the universities would carry our civilization still farther from the life of the spirit, perhaps nearer to a "brave new world."

What then does Sir Walter suggest as a remedy for the crisis? He has no easy cure of clear promise, but he has a suggestion. He, himself a devout Christian, suggests that small Christian groups within the great universities should make themselves felt and heard, becoming what Toynbee would term "creative minorities." He would not try to make the universities officially Christian or even to fill them with Christian teachers or students by some selection process.

> Christians should work for an "open university." This does not mean [one] which is shapeless or neutral. But it means one . . . which is hospitable. . . . No thinking will be suppressed as "dangerous." Above all there will be no "tests for teachers," no articles of faith, . . . prescribed as a condition of service.

But he would say to those who are Christians, "Speak your mind. Even in your academic work let your principles appear. Where you see right or wrong, say so. Continue a discussion into the field of religion or ethics without fear." At first this seems a rather specialized solution, but as one reads Sir Walter's good sense and moderate words one realizes that he, as a wise, believing Christian is advocating in his own terms what would apply in much the same way to groups with other beliefs. I think he would welcome the growth in the universities of other religious groups similarly intent on making their spiritual thinking and moral minding felt. So I would read his advice, perhaps without his entire agreement, as this: Let us, at the expense of some comfort and some academic progress, encourage the growth of serious thinking and ethical discussion, encourage a sense of the value of having values, by means of any groups of people, Christians and others, who will seek a clearer view and speak their minds on the ultimate problems of the day, who feel that "people matter," who would agree, perhaps, with the old saying:

"Labor, art, worship, love: these make men's lives."

The Question of Plasmagenes

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WITH THE PERSPECTIVE of a triumphant chromosome theory of heredity, E. B. Wilson (*5*) could write in 1925:

> Modern genetic experiment has given an overwhelming demonstration not only of the leading role played by the nucleus in heredity, but also of its particulate or corpuscular organization, in the sense that it is composed fundamentally of small entities ("genes," "factors," or the like) that are self-perpetuating and within certain limits independent of one another. We have very little genetic evidence in the case of the cytosome; but the fact that it is available in the nucleus predisposes us to adopt a similar conception of the cytoplasm.

The proceedings of the 1948 Paris symposium *Unités Biologiques Douées de Continuité Génétique*,[1] published not quite 25 years after Wilson's magnificent survey, are useful as a report of progress in the analysis of cytoplasmic heredity. Thanks are due the editors and organizers of the symposium for an imaginative approach. It was originally intended, apparently, to provide a coverage more closely approximating the title; but H. J. Muller, who was to have discussed the chromosomal genes, was unable to participate. The result is not, as might be thought, Hamlet without the Dane, but an attempt to ascertain the principles behind the phenomena of genetic continuity.

What are the advances in the period since Wilson's book was written? They perhaps fall into two categories, those having to do with the chemical identification of the self-perpetuating bodies, and those having to do with the refinements of technique for detecting these bodies. In the first category, combined cytochemical and genetic techniques and the identification of viruses as nucleoprotein in constitution make it seem probable that cellular structures containing nucleic acid possess genetic continuity. The advances in genetic technique, in the detection of extrachromosomal heredity, are not so much advances in principle as in application of the standard Mendelian techniques to organisms in which cellular heredity can easily be studied—the "acellular" Protozoa, and other microorganisms. The newer studies

[1] *Unités Biologiques Douées de Continuité Génétique.* Colloques Internationaux du Centre National de la Recherche Scientifique, Paris, Juin-Juillet, 1948, Vol. VIII. Paris V^e: Publications du C.N.R.S., 1949. 205 pp. 1000 fr.

of biochemical systems and their genetic control enter the picture in the discussion of the role in gene action of self-perpetuating cytoplasmic elements.

With the analysis by Sonneborn of the kappa factor in *Paramecium* as a cytoplasmic element, and the discussion by Spiegelman and Lindegren of the so-called adaptive enzymes as self-perpetuating elements, the recent discussion of cytoplasmic factors in heredity may fairly be said to have begun. The data were seized upon by Darlington, and integrated with the studies of viruses in a provocative essay on "Heredity, Development and Infection." It should be kept in mind that similar approaches date back to the 1890's, when Altmann's bioblasts, and the intracellular pangenesis of De Vries were in the foreground. Indeed, the statement of Wilson regarding the chondriosome theory of Benda and Mèves is not without its contemporary applicability: "But as most leading investigators in the field have recognized, what was new was not the thing itself, or even its theoretical treatment but only an impulse to its further investigation.

Darlington's own presentation of the plasmagene theory in the present symposium lays its emphasis on the corpuscular nature of cytoplasmic heredity. The historical picture he presents is somewhat slanted: according to this, the emphasis on chromosomal heredity was owing to the isolation of European and American genetics at the time of World War I, the European workers being concerned with the cytoplasm, the Americans with the nucleus. The error in this picture is of more than casual importance. Aside from the fact that the workers on *Drosophila,* for example, were fully aware of the possibilities of cytoplasmic heredity (see the section on cytoplasmic inheritance in the first edition of the *Mechanism of Mendelian Heredity* (*2*)), a question of technique is involved. The genetic experiments which were the support of the chromosome theory of heredity were not carried out on mutants produced for the purpose. Each new mutant was an independent discovery, its analysis a research in itself. Exceptions to the standard Mendelian rules were eagerly seized upon, and their place in the scheme of things determined. The cases of maternal inheritance were recognized as important in the study of nucleocytoplasmic relations, carefully analyzed, and found to depend on specific chromosomal genes. But the fact is that in the hundreds of mutants analyzed, there has been found only one exception (discussed by L'Heritier in this symposium) to a strict chromosomal inheritance. These facts, it would seem, provide positive evidence either of a deficiency in the genetic technique, or of the relative unimportance of the cytoplasm in heredity in *Drosophila,* and indeed in most animals.

A possible defect in the genetic technique for the study of cytoplasmic heredity has indeed long been obvious. The small amount of cytoplasm carried into the egg by the sperm places the quantitative advantage with the egg cytoplasm, and only under very special assumptions concerning rates of multiplication could competing elements survive a cross in which they entered with the male parent. Such arguments were not unfamiliar during the time that Darlington supposes American genetics to have been insulated from the facts of cytoplasmic heredity (Loeb's "embryo in the rough," and the discussions of Conklin). One could conceive that selective forces in evolution had so operated that nucleus and cytoplasm were mutually conditioned—and under these circumstances experiments of a different type than the genetic would be required to determine whether the cytoplasm acted as a supply of nutrient for the nucleus, the metabolism of the whole cell then being considered as a by-product of the reproduction of the genes—or whether the cytoplasm itself contains systems of autonomously replicating units, the cell as a whole operating through the integrated action of the nuclear and cytoplasmic units. The difficulty with this type of analysis, to which attention will be paid later, is that the function of the nucleus in the developing egg becomes manifest only at the later stages of cleavage. Clearly, it is essential for the further analysis of the problem to study not the organism as a whole, but the heredity of the individual cell type.

Indeed, the studies of the heredity of microorganisms have been rewarding in just this direction. Such work is represented here by the papers of Lwoff and of Sonneborn and Beale on Protozoa; of Delbruck on the bacteriophage; of Bawden on the plant viruses; of Taylor and of Hotchkiss on the transforming agent of pneumococcus; of Ephrussi on yeast; and of Monod on the adaptive enzymes of bacteria. In the Protozoa, the transmission of the formed bodies of the cytoplasm at each cell generation is a visible evidence of cytoplasmic heredity, a fact which Lwoff traces through the complexities of its manifestation. He shows that the structures maintained owe their being essentially to two types of element, one related to the centrosomes and centromeres of the Metazoa, the other to the plastids of plants. Thus the differentiation in bands of cilia is maintained by corpuscles which are seen under the microscope to divide, to orient after division, and to take part in the formation of substances around them. Similar cases in Metazoa, it may be noted in passing, have been shown to be under nuclear control, and even, in the spectacular case of the apyrene sperm of the gastropod mulluscs, have been shown by the Pollisters to involve the migration of the centromeres of the chromosomes into

the cytoplasm. One would perhaps hesitate to offer this case as a model for those who discuss gene-initiated plasmagenes, for in the apyrene sperm the centromeres do not multiply in the cytoplasm; they simply function as centrosomes, acting as synthetic centers for the formation of sperm tails. This relationship of the cilia of the Protozoa, and their formed structures in general, to the two types of autonomous element was familiar to the older workers, and may be found summarized in Wilson's book. It is a useful service to have interest in these structures revived in the modern context. Not the least remarkable fact is that the types of genetically continuous unit that are established with certainty are still only those discovered in the early explorations of biological material with the oil immersion lens of the microscope: centrioles, plastids, and chromosomes. The behavior of the mitochondrial granules is no less in doubt today than it was in Altmann's time.

The approach of Sonneborn and Beale, on the other hand, is novel. Given a specific cytoplasmic component that can be destroyed experimentally, and the means of testing its regeneration under diverse environmental and genetic conditions, it is clear that results of the highest importance for the general problem of nucleocytoplasmic relationship should be obtainable. Sonneborn has used the antigenic behavior of *Paramecium aurelia* for this purpose. In clones descended from single animals antigenic diversities are shown to be purely cytoplasmic, and transformation from one to another of the different types can be brought about by appropriate treatment with antiserum, and choice of culture condition after treatment. When, however, crosses are made with another clone, displaying a different range of antigens, the antigenic potentialities of the offspring depend upon the nucleus and thus are genically controlled. This is a situation explained by Sonneborn and Beale in terms of plasmagenes, which in this case must be conceived to be gene-initiated, since their characteristic specificities appear only in the presence of the appropriate chromosomal genes. It appears from later work that Sonneborn inclines now rather to the view that the assumption of plasmagenes is not required to explain the facts of cytoplasmic heredity in these cases, but views them rather as alternative steady states in a system of alternative pathways from common precursors. The products of reaction are mutually inhibitory of each other's formation, so that whichever is first formed persists. This possibility was pointed out by Delbruck as an alternative to the plasmagene idea during the symposium under review. The existence of such an alternative helps to dissociate two separable ideas, one the existence of competition for substrates and the like in the cell, the other the question of demonstration of the self-perpetuating units, easy when they are visible under the microscope, but quite difficult otherwise.

What are the criteria of self-perpetuation in systems where only the activity or the amount of a substance can be measured, and reproduction cannot be seen? They have been much discussed in connection with adaptive enzymes, in the present volume by Monod, and elsewhere by Spiegelman (*4*). The essential point appears to be the increase of adaptive enzyme according to an autocatalytic curve, which Spiegelman explained as due to the synthesis of replicas of the enzyme-substrate combination, for which he used the term plasmagene. Monod takes a different point of view, having based it on analyses of two systems of gene-controlled enzyme, where the enzyme activity was studied *in vitro,* demonstrated to be present in the bacteria adapted to a given substrate, and absent in the nonadapted cultures. He prefers, rather than the plasmagene speculation, to consider the kinetic possibilities inherent in the combination of gene products of low molecular weight, with protein precursors and substrate. The question may be raised as to whether this is more than a formal difference. As Monod points out, the essence of the concept of self-perpetuation is the necessity of a preexistent molecule of similar structure. Where the **S**-shaped curve can be obtained without such postulates, the plasmagene concept is unnecessary—but this does not, of course, disprove it.

The definition of the plasmagene is a loose one at present. Both Sonneborn and Darlington are inclined to call any self-perpetuating element in the cytoplasm a plasmagene, be it the kappa particle concerned with the killer phenomenon of *Paramecium*, the plastids of plants, a viruslike element such as L'Heritier's "genoid" in *Drosophila*, or what have you. For a group including the bacteriophage, cases of viruses transferred by grafting, and possibly also kappa, Darlington prefers the term "proviruses," supposed to have been derived more recently in evolution from the plasmagenes. As is not unusual with Darlington, this is perhaps more a metaphor than an analysis. As the individual cases are inspected, the discussion transforms itself in the other papers into the familiar one of the evidence for the intrinsic rather than the extrinsic origin of the viruses.

For example, Delbruck's beautiful presentation of the genetics of the bacteriophage (bacterial viruses) gives us a picture of an organism of considerable complexity, composed of a considerable number of subunits, and thus not to be thought of easily as a single protein molecule without stretching the term. The intensive genetic analysis of the phage and of

the relations with its host opened up by the studies of mixed infections (crosses), are a far cry from the generalities of Darlington's discussion. And in her studies of the lysogenic strains of *Staphylococcus,* in which the bacteriophage operates as a masked virus, Rowntree favors an extrinsic rather than an intrinsic origin of the virus. L'Heritier's paper on the virus-like body (the genoid) responsible for sensitivity to CO_2 in *Drosophila* leaves the question of origin open. But a large part of the argument for considering this body a plasmagene rests on the case of kappa in *Paramecium.* And in the case of kappa itself, the recent studies of Preer (*3*) have shown this particle to contain desoxyribonucleic acid, and have thus presented a plasmagene with the chemical composition of a nucleus, at least in part.

The problem of the chemical composition of self-perpetuating bodies has been conceived in terms of nucleoproteins since the time of Miescher, one may suppose. The recent approach stems from the studies of the chemical composition of viruses and from cytochemical studies of chromosomes, the association of the nucleic acids with biological self-reproduction having emerged from a variety of studies. The most striking demonstration is perhaps the work on the transforming agents of the bacteria, to which three papers are devoted in this symposium. Following the work of Avery, McLeod, and MacCarty, in which the transformation of polysaccharide type in pneumococcus could be induced by a desoxyribonucleic acid fraction giving no protein test, Hotchkiss has studied the amino acid composition of such fractions. He estimates that his preparations contain not more than 0.2 percent protein, and is hence inclined to look toward the nucleic acid as the bearer of specificity. Work still to be regarded as in its early stages gives indication of differences in the ratios of the purines and pyrimidines in different types of nucleic acid, thus opening an exciting prospect of studies of nucleic acid structure in relation to specificity. The contribution of Boivin, Vendrely, and Tulasne takes the same point of view, extending it to the general possibility that the ribonucleic acids of the cytoplasm may also be the determiners of the specificity of the proteins. This is perhaps the trumpet call of a revolution in thought about the chemical basis of biological specificity; even if it should turn out to be only the flourish of a minor engagement, the present possibilities are too intriguing to be disregarded. Especially is this emphasized by Taylor's finding that the pneumococcus preparation itself has at least two components, each responsible for a specific transformation.

The pneumococcal nucleic acid is of the desoxyribose type, like that of the nuclei. The plant viruses, on the other hand, contain only ribosenucleic acid, like the plant plastids. In these cases, the specificity has been thought of largely in terms of the proteins, due chiefly to the differences found by Stanley and Knight, and more recently by Knight (*1*) in the amino acid content of some strains of virus. Bawden is critical of these views in his discussion, coming to the conclusion that at the present time the relation between the composition of the viruses and their specific effects upon their hosts remains obscure, and that these differences may just as well be correlated with the nucleic acid as with the protein moiety of the virus.

With the view that the nucleic acids can be regarded as associated with processes of synthesis and self-perpetuation, it has been tempting to consider the nucleic acid-containing granules of the cytoplasm as self-perpetuating—a view emphasized by Claude. This view derives its support from an analogy with the behavior of the plant plastids. Thanks to the analysis presented by Rhoades, these also give one type of model of the interaction of nuclear and cytoplasmic units. Rhoades was able to show that a specific type of chlorophyll variegation in maize, inherited as a recessive gene, actually is due to mutations induced in the plastids under the influence of the specific genotype. A case in yeast, reported by Ephrussi, of a mutation in colony type induced by acriflavine treatment, possibly also involves a plastid-like body, containing the cytochrome oxidase system. Here there is no relation as yet found to the nuclear genes. In both cases the cytoplasmic units can be considered as symbionts. But the fact that gives pause is that both (assuming the yeast unit to contain nucleic acid) do contain the nucleic acid commonly associated with the cytoplasm in animals. Accordingly, the treatment of the problem of plasmagenes in animal development, by Brachet, is most welcome, filling a needed place in the symposium. Oddly enough, his examination of the embryological facts in animals is more to the point of the symposium than the two papers on plant development by Camus and by Gautheret. These studies, interesting aspects of the relations of the auxins to morphogenesis and tumor formation in plants, present material still to be analyzed from the point of view of the units in nucleus or cytoplasm responsible for the changes.

Brachet faces the issue squarely, considering the types of evidence needed to show that there are in the cytoplasm self-perpetuating particles whose varied distribution in the cells of the organism is responsible for its differentiation. From the combination of genetic and cytochemical experiments with those of experimental embryology that is possible in his amphibian material, he reaches the conclusion that at the present no evidence exists for the autono-

mous determination without nuclear participation of the specificities of cytoplasmic particles. Following a hypothesis by T. H. Morgan, he finds the most attractive speculation on the nature of differentiation in a sequence of changes induced reciprocally on each other by nucleus and cytoplasm—a point of view the present writer has also taken.

All in all, one is left with the feeling that the concept of gene-initiated plasmagenes has received no support in this volume, especially in the light of Sonneborn's more recent work. But the importance of this type of work for the understanding of cellular heredity cannot be overestimated. The plasmagenes are only one hypothesis; it is from the experimental material that new ones are born. The plasmagene hypothesis itself, aside from Spiegelman and Monod's kinetic considerations, was essentially the full recognition that a hierarchy of hereditary units may exist, in which the genes take precedence. The nomenclature is unfortunate; as said before, the most diverse types of material have been called plasmagenes. That this should occur at a time when the approach is being made to a definition of the gene in terms of a single function per gene has not conduced to clarity in thought. Defining the term *plasmagene* in one paper as an incomplete gene replica, and in another as an independent symbiont is not helpful.

One aspect of the results that may be stressed is the substantial importance of symbiosis in biological systems. We have become increasingly aware of the important role of the intestinal flora of such organisms as the mammals. In the context of this symposium, the problem of symbiosis appears on an intracellular basis, where the statistical considerations of the competitions between types are difficult to distinguish from those involved in such systems of chemical reactions as that postulated by Delbruck as an alternative to plasmagenes. Indeed, if plasmagenes existed, they might very well behave according to Delbruck's "alternative." It is necessary to develop concepts of the kinetics of self-perpetuation which might permit a testable differentiation.

It is evident, with this resumé, that the only definite cases of self-perpetuating elements in the cytoplasm that require the presence of identical preexisting elements for their formation, and that perpetuate specific changes in their own structure (mutants), are plastids, viruses, and the "central apparatus" in plants and animals. The existence of subsidiary levels of self-perpetuation remains in the questionable state it occupied in Wilson's time. Such phenomena are by no means excluded, but ways of testing for them have still to be devised—methods that will directly attack the function of the nucleus and its relation to the growth of cytoplasmic units.

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The Committee on Foreign Compendia

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THE COMMITTEE OF American Chemists which eventually became the Committee on Foreign Compendia of the American Chemical Society had its beginning when Aristid V. Grosse, then with the Houdry Corporation, proposed the idea to me on Thanksgiving Day in 1945. Dr. Grosse offered to take on the burden of being secretary if I would serve as chairman. We held these offices until January, 1950, when Dr. Grosse was prevailed upon to accept the chairmanship. At present the other members of the committee are: Roger Adams, Marston T. Bogert, W. Conrad Fernelius, Henry Gilman, Ernest H. Huntress, C. S. Marvel, Linus C. Pauling, Glenn T. Seaborg, and Floyd T. Tyson.

The purpose of the committee is to follow the situation with respect to the two most important encyclopedias of chemistry: Beilstein's *Handbuch der organischen Chemie,* and Gmelin's *Handbuch der anorganischen Chemie.* It was fairly obvious that the devastation of World War II must have interfered seriously with the functioning of these two organizations. A poll of practicing chemists disclosed no one who felt that these great handbooks were dispensable. The important questions were: Could the compendia be saved? What could we do to help?