this latter group of 3408 comparisons was used for a detailed study of the reliability of the machine linkage process. (Revised tables of binit values were also derived from these comparisons.) Two of the 3408 comparison cards were removed because in each case one of the ages was missing. Of the remaining 3406 cards, 2174 represented genuine linkage (2173 positive cards plus one negative card) and 1232 represented accidental Soundex agreements (4 positive plus 1228 negative cards), as judged by comparisons of the full Christian names in all cases where the binit values fell within the range from minus 10 to plus 10. It will be noted that of the 6500 births of 1955 which were studied, 3484 (54 percent) were from marriages contracted in British Columbia during the 10-year period 1946-55. For a description of the manner in which visual record linkages (as distinct from computer linkages) were used to assess the losses due to spelling discrepancies, see footnote to Table 1.

11. R. M. Walker, D. E. Rosenheim, P. A. Lewis, A. G. Anderson, *IBM J. Research and Develop.* **1**, 257 (1957).
12. R. F. Rutz, *ibid*, **1**, 212 (1957); D. A. Buck, *Proc. I.R.E. (Inst. Radio Engrs.)* **44**, 482 (1956); J. W. Crowe, *IBM J. Research and Develop.* **1**, 295 (1957).

Genetics and the Hierarchy of Biological Sciences

Genetics is binding biology at all levels, from macromolecule to species, into a unified discipline.

Sewall Wright

"History shows that throughout the centuries . . . natural history constitutes the perennial rootstock or stolon of biologic science and that it retains this character because it satisfies some of our most fundamental and vital interests in organisms as living individuals more or less like ourselves. From time to time the stolon has produced special disciplines which have grown into great, flourishing complexes. . . . More recently another dear little bud, genetics, has come off, so promising, so self-conscious, but alas, so constricted at the base."

This quotation from William Morton Wheeler (*1*) expresses a common viewpoint of non-geneticists of Wheeler's time. There were even geneticists who saw little future in genetics, not because its field seemed trivial, but rather because they were so dazzled by the achievements of the first two decades of the century that they felt that there was little left for them to do. I recall a talk I had about that time with a prominent geneticist who had decided to go into a different field. "Genetics," he told me, "is a cow that has been milked."

There are two polar interests in biology. One is the fascination with the diversity of life which Dr. Wheeler so notably exemplified. I can testify to the enthusiasm which he could arouse by his lectures and the exhilaration which one felt during field trips conducted by him. At the other pole is the fascination with the interconnectedness of things. My thesis is that genetics has become the stolon, in a different sense from Wheeler's, which is most effectively binding the whole field of biology into a unified discipline that may yet rival the physical sciences.

Classification of the Biological Sciences

There are many ways in which one may classify the biological sciences. I will not pause on classification by utility—medicine and public health, the agricultural sciences, forestry, etc.—though genetics has much to contribute to these. Nor will I pause on classification by kind of organism—mammalogy, ornithology, and so on down. Genetics cuts across them all. Branches of science also tend to grow out of techniques. Genetics centers in the techniques of breeding organisms. Breeding has turned out to be a remarkably penetrating technique, and one capable of joining forces with other techniques of the most diverse sorts in fruitful ways. For our purpose, however, the most instructive classification is by principles (*2*).

Biology deals with a hierarchy of entities. The primary subdivision of biology is perhaps best made according to level in this hierarchy. Biology began with *individuals*, Wheeler's natural history. It worked down through *organs* and *tissues*, categories that cut across each other, to the *cell*, as the almost universal unit of structure and function, and one that behaves in significant ways as an autonomous organism on its own account. For many years, biologists thought of the cell as the ultimate unit of life, composed of ordinary non-living molecules but organized in a way that conveys the properties of life. The geneticist has added a new level, the *gene*, an entity present in large numbers in the cell, controlling the specific properties of the cell but itself autonomous with respect to its specificity.

Moving in the other direction from the individual, towards larger units, we may proceed through local interbreeding populations (*demes*) to the *species*, an entity that persists with certain properties in spite of frequent complete replacement of all of its constituents. The integrating principle of the species is biparental reproduction. Cutting across this, somewhat as organs cut across tissues, are *ecologic systems* which maintain more or less constant patterns by means of self-regulatory interactions among the local representatives of many species. Finally, we have the entire *fauna* and *flora* of the world as a single, interconnected, more or less persistent system, a vast symplasm, to use Wheeler's word.

At all levels there are problems: (i) of describing the persistent entities and (ii) of accounting for their persistence; (iii) of describing and (iv) accounting

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for the orderly second-order changes by which biologic entities characteristically develop; and finally (v) of describing and interpreting the processes by which the entities at the lower levels multiply (Table 1).

Genetics at the Level of the Individual

Genetics began at the level of the individual with curiosity about the similarities and differences among individuals related by descent. Rapid exploration in many species of animals and plants, once the key was given, led to the generalization that the rules of inheritance are everywhere much the same. Genetics, thereafter, settled down largely to the intensive study of a few especially favorable higher organisms: for example, *Drosophila,* the silkworm, the mouse, and the domestic fowl among animals; the garden and sweet pea, maize, antirrhinum, cotton, and tobacco among plants.

In the last few years, however, our concepts have been greatly enriched by a tremendous development of the genetics of microorganisms, some of which could not even be crossed until recently: *Paramecium, Neurospora, Aspergillus,* yeast, various bacteria and their phages, and others.

I believe that the list of organisms that can contribute significantly is not yet exhausted. Many of those that have been studied less extensively have contributed interesting but often overlooked phenomena, not encountered in the major objects of study. I am thinking of such things as the very odd genetics found by Metz in *Sciara* (*3*). There is still a tremendous field of comparative genetics that will reward pioneers.

Genetics and Cytology

Mendel's laws of heredity and a knowledge of the behavior of the chromosomes in mitosis and meiosis first entered the same minds very shortly after 1900. The firm establishment of the chromosome theory of heredity was the great achievement of the next two decades. Cytology became the first major branch of biology with which genetics became welded, to form the field of cytogenetics.

In the middle period of our history since 1900, the discovery of modes of inducing gene and chromosome mutations, and the demonstration of one-to-one relations between details of the linkage maps and those of the salivary chromosomes of *Drosophila melanogaster,* were among the outstanding events at this cytogenetic level.

Recently, the electron microscope has provided means for carrying the analysis of chromosomes much farther. The threadlike leptotene chromosomes as seen with the highest-powered light microscope, readily suggested the notion of single giant molecules. The tropical jungle of twisting lianas which the electron microscopists present as the real appearance of these same objects reminds us that the chromosome is separated from even macromolecules by several orders of magnitude (*4, 5*). The Watson-Crick molecule of DNA is some 20 A in diameter. The numerous chromosome fibrils, revealed in electronmicrographs, seem to be some ten times this in diameter, and the finest threads distinguishable under the light microscope are some ten times again as thick. The relation between a DNA molecule and a leptotene chromosome is thus somewhat like that between a wire 1 mm thick and a cable some 10 cm thick.

There are obviously still plenty of problems in cytogenetics. With the new techniques, including radioactive markers (*6, 7*), as well as the electron microscope, there are exciting prospects.

The Gene: Earlier Ideas

We come now to the level in the biological hierarchy that is the distinctive contribution of genetics, the gene. It was easy enough when I first used this two-dimensional classification of the biological sciences some forty years ago to subdivide the bottom row, the theory of the gene, into formal categories, similar to those at the higher levels, but these had little substance, and it was hard to imagine that they ever would have much. The recent period of our history has, however, been characterized especially by giving substance to just these aspects of genetics. On the other hand, the disconcerting question whether there is any such thing as a gene has been raised by Goldschmidt (*8*), a very great geneticist, whose provocative points of view we are going to miss badly. I wish to devote most of my time to questions at this basic level.

For his dominant and recessive units Mendel used the word *Merkmal,* which Bateson translated into English as "character." The term *unit character* seemed to imply a return to the discredited preformation theory of heredity and doubtless contributed to the suspicion of genetics felt by other biologists. It was, however, rapidly established that the heredity of characters tended to split up into many independently segregating pairs. It came to be recognized that *unit factor* was a better term than *unit character,* and, a little later, Johannsen's term *gene* was welcomed as a distinctive one for the basic unit of heredity.

There has remained some ambiguity in the frequent use of this term for both the common substrate of alternative units and a particular one of these. I will use the later term, *locus,* for the substrate and restrict *gene* to a particular representative of a locus, considered by itself.

The fact that analysis seemed to indicate the existence of dominant and recessive pairs led to the presence and absence hypothesis of Bateson and Punnett. As early as 1904, however, Cuénot (*9*), on analyzing the heredity of coat color of the mouse, had clearly demonstrated a set of multiple alternatives, as well as several independent pairs, and it came to be recognized by 1915 that multiple sets were not uncommon.

It was natural at first to extend the presence and absence theory to multiple alleles by postulating differences in quantity of the gene. It was soon realized, however, that qualitative differences in the gene and its primary product, conjectured to be an enzyme, might register physiologically as mere quantitative variations of characters. Then it turned out that pleiotropic effects of multiple alleles did not always fall in the same order. I strained myself considerably at about this time (*10*) trying to account for lack of parallelism in the effects of four (later five) alleles at the albino locus of the guinea pig on various colors of coat and eye, on the basis of differences in thresholds and competition or its absence. In the end (*11*) it could only be concluded that the five alleles determined five qualitatively different tyrosinases, even though different thresholds and competition effects were certainly present.

The patterns of differential effect within multiple sets of alleles have indeed turned out to be extraordinarily diverse, even though one can usually trace a thread of physiological similarity of some sort. We find complementary (*12*) as well as noncomplementary recessive alleles of wild type, differences in localization of patterns (*13, 14*), differences

in order of effect on different characters that lead in extreme cases to alleles that seem to have no more in common in their differences from type than random nonalleles (such as some of the alleles at the dumpy and spineless loci of *Drosophila melanogaster* (*15*). There are series in which many antigenic properties occur in all possible relations among the alleles (*16*): incompatibility, positive or negative correlation, and asymmetrical dependence, as well as apparent independence. Finally we have such curious manifestations of qualitative diversity as the self-incompatibility series of many plants (*17*) and Whiting's (*18*) nine sex-determining alleles of *Habrobracon* (any heterozygote: female; any homozygote or hemizygote: male).

It should be noted, in view of the current confusion in the use of the term *allelic*, that I am using it to describe a genetic relation, not a physiologic one, in conformity with Bateson's (*19*) definition of *allelomorphic* (of which *allelic* is a contraction), "alternative to each other in the constitution of the gametes." I am using allele as a representative of a locus, considered in relation to another, irrespective of physiological relations.

Conceptions of the locus as a physical entity were, of course, guided by cytologic observations. The early demonstration of the persistence of individualized chromomeres and their pairing in synapsis (*20*), Belling's demonstration (*21*) of as many as two thousand such particles in favorable materials, culminating in the demonstration of some five thousand identifiable bands in the salivary chromosomes of *Drosophila* and the location of particular loci in or near such bands by Painter (*22*) and Bridges (*23*), led to general acceptance of the particulate nature of loci. Estimates of average size of loci in the millions in terms of molecular weight, by Morgan (*24*) and Muller (*25*), seemed to give adequate scope for patterns capable of mutating at hundreds of different sites within a single locus and thus an adequate basis for the complexity of the observed allelic series.

Chemical Basis of Heredity

Perhaps the most revolutionary achievement of the recent period of our history has involved the chemical basis of heredity. It had been known since Miescher's work in the 1870's that chromosomes (of fish sperm) are largely composed of protein and nucleic acid. Until rather recently, nucleic acid seemed ruled out as the site of specificity by its supposedly monotonous tetranucleotide structure. Most geneticists up to the middle 1940's assumed that there was little choice but to suppose that specificity resided in a pattern of successive amino acids. Then came the discovery that the pneumococcus transforming principle, acting like a free gene, was probably pure DNA (*26*), and the recognition by biochemists that there was after all an adequate basis for specificity in the sequence of nucleotides in chains of indefinitely great length. The demonstration of constancy of DNA per chromosome set (*27*) added to the confidence in its genetic significance.

There was a transition period when the conjecture of a reciprocal relation between protein and DNA, each imposing specificity in synthesis of the other (*28*), seemed most attractive, but soon Watson and Crick (*29*) gave us a model of DNA which indicated a reciprocal relation between two intertwined complementary but oppositely directed strands of this material itself. As this model was based on precise analysis of the x-ray diffraction pattern, it marks a tremendous step beyond mere conjecture toward understanding the actual chemistry of heredity.

This, of course, is only a beginning. The problem of the untwisting of the complementary strands is one that is difficult to contemplate without vertigo, at least if it must proceed through the whole length of the chromonema, with its hundreds of thousands of gyres (*30*). The difficulty would, of course, be mitigated if the DNA were broken up without disruption of order into units with molecular weights of perhaps 10^6 (some 150 gyres) all capable of untwisting simultaneously.

The problem of how DNA imposes patterns on other macromolecules (RNA, proteins, polysaccharides) has not yet advanced beyond the stage of conjecture. Especially disconcerting is the fact that some viruses have only RNA and protein and no DNA at all.

The problems of the chemical basis of heredity are thus far from solved. An important step has, however, been taken, and the nucleic acids, their processes of specific synthesis and of imposition of specific patterns on other macromolecules, have now become the focus of intense effort by biochemists. Genetics and biochemistry have made a contact here that promises to be as fruitful as that of genetics and cytology a generation earlier.

Fine Structure of the Gene

The field that has been investigated most intensively in recent years by distinctively genetic techniques is that of the fine structure of the gene. Present concepts were foreshadowed by the theory of step allelomorphism of Dubinin (*14*) and Serebrovsky (*31*). Oliver's demonstration (*32*) of crossing-over between supposed lozenge alleles in *Drosophila melanogaster*, with reconstitution of wild type, and that by Lewis (*33*) of position effects associated with crossing-over between star and asteroid, probably located in the components of a double salivary band, initiated a period of successful splitting of many supposedly single loci in this organism. Similar results have been obtained in several other organisms, notably maize (*34, 35*), *Neurospora* (*36*), *Aspergillus* (*37*), yeast (*38*), *Salmonella* (*39*), and phages (*40*).

Interpretation has taken two directions. In some cases, subdivision of a system of supposed alleles with multidimensional variability has seemed to yield components with single types of effect, and thus has led to the hypothesis that heredity is made up, after all, of ultimate particles that behave as units both structurally and physiologically. Some proponents of this view have indeed not hesitated to divide seemingly complex loci into simple components on the basis of physiological effect alone. Unfortunately, thorough analysis of the effects in cases in which complex loci have actually been divided by crossing-over has often not indicated any clear-cut separation into physiologically simple loci (*41*). It is probable enough that there are unitary patterns in the genic material, whether divisible by crossing-over or not, that determine patterns in a single macromolecular product, but also that there are a vast number of different sites for mutation and possibilities for multidimensional variability in the activity of this product.

The other interpretation favors complete abolition of the classical structural gene, that is, the view that disruption by crossing-over or by other means, may occur between any two nucleotide pairs of the Watson-Crick molecule. Pontecorvo and Roper (*42*), for example, have pointed out that the ratio of amount

of recombination (5×10^{-4}) between the outer two of three demonstrated components of the white superlocus of *Drosophila* and the smallest amount between two (8×10^{-6}) is 62, and that a similar calculation from four separable mutations in a superlocus of *Aspergillus* gives 150, suggesting the possibility of almost unlimited subdivision. On the other hand, such facts by no means preclude the possibility that there may be particulate loci varying greatly in length and that the intervals between them may vary greatly in ease of breakage, as is indeed suggested by the very heterogeneous appearance of the salivary chromosomes of the Diptera.

The process of actual subdivision of blocks concerned with single physiological processes has gone farthest in studies of phage (*40*) and bacteria (*39*). From estimates of the total number of nucleotide pairs in the phage, it appears likely that there is no limit to divisibility, short of the nucleotide pair.

Interpretation of these cases and of some cases of apparent rare crossing over in higher forms has unfortunately been made somewhat doubtful by the recognition (*43*) of a class of mutations, "conversions," that occur only in heterozygotes, not by crossing-over, although they are likely to occur in the neighborhood of a crossover. This phenomenon, foreshadowed by a study of a mutable locus of *Drosophila virilis* by Demerec in 1928 (*44*), and by Winkler's (*45*) conversion theory of abnormal tetrad ratios in fungi and mosses, is of great interest in itself as a further inroad on the wastebasket category "mutation." Its occurrence also raises the question whether it is pedantic to use even firmly demonstrated crossing-over at rates characteristic of mutation in defining the boundaries of the basic genetic unit. At rates of 10^{-5} or less per generation between similar mutations, crossing-over itself becomes essentially merely another kind of mutation.

Again it is not clear that recombination in the process of synthesis of naked DNA of phage can be considered as the same phenomenon as crossing-over between homologous chromatids of higher organisms, some two orders of magnitude greater in diameter. Thus, even if phage and bacteria are shown to contain no structural genes, it is quite possible that there has been an evolutionary development of such structures with the several-hundredfold increase in the amount of genetic material in higher organisms.

There are some general reasons for suspecting the existence of preferential breakage points in *Drosophila*. Let us assume that the chromonema consists of a succession of physiological units, each involving some thousand nucleotide pairs. If the breakage points of chromosome rearrangements occur at random between nucleotide pairs, there would be only one chance in a thousand that a break would not disrupt a physiological gene and only one in a million that there would be no disruption at either end. Yet 40 percent of 332 random translocations observed by Patterson and his associates (*46*) in *Drosophila melanogaster* were viable as homozygotes, and over 90 percent of these were fertile. Moreover, some or all of the damage may well have been due to disruption of interactions between adjacent genes.

Similarly, crossing-over would usually cause at least isoallelic mutation if one supposes that the population carries many isoalleles at high frequencies in

Table 1. Classification of the biological sciences. The locations of branches of genetics are indicated in italics.

Biological level		Climax phase		History		Multiplication
		Description	Dynamics	Description	Dynamics	
Ecologic system	World biota	Biogeography	Biotic stability	Paleontology	Biotic evolution	
	Local biota	Ecology (community)		Ecologic succession		
Interbreeding population	Species	Taxonomy	Species stability	Phylogeny	Macroevolution Transformation	Species cleavage
	Deme	Demography (7) *Population genetics*			Microevolution (7) *Population genetics*	
Multicellular organism	Individual	External characters	Behavior (6) *Genetics of behavior*	Life history		Physiology of reproduction (1) *Formal genetics*
	Organ	Anatomy	Gross physiology	Descriptive embryology	Morphogenesis (5) *Developmental genetics*	
	Tissue	Histology			Histogenesis	
Cell	Cytoplasm and nucleus	Cytology	General physiology (4) *Physiological genetics*	(2) *Cytogenetics*		Mitosis
Autonomous macromolecule	Gene	(3) *Theory of the gene*				
	DNA	*Gene chemistry*	*Gene physiology*	*Gene mutation* *Description*	*Process*	*Gene duplication*
Nonautonomous molecule		Biochemistry				

each physiological unit. Such mutations may well occur, but an evolution toward greater stability of successful patterns would seem likely, if possible.

In addition to such general arguments, we have the intensive study of Muller (*47*) on rearrangements involving a restricted region of the X-chromosome of *Drosophila melanogaster*, which indicated a very limited number of breakage points. The study of the Greens (*48*) of 18 lozenge mutations indicated, in very extensive tests, that these fell into just three groups such that crossing-over occurred between but not within them. The studies of David Bonner (*49*) and his associates in *Neurospora* may also be referred to here.

We must, however, note the possibility that physiologically significant patterns in the DNA are separated by large inert stretches. The results of Patterson and his associates could be accounted for if there is twice as much inert as active material, even if breakage occurs at random.

Mazia (*50*) has found indications that DNA polymers, 4000 A long, are bound together longitudinally by Ca or other divalent ions, which present points of relatively easy separation under certain conditions. Kaufmann and MacDonald (*4*) have, however, questioned this interpretation of the experimental evidence.

Still another possibility, not necessarily exclusive of either of the preceding, is that there is an evolutionary mechanism for protecting useful sequences of nucleotides from disruption. The identification of Belling's ultimate chromomeres with genes has been questioned on the ground that these are observed to be merely sites of incipient coiling in leptotene (*5*), but if, as is generally agreed, they occur always at certain definite sites, they must be indicators of real entities. Precocious coiling of definite regions suggests intrachromatid synapsis of tandem duplications of about the period of normal coiling. Perhaps very short tandem duplications have been very much more common in the course of evolution than even Bridges (*23*) or Metz (*51*) supposed and actually constitute the structural genes by largely restricting breakage to unduplicated intervening regions.

The difficulty may be raised that such duplication would usually interfere with the expression of inactivating mutations. One would, however, expect such duplicants to differentiate, each tending to become inactivated in respects in which the other has retained activity. Moreover, only about 10 percent of the loci of *Drosophila melanogaster* (if identified with salivary bands) seem capable of conspicuous viable mutation, suggesting that most loci actually are protected from this sort of mutation.

It has long been evident that inversions are also very common in the course of evolution. The result of tendencies toward repeated duplication by unequal crossing-over, toward differentiation of the duplicants, and toward the occurrence of inversions of various lengths would be subdivision of the chromonema into regions of more or less similar material, bounded by unconformities. One might consider such regions as supergenes or gene clusters, consisting of several or many highly stable genes (that is, single duplications) separable with varying degrees of difficulty according to the amounts of intervening unduplicated material.

While the modes of origin of physiological genes, that is, physiologically significant patterns of nucleotides, and of structural genes are independent on this view, one would expect natural selection to bring about a tendency toward coincidence and to restrict unduplicated material to regions of no physiological significance, in which disruption, not necessarily at exactly the same level in all strands, would have no physiological consequences.

One of the difficulties of most hypotheses of crossing-over has been the requirement that the exchange points of the two chromatids correspond exactly in position; and this is certainly exacerbated if each consists of numerous separate strands. Belling's hypothesis (*52*) escaped this difficulty by postulating that the genes are connected by extensive nongenic material which produces crossovers in pachytene by shifting of old connections and forming of new ones along lines of minimum distance at half-twists.

A modification of this hypothesis is possible with chromatids, constituted as suggested above, even if the DNA is continuous, by supposing them to be rather plastic where unprotected by internal synapsis of tandem duplications. The duplicated, physiologically active regions correspond to Belling's genes and the unduplicated, physiologically inert regions to his intergenic material.

Under this hypothesis, corresponding regions of the leptotene chromosomes, already with double amounts of DNA (*53*) and with physiologically active regions already forming chromomeres, attract each other to give zygotene. At pachytene, each chromosome divides lengthwise by equational apportionment of ultimate strands into sister-chromatids. The results of Taylor, Woods, and Hughes (*7*) with radioactively marked chromosomes seem to require, as they note, that all newly synthesized strands be apportioned as a block.

We assume that exchanges between ultimate strands are highly improbable if they are parallel, whether within or between chromatids, but that exchange occurs more or less frequently between the crossed strands of the homologous chromatids that are most closely pressed together at an overlap point, established, as in Belling's hypothesis, by accidents of position and pairing in synapsis. We must suppose, moreover, that if such exchange begins, it continues throughout these two chromatids, which thus give rise to shortened crossover chromatids. It appears that the greater the length of an overlap, the greater the chance of exchange at the overlap points (*54*). We must also suppose that there is more or less twisting of sister-strands along each chromosome in order to account for the randomness of the pairs of homologous chromatids that exchange in successive chiasmata, but that this does not bring about sister-strand crossing-over (*55*).

The requirements for accounting for the phenomena of crossing-over are undoubtedly somewhat severe if the chromatids contain many strands. Yet it seems necessary to consider the possibilities in view of the situation revealed by the electron microscope.

Continuing with this model, we may suppose that short double exchanges may occur under very rare conditions among groups of parallel strands, leading to unstable mutations of the conversion type if they occur between strands of homologous chromatids of a heterozygote. Mutations might also arise occasionally from such double exchanges between paired strands of differentiated tandem duplications within a coiled chromomere.

Terminology

Within the boundaries established by rearrangements, we expect a hierarchy of structures with varying degrees of physiological complexity and differentiation, culminating perhaps in differences so great that no relationship can

be recognized. We need a hierarchy of terms. *Locus* should I think be used for systems of multiple alleles, however complex, as long as no cleavage has actually been observed. To divide a locus on the basis of physiological effects alone involves a dangerous begging of the question of structure. If, however, cleavage has been observed, it becomes a question whether one prefers to recognize a single locus with subloci separable at rates like those of mutation, or a superlocus or locus cluster with component loci. In the former case, we should recognize a qualified allelism between separable components. One might use *euallelic* for strict allelism as far as known, and thus *aneuallelic* where there is very rare crossing-over within what seems most convenient to recognize as a locus, on the occasions in which it seems necessary to make a distinction. The terms *identical* and *nonidentical alleles,* which have been suggested (*39*) seem confusing since strict alleles need not be identical physiologically. The terms *homoallelic* and *heteroallelic,* which have also been suggested (*38*) would be appropriate except that they seem too much like the terms *homallelic* and *heterallelic,* which have been used since 1937 (*56*) for important concepts in population genetics. A population is homallelic with respect to a locus if all individuals are homozygous in the same sense; otherwise it is heterallelic. An isogenic population is homallelic in all loci.

It would seem well to restrict *pseudoallelic* to description of genetic relations between loci of a recognized superlocus or locus cluster, because of its implication of spuriousness.

Heterochromatin

Selection may operate to build up a large number of undifferentiated longitudinal replications of a physiological gene. The suggestion of Casperssen (*57*), developed further by Pontecorvo (*58*), that heterochromatin may consist of many replications of a few genes, the products of which are needed in bulk, is an attractive one.

This could account (*59*) for the irregular organization; the easy disruption in some but not all cases (in contrast with the postulated stabilization by one tandem duplication); the tendencies toward apparent non-homologous pairing after rearrangement; easy transposition of probable heterochromatin blocks in maize (*60*); relative dispensability, including that of supernumerary chromosomes (*61*); restriction of observed differential effects on characters to quantitative modifying action (*62*); and the inhibition of the activity of euchromatic genes brought into proximity (*63*).

Large masses of the same active material might be expected to become low points in concentration gradients of raw materials and high points in concentration gradients of products (especially at low temperatures) (*64*). The V-type position effects of masses of heterochromatin on unadjusted genes (*63*), the inhibitory effect on adjacent genes of the transposable elements in maize (*60*), the inhibitory effect of extra Y-chromosomes on sensitive genes of *Drosophila* throughout the genome recently described by Cooper (*65*), and its greater inhibitory effect on other heterochromatin and hence on the V-type position effect itself by double negative action (*66*), may be examples. So also depletion of raw materials may account for negative heteropycnosis under some circumstances in contrast with positive under more favorable circumstances, for slow multiplication where euchromatin is multiplying rapidly (salivary chromosomes of Diptera), and perhaps for unequal effects in different cell lineages (variegation).

One might also, perhaps, expect that the accumulation of many tandem replicates of the same genic material would lead to non-equational mitosis in it and hence to variegation for a different reason. Also to be expected is relatively frequent irregularity in meiosis by unequal crossing-over, especially if there are great differences in number of replicates in parental heterochromatic regions, and thus a sort of semi-Mendelian heredity of any effect. This should simulate somewhat the effect of multifactorial heredity and occasionally contribute something to the mode of heredity of quantitative variability.

These are conjectures. I suspect that experimental work of the next few years, perhaps work to be reported here, will do much to clear up the relations between structural and physiological genes and between euchromatic and heterochromatic ones.

Physiological Genetics

The idea that genes control the properties of cells by determining the enzymes that are present goes back in a sense to the earliest years of the century, and the idea that genes act by imposing specific patterns in the process of synthesis of macromolecules, whether in their own duplication, in the production of antigenic specificity, or in that of the enzymes, is also far from recent (see *67*). These conjectures had, however, little or no real impact on general physiology. Until very recently, the textbooks in that subject rarely made any mention of the gene and treated the cell as the ultimate unit of life.

The real breakthrough came recently when systematic exploration of the control of elementary processes of the mould *Neurospora* was made by the combined efforts of a geneticist and a biochemist, Beadle and Tatum. Now we have a rapid expansion of biochemical genetics or genetic biochemistry (*68*). What had been two almost airtight compartments of biology are now inextricably interwoven.

Studies of the relations of gene and cytoplasm and of cytoplasmic heredity began early with Correns and have continued on a relatively modest side. Nevertheless, some of the most important results of the recent period have been obtained in this field. I regret that the time at my disposal forbids any discussion here. The time seems ripe for a major breakthrough.

Developmental Genetics

A step up in the biological hierarchy is the problem of development. There is not much of a non-speculative character that can be said of histogenesis, which rests on the still enigmatic relations of genes and cytoplasm to which we have referred. With respect to morphogenesis there is at least increasing contact between geneticists and embryologists. There was a period not long ago when experimental embryologists would trace the interactions of various factors in the development of an organ —pressures and tensions, inductions, hormones, neural stimulation, environmental conditions—and perhaps, at the end, list heredity as a sort of magic that operated through other than physiological channels. More recently, many trained embryologists have turned to genetically determined abnormalities as useful material, with illuminating results. The systematic study of the interaction effect of numerous loci on particular characters is especially promising.

The complete analysis of the development of a higher organism nevertheless remains one of the most intractable

problems of science. Perhaps it is beyond human grasp. But I suspect that there will be great advances in understanding and am sure that this can come about only in the conjunction of the two disciplines.

Beyond morphogenesis is the genetics of behavior on which a beginning has been made.

Population Genetics

Finally, we pass to the level of the genetics of populations. To a considerable extent this can bypass the levels of developmental and cellular biology and treat populations merely as systems of gene or aberrational frequencies, subject to various abstract pressures. There has been a considerable mathematical development of theory along this line from fairly early in our history. Somewhat divergent conceptions have been reached, which I have discussed elsewhere (for example, in *69*) and do not propose to go into here. I may say, however, that it is apparent that we need a more adequate theory of quantitative variability, based on generalizations at the levels of physiological and developmental genetics, and also more understanding of the implications of population structures and ecologic relations.

It is hopeful that the recent period has been characterized by rapidly increasing interest in the genetics of human populations, in the study of laboratory population of various organisms, and in studies on a large scale of the genetic properties of populations in nature, such as those under the leadership of Dobzhansky and of Clausen.

In this last we come full circle. The geneticists, systematists, field naturalists, and even the paleontologists find that they have problems that can only be solved by joining forces (*69*).

Conclusion

A subject which at its origin seemed to many to be destined merely to grind out endless 3:1 ratios has penetrated through the biologic sciences from the level of the individual down to a new biological entity at the level of the macromolecule and back through various disciplines to the level of the population. It has become inextricably linked with cytology, biochemistry, general physiology, experimental embryology, the behavioral sciences, ecology, systematics, and even paleontology. If it should ever disappear as a separate discipline, it will only be because all theoretical biology has been bound together into a single field, to a large extent through its efforts. In relating the formerly mysterious, almost magic, subject of heredity to the chemistry of a particular class of molecules, it has also played a major role in binding all science into one coherent whole.

If this unified science indicates from one point of view that all that pertains to the most complex organisms, including man and his behavior, is merely the resultant of laws of nature governing molecules, atoms, and ultimately elementary physical particles and their fields, it indicates from the opposite point of view (*2*) that these same molecules, atoms, and particles are little creatures whose mainsprings of action must be essentially similar in kind to those of their derivatives, the complex creatures in which Dr. Wheeler took such delight (*70*).

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