may mean every single character of the species.

Let us now contrast with this picture the aspect of the problem as it is seen from the other basic point of view. Sex is a primary property of almost all organisms. Thus, the genetic determination of an organism contains also the possibility of a sexual alternative for, minimally, the sex cells and, maximally, for every cell of the body, with all gradations in between as seen in different organisms.

As a rule, the sexual alternative is decided by the genetic mechanism of sex determination. But the decision can also be brought about by external agencies. An injection of a genetically female chicken's egg with male hormone makes every cell, including the sex cells, decide for male differentiation. A female pupa of a gypsy moth will be induced to male development of the antenna by a temperature shock; a male pupa under the same conditions of experiment will start a female-like development of a part of the genital armature. Similar effects are produced by abnormal genetic constitution in the case of intersexuality. For example, one sex cell in an individual with one X-chromosome of proper genetic constitution will grow into an egg; another one nearby a little later, into sperm.

If we look for comparable cases outside the sphere of sex, we find cases such as these: The plant *Limnophila* produces normal leaves in air, laciniate leaves when grown under water. Many plants in juvenile condition have leaves that are completely different from those of the adult. Many fresh-water organisms, such as *Daphnids* or *Rotatoria,* assume largely different forms in warm or cold water. These and innumerable comparable cases are considered to be examples of the reaction norm concept of genic action. This means that genic action can be described only in terms of a specific external and internal (and also genetic) environment. In some cases, as in the plant *Limnophila,* this means an alternative norm of reaction, based upon, first, a genetic setup involving the possibility for an alternative norm of reaction and, second, an agency, here air and water, that decides the alternative.

Applying these models to the case of sex, we say that the genetic basis of sexual development is the ordinary one of the species. But some or all cells and organs have an alternative norm of reaction, male or female, also depending for decision upon an outside agency, the products of the sex determiners, which we

may call, in a general way, sex hormones without discussing the correctness of the nomenclature. Thus, we need no groups of female and male sex-promoting genes and the complicated process of selection that has built them up but only the unavoidable, general genetic constitution of the species, endowed with an alternative norm of reaction (which in detail is a problem of thresholds and probably an old, inherent property of sex, invented phylogenetically together with sex). With this genetic and physiological system, the products of the balanced sex determiners are reacting. There are many facts available to show that this simple system is present in well-studied material. But we do not want to go into the technicalities of the problem of sex determination. The point we want to make is only to show that the statistical attitude calls for explanations in terms of additional genes for whatever has to be explained, while the physiological attitude looks for interpretations in terms of genic action upon development.

There is, of course, no field of genetics in which the two basic attitudes are more pronounced than in the study of evolution. There is a reason for this. Selection is the uncontested major factor in evolution; and selection within varying populations, the prerequisite for evolution, is to a considerable extent a statistical problem. Thus, it is evident that the study of evolution via one of the approaches—namely, population genetics—is best suited to the statistical mind. This has led not only to very important insight but also, I may say even necessarily, to the extremest development of the statistical viewpoint as observed in the realm of Neo-Darwinian evolutionism.

It is primarily here that the way of thinking has developed which I called before hyperselectionism and hyperatomism. This means that innumerable individual groups of facts are explained as a result of selection involving more and more modifier systems, without inquiring whether this explanation is necessary. I do not mean by this the obvious phenomena of adaptation by selection of already present combinations of mutant loci, which are above discussion. I mean the trend to find selection behind almost any observed fact—for example dominance—or sexual differences of the type mentioned in the foregoing discussion of dosage compensation, or every instance of polymorphism, such as the ones mentioned before for wing-plexation and inversions in *Drosophila*. This attitude necessitates what I just called hyperatomism, the invention of more and more modifier systems upon which selection can work. If one were to put together all the cases for which such systems have been claimed, one would shudder at the number of otherwise unimportant genes needed to make the scheme work.

This viewpoint, powerfully aided by the fact that just such an imagined system lends itself to impressive mathematical treatment, neglects completely the fact that at the basis of all evolution is the organism itself. No evolutionary change is thinkable that is not contained within the developmental potencies of the organism; and, vice versa, any change of development—small, large, or very large—that is possible without major and unadjustable damage to the emerging individual may be the starting point for evolutionary diversification. Thus, the happenings within a varying interbreeding population studied from the point of view of selection of recombinations are only one aspect of evolution. The other aspect is the study of the potency for variation as seen in the potentialities of development, brought to light by proper experimentation. Again, I propose to take up a single example of an evolutionary problem and contrast the two ways of analyzing it.

The example is one that involves a major case of adaptation, quantitively far beyond the adaptations usually studied on the subspecific level, such as adaptation to climate, soil, and so forth—that is, all the types that I have called existential adaptations. I mean that part of the mimicry problem which deals with the mimetic polymorphism of butterflies. The well-known basic facts are these. In some species, a number of different types of females are found which look very different from the standard type of the species as preserved in the males or, sometimes, in one type of female. They resemble rather closely in form, pattern, and color poisonous members of different species, genera, or completely different families. In detail many different types are found: for example, only females are mimetic; both sexes are mimetic; only one mimetic type exists or a number of them; all females are mimetic; mimetics and nonmimetics are present among females.

We shall consider only one case, in which all females are mimetic and are of two or three widely different phenotypes, mimicking poisonous members of other families. We may accept it as a fact without further discussion that this is a case of true mimicry protecting the mimics from their enemies. The decisive fact that makes this case a good example of the alternative philosophies of genetics is that, in all cases in which the genetics is known, the mimetic types differ from one another and from the nonmimetic type by simple Mendelian differences involving one or two pairs of alleles, the recombinations of which produce all the known types. The discoverers of these facts drew the obvious conclusion that such huge evolutionary departures as are involved here can be produced in a single step by simple Mendelian mutation. The chief proponent of the Neo-Darwinian type of selectionism realized, however, that here was a test case for his views and, therefore, developed an interpretation in conformity with the statistical philosophy. He starts, as is well known, from the idea that selection acts upon the gene complex, not upon the individual locus modifying the response of the organism to the particular single locus in question, which itself remains unchanged. The classic application of this idea is found in the theory of the origin of dominance by selection of modifiers. The decisive point for the present discussion is that the basic activity of a gene may be completely unaltered while selection acts upon modifiers for the phenotypic end-effect. In polymorphic forms,

this selection will be more rapid, because the heterozygotes will be more plentiful. When now a mutation produces by chance a "remote" resemblance to a more protected species, from which "some advantage, however small," may be derived, the deception will constantly be improved by selection of the proper modifier system. This, working in the end upon the whole residual heredity, will result in a gradual change in the effects of the gene concerned. But the gene itself is unaltered and remains as a switch, turning on one or another set of characters, subject to variability and selection.

We do not intend to discuss the facts considered to favor this ingenious interpretation or the criticism that can be leveled against the entire group of interpretations when the facts are analyzed in detail. We just state that here is a typical example of the statistical philosophy of genetics and contrast it with the way the opposite type of mind would look at the facts. In view of the basic fact that genetic differences between the mimetic and the nonmimetic and among the different mimetic types appear to be simple Mendelian differences, the geneticist who thinks dynamically in terms of genic actions would ask himself first whether it is possible, on the basis of known facts of development and phenogenetics, that the huge differences in form, color, and pattern between these forms can all be based upon simple chance mutations which at once offer to selection the complete, or almost complete, array of adaptive traits. He would, therefore, enter into the details of pattern formation on the Lepidopteran wing. He would find that mutants exist which affect only small features of localized parts of the pattern, including color; that other mutants affect simultaneously a series of such features; and that still others affect basic features of the patterning process, such as presence or absence of bands, or their typical localization. In conformity with other knowledge, he would conclude that the earlier the genic action upon the processes of pattern determination takes place, the more extensive the change will be. He would then inquire into the potentialities of the developing wing for change in pattern without genetic change. There he would find, among many important facts, the cases of seasonal dimorphism in which the same species can develop two different patterns, sometimes as different as, or even more different than, the mimetic patterns under discussion, and controlled in nature and experiment by temperatures and by the hormones for the initiation of diapause. He would also find instances in which extreme sexual differences, of the order of magnitude of very large mutations, can be completely equalized by simple experimentation, for example, the use of temperature shocks. He would also remember that all known mutants of *Drosophila,* small or large, can be mimicked phenotypically in the experiments on phenocopy, with the corollary that the ability of the organism to undergo large genetic changes in a single step is limited only by the power of the developing organism to change development considerably and, nevertheless, produce a harmonic whole by embryonic regulation and integration. Thinking analytically in such directions, he would come to the conclusion that the production of the mimetic patterns as single mutant steps is within the domain of the potentialities of development and, therefore, he would feel no need for switch genes and selected modifiers and would look critically into any and all alleged proofs for their existence.

Only one more example for the two opposed philosophies will be presented, one which I believe to be pregnant with future possibilities for the understanding of the ultimate problems of genetics. During the past 15 years ideas on the nature of the genetic material in the chromosomes have been developed, which are rather different from those of classic genetics and, therefore, were not too well received in the beginning but now are attracting an increasing number of friends. Confining the discussion to the topic of the present address, these ideas try to replace the statistical, atomistic views of classic genetics by a dynamic, relational view which sees in the chromosome a heirarchical system of a polarized structure, the parts of which may function in different subunits of hierarchical order. We chose from the groups of facts from which such views were derived only one, which permits again the contrasting of the two genetic philosophies and points to the one which offers hope of future biochemical analysis.

A long time ago, it was realized that the phenomenon of multiple allelism was best suited for attacking the problem of the nature of the gene and its action. A first step beyond the classical concept of the gene was made when multiple alleles were conceived as different quantities of genic substance, thus introducing the dosage concept into the gene itself. A step still farther away from the classic gene was made when a group of Russian geneticists introduced the idea of step-allelomorphism, which claimed, within a group of multiple alleles, a definite and strange spatial arrangement within the chromosomal segment called a gene. Although both these ideas were unable to survive in their original form, their basic attitude pointed in the right direction.

It has since become clear that in *Drosophila* the genetic loci in the chromosomes are segments of different lengths, some containing up to an unknown maximum number of salivary gland bands, these segments constituting physiological units. This means that whatever happens within such a segment produces a definite effect—namely, that of a mutant—with small variations according to the individual causative happenings. To take a concrete example: within a group of bands in the scute or yellow regions so-called point mutation can occur—that is, a mutative change which cannot be detected with the light microscope. The effect will be a scute or yellow phenotype, respectively. If within the same region and at any interval a rearrangement break occurs, the scute (or yellow) type again appears as a position effect. All these changes of whatever kind not only produce the scute phenotype with typical small differences but also con-

stitute a group of multiple alleles. Allelism is, thus, bound to the section in question and applies to whatever change occurs within the segment.

Let us first look at the explanation that such facts have received on the basis of the classical theory, which means, for the present discussion, derived from the statistical philosophy. This explanation is based upon one partial fact not yet mentioned, namely, that crossover breaks can occur within such a segment with the result that what were considered before two or three alleles now become separable genetic units and are, therefore, called different genes. But in spite of this the two actions remain allelic. This means that, if each of a pair of chromosomes contains at least one of the recessive mutant loci, we get the homozygous phenotype. In order to explain this basic fact, it is assumed that the two or three and in some cases many loci that can be separated by crossover breaks are duplications, triplications, and so on, of one original gene. After duplication, the new gene assumed a somewhat different function of the type of a multiple-allelic difference. But its faculty of being allelic remained, but only if the old and the duplicated genes are located in different homologous chromosomes. Therefore, the phenomenon is called pseudo-allelism and the alleles, position alleles. A corollary of this is that the duplicated genes might, in time, become so different that they no longer affect the same character and lose their allelism.

The alternative explanation is based on the recognition of the segments of identical action already mentioned and the fact that submicroscopic mutation, as well as position effect within the segment, produces multiple alleles. Thus, it is the normal or disturbed order, visible or invisible, that distinguishes the normal and the mutant effect. Since the segment is the unit of action, controlling, say scute or yellow if changed, changes in homologous chromosomes are allelic, and there is no need for pseudo-allelism and position alleles. The reason for this is obviously that the whole segment is in control of one chain of reactions which will be interfered with in a similar way by whatever change happens within the segment, producing always, for example, a scute or yellow effect. But here a quantitative element enters: if the segment is taken apart by a rearrangement break or organized in a different order after a crossover break, the chain of reactions still of the same type—for example, leading to yellow pigment—is affected quantitatively to produce the slightly different phenotypes of the yellow alleles. Thus, by the way, crossing over, a purely mechanical feature happening wherever the breakable parts of the chromosome are found, does not enter the definition of the basic unit. It may also happen within it.

The great difference between the two interpretations of the same facts is that the statistical one leaves room only for more and more genes of the same type and has to invent specific features, such as position alleles, to explain facts beyond the scope of the classic gene. The dynamic interpretation not only unifies the different facts as the product of one single structural principle. In addition, it leaves room for future developments that might lead to real biochemical understanding. If sections of basic action are integrated into the next higher hierarchical unit, one can conceive —forgetting completely the gene—that they control, again as a unit, nearly related but branching chains of reactions, which control larger elements of the developmental process. I would look for such an explanation if it is found that mutants affecting the same organ are frequently located within a larger section of the same chromosome. In the same way, a hierarchy of action could be conceived, up to the chromosome as a unit of action. It is improbable that, in a higher organism, the biochemical meaning of such a hierarchy could be elucidated, except in the cases where serological effects are involved. But in microorganisms, facts have already been found that give some hope that here further insight is possible. My own personal opinion is that the classic theory of the gene will lead only into a blind alley in this search for the biochemical nature of the hereditary material, while the way of thinking which I called the dynamic philosophy of genetics will lead to ultimate success.

Apart from purely genetical considerations, there is also a very general reason for the attitude I have taken. This is the fact that the hierarchical order is clearly essential in living nature, although it also exists in inanimate nature, as the order nucleus and electron, atom, radical, molecule, macromolecule, crystal shows, each higher member of the hierarchy being composed of the lower ones but different in its qualities from a mere sum of these. It is clearly not the sum but the orderly relationships of the components that are responsible for the actions at the different levels of the hierarchy. Therefore, at these different levels also, new types of interrelationships appear, say in inorganic nature the Van der Waals forces on top of ordinary valencies. In view of such facts a biologist, studying a clearly hierarchical system of activities like that of chromomere, chromosomal segment, chromosome, genome, would hardly expect to meet with a situation even simpler than that present in inorganic nature—namely, total action being the sum of all partial actions, as assumed in the classic theory of the gene. He would rather expect to find a still more complicated relationship in which the parts, in a hierarchical order work together via spatial relationships, orders, patterns. This is one of the reasons why I am convinced that the new way of looking at the nature of the genetic material will have to supplant the statistical classical theory of the gene, before the attack on the ultimate biochemical problems is possible. But with these statements I have already gone beyond the scope of contrasting what I consider to be the two basic philosophies of our great science and fallen into the trap of stating my own opinions.

The four examples that I used to contrast the two major philosophies of genetics were, I think, a fair sample of basically different interpretations of facts. I did not try to hide, and as a matter of fact would

not have succeeded if I had tried to hide, on which side my own sympathies are found. This does not mean that I am blind toward the merits or ungrateful for the brilliant results of the work of those whose basic philosophy I do not share. I am perfectly aware of the fact that science, in all its different fields, makes progress only by the clash of ideas, which are not all good or all bad, but good only as far as they give inspiration to new experimental attacks. What becomes, in the end, of either of the opposing ideas is rather unimportant. Probably neither of them will survive finally. But while we are working and trying to open new ways of attack on basic problems, it will be helpful to stop occasionally, look at the basic philosophies lying behind our mental procedure when deriving generalizations, and in doing so clarify our own thoughts by analyzing different thoughts sympathetically but also critically. Then it will turn out, after all, that the Queen in the storybook acted under some illusion when she practiced believing a series of impossible things before breakfast—namely, the illusion that anybody could decide what is possible or impossible. But there is at least one thing we can do, which Willard Gibbs expressed in these words: "One of the principal objects of theoretical research in any department of knowledge is to find the point of view from which the subject appears in its greatest simplicity." Convinced of the correctness of this statement by a great thinker, I have repeatedly prefaced works of mine with the old formulation of the rule of parsimony *"Frustra fit per plura quod fieri potest per pauciora."* This is exactly what I have tried to apply also today. If I have failed I must exclaim with Job: "Is there iniquity in my tongue? Cannot my taste discern perverse things? Teach me, and I will hold my tongue: and cause me to understand where I have erred."

Some Aspects of the Chemistry and Biochemistry of Cholesterol*

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CHOLESTEROL, discovered by Chevreul in 1815 and readily available for experimentation from gallstones or brain, has been the subject of innumerable researches for more than a century, but it still presents certain problems of interest that are under active inquiry. This solid alcohol of the formula $C_{27}H_{45}OH$ is no minor constituent of the animal body. The total quantity of cholesterol in a man weighing 65 kg is approximately 210 g, or 0.3 percent of the wet weight (*1*). The largest amounts are present in the skin (51 g) and nervous tissue (35 g); the tissue concentration varies from 0.14 percent (muscle) to 4.5 percent (adrenal gland). The sterol normally present in plasma to the extent of 0.2 percent is partly free (27 percent) and partly as esters of higher fatty acids, while that present in red blood cells (0.12 percent) and in nervous tissue (1.9 percent) is completely unesterified. The cholesterol of herbivorous animals is derived exclusively by biosynthesis, while that of man is supplied by a combination of biosynthesis and diet. R. P. Cook has demonstrated (*2*) that the intake of 0.58 g of cholesterol per day from an average normal diet (*3*) can be increased to 6.9 g by a regime of menus involving consumption of 20 eggs per day.

What is the role of cholesterol? In what way or ways is it useful to the animal organism? The free cholesterol of nervous tissue appears to serve the function of forming a component of a structural unit of the tissue; Finnean (*4*) has postulated a specific orientation of the molecules of cholesterol and phospholipid in a complex that, in combination with protein, constitutes the structure of myelin. It seems to me likely that the cholesterol in plasma plays a key role in the transport of neutral fat, by the mechanism suggested in the following idealized representation:

$$\text{Lipoprotein A} \begin{cases} \text{protein} \\ \text{phospholipid} \\ \text{cholesterol} \\ \text{glycerides} \end{cases} \underset{+\text{ glycerides}}{\overset{-\text{ glycerides}}{\rightleftharpoons}} \text{lipoprotein B} \begin{cases} \text{protein} \\ \text{phospholipid} \\ \text{cholesterol} \end{cases}$$

The protein may be the cart, and the lipid part of the sterol may supply a lining for reception of the cargo of other lipid. A possible function of the free cholesterol present in high concentration in the membrane of the red blood cell is to form complexes with, and so detoxify, substances that otherwise would have a hemolytic action (*5*). The metabolism of cholesterol is surely associated with that of the steroid sex hormones and cortical hormones, since Bloch (*6*) has demon-

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