

COLD WAR IN BIOLOGY



CARL C. LINDEGREN

THE COLD WAR IN BIOLOGY

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It is one of the very real advantages of capitalism that the individual entrepreneur is free to sponsor creative activity in any field. It is a pleasure to dedicate this book to the late Mr. James Diego Veron of Anheuser-Busch, Inc., who assumed the responsibility of sponsoring yeast genetics during a most crucial period.

Preface

The history of science like the history of nations is a history of conflict. Just as nationalists often try to rewrite history to the credit of their nations, scientists with specific prejudices try to justify their intolerance of those who dissent from what they believe to be the "correct" or "true" point of view. Creative science can thrive only in an atmosphere of tolerance, but scientists are often fanatically intolerant of dissent. In biology, where basic principles are far from having been established, where even the definition of living matter is currently subject to debate, the same questions which were argued in the distant past are currently being debated and one observes frequent reversals of opinion.

Biologists have never agreed unanimously on the relative importance of heredity versus environment in determining the characteristics of an individual living thing or the characteristics of its offspring. At the present time in the U.S.A., the younger biochemists, and a majority of the geneticists, favor the view that genes control both the characteristics of the living individual and those of his offspring. They have emphasized the significance of one component of genes, the nucleic acids, which are remarkably stable substances relatively unaffected by the environment, and they hold that nucleic acids alone are the hereditary materials. Biochemists and geneticists employ specific languages which intimidate other biologists and make communication difficult. Although most other biologists have generally deferred to the geneticists and biochemists, there is a rising tide of interest in the structural (as opposed to the chemical) aspects of hereditary materials developing from the extensive work of Bungenberg de Jong on coacervates. Coacervates are considered by some to be hereditary substances which, unlike nucleic acids, owe their significance in heredity to spacial and structural relations (rather than to chemical specificities) and which are significantly affected by the environment. It is commonly thought that the chief protagonists in the controversy concerning the respective importance of the genes, with their nucleic acids, and the cytoplasm, with its coacervates, are the American-Mendelists and the Russian-Michurinists, but this over-simplification is incorrect; actually there are more disagreements and conflicts and a greater variety of attitudes among the scientists of the Western World than have been generally recognized.

Tolerance would ease many of the tensions characteristic of biological controversy and would hasten the exposure of indoctrination, but tolerance is difficult to achieve in biology because humans are themselves living animals and, hence, are inclined either to oversimplify their complexities and to consider themselves "machines," or to consider themselves beyond the scope of the ordinary laws of chemistry and physics. If a biologist could define himself simply as a "mechanist" or a "vitalist," and could define the extent of the idealism present in his concepts, the lines of controversy could be clearly drawn and one might be able to classify himself and his opponent without ambiguity. But vitalistic concepts are often concealed in the philosophy of one who considers himself a mechanist and vice versa. It is clear, therefore, that no one can be free from the taint of error and that nothing is more hazardous nor more liable to reversal than a judgment on the relative merits of a biological controversy. It is equally true that only by attempting to study the evidence and by attempting to come to a final judgment can one justify his career as a biologist, and it is from this viewpoint that the writer has undertaken to describe the different points of view of the various protagonists and to attempt to assess the validity of their claims.

C. C. L.
Carbondale, Illinois
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CHAPTER 1

The Game of Science

What Is Science?; Philosophy Versus Doctrine; The Rules of the Scientific Game; The Importance of the Political and Religious Beliefs of Scientists; "Pure" Science; Scientific Integrity; "Facts"; Scientific Theories; Instruction by Indoctrination; The Control, Support, and Application of Science; Academic Freedom and Creative Science; Factors Limiting the Freedoms of Thought and of Expression of the Scientist; The Fundamental Problems of Biology; The Conflict in Genetics.

What Is Science?

It is the purpose of this book to discuss a series of "scientific" controversies in biology, but a paradoxical aspect of such controversies is that each side usually calls the other "unscientific." Hence, before one can form a judgment concerning the merits of the disputes, he must first form a judgment of what is comprised under the label "scientific." Everyone is agreed that science involves knowledge, but not all knowledge is considered to be scientific knowledge. Scientific knowledge is said to be "organized" knowledge, but the nature of the organization is not specified. For example, few persons today consider astrology to be a science, although only a few centuries ago it was a highly reputable science, and many still consider it to be a scientific exercise. These facts suggest that there is a matter of subjective judgment involved in the designation of an activity as scientific. Science is sometimes considered to be the opposite of superstition, but this definition poses somewhat of a problem since the highest level of what is undeniably science is practiced by Christian gentlemen who believe in Heaven and Hell with capital H's and a God and a Devil, both of whom have an apparently unlimited capacity to perform miracles. Hence, science and superstition can obviously live side by side in perfect (or almost perfect) harmony. It appears that one must be satisfied to conclude that scientific knowledge is almost any kind of organized knowledge and that scientists are those who occupy themselves with organized knowledge.

Now, what do people do with organized knowledge? Well, to begin with, some people learn it. The learner is generally classified as a "student" as long as he confines his activity to learning. When one begins to teach what he has learned, he begins to earn the title of "scientist" because he usually finds that he can improve the current organization of the subject, and he begins to reorganize what he has learned to be better able to teach it. Others apply organized knowledge to useful ends, and they are considered to be practitioners of "applied" science. The layman usually considers that the function of science is to improve the lot of mankind, and whenever laymen control research activity, they try to direct it toward this end. And many scientists also make the application of science their chief aim. But there are many other scientists who look upon science as an escape from society rather than a service to society; as an opportunity to dream about possible worlds—or impossible ones—rather than a means of assistance in this world; as a means of pleasure to themselves, rather than a benefit to humanity. In this context, science is an intellectual exercise, a separate, dedicated way of life that is not easy to share with, or explain to, an outsider except to say that it is pleasurable. The pleasure is derived from an exercise which has the different aspects of solving a puzzle, of building a structure, and, beyond these, of discovering something entirely new. It tends to be a solitary and a secret activity; this activity is tolerated, and even supported by society, because it is the source of many benefits, but the scientist himself is often a more or less asocial, if not an antisocial, animal.

Philosophy versus Doctrine

Every scientist (1) is guided by a personal philosophy and (2) is the proponent of some doctrine. These attributes are, in a sense, antithetical. A scientist's philosophy tends to make him a free man

by helping him to understand how his mind works on the facts that are revealed to him and by preparing him to change his philosophy when the need arises. His philosophy is developed by introspection, by speculation, and especially by study of the history of the development of ideas, not only in science but in the arts as well.

Pirie has emphasized the importance of a scientist's philosophy:

Some people think that the philosophy a scientist accepts is not of very much importance; his job is to observe phenomena. This is a gross oversimplification and it involves the subsidiary hypothesis that all scientists are fully equipped with serendipity. A sensible philosophy controlled by a relevant set of concepts saves so much research time that it can nearly act as a substitute for genius; it may be that this is what we mean by genius. Thus equipped we avoid the pseudo-problems or, more correctly, the problems that are real in adjacent fields but pseudo in our own. A scientist can have no more valuable skill than the ability to see whether the problem he is investigating exists and whether the concepts he is using are applicable, but the lure of a concept that clarifies another field is strong and many of us follow it, like the music of the Pied Piper, to our scientific detriment.¹

Although his philosophy tends to make a scientist free, his doctrine generally tends to limit his freedom. Indoctrination enables him to maintain an unwavering attitude even in the face of contradictions. Indoctrination is important and useful when it keeps the scientist at his table in the face of obstacles that would seem insuperable except for his faith in the eventual outcome. A scientist's doctrine includes the assumptions which he uses to interpret his data or to plan his experiments. These assumptions are usually summarized in the natural laws which the scientist has accepted as the basis for understanding the physical world. Although the natural laws are more or less clearly stated, the scientist is constantly making new assumptions which he cannot always bring into his fore-conscious mind. The difficulty in recognizing these concealed assumptions is that they are based on "common sense" and arise from an intuitive, unstated attitude toward the cosmos. These implicit assumptions are not brought to light unless the scientist has the leisure to indulge in extensive introspection, and the insight to detect the unstated assumptions. Once he has specified the hitherto undetected assumptions, he will have made a great advance in understanding his problem and, hence, in its solution. The greatest scientific discovery in the past 200 years was the result of Einstein's exposure of the fact that physicists had assumed that the concept of simultaneity was a self-evident truth.

The Rules of the Scientific Game

Science is actually a game which is played according to a rigorous set of rules, and the simplest way to begin to explain science is to explain the rules under which the scientist works. It is generally supposed that these rules reduce the possibility of making serious blunders, but of course no set of rules can achieve this objective. However, one can say that the more precisely a player follows the rules, the more he deserves to be classified as a scientist. The rules are as follows:

1. Each item the player uses must be named and defined. Neither the name nor the definition may be changed during the game. A system of names and definitions makes communication possible between scientists.

2. The observations or the experiments must be such that other players could make them also if they had the opportunity. This does not mean that a player is handicapped by his skill, but it would lead to serious difficulties if only one person in the world could make a specific kind of observation.

3. One assumption is always made: It is generally supposed that the observations in question are not hallucinations. One could spend a great deal of time worrying about this assumption; it is most commonly disposed of by a second assumption: Different people in different places should not have the same hallucinations. But no one is completely convinced by this argument.

4. One must state as many of his assumptions as precisely as he can. One's capacity as a scientist depends to a large extent upon the precision with which he specifies his assumptions, and scientific capacity depends especially upon the ability to detect assumptions which competing players have not been able to detect. These assumptions reveal one's prejudices and preconceptions, or the absence of prejudice and preconception. But, according to the rules of the game, any player is privileged to make any assumption which he chooses, however fantastic the assumption may appear to others, as long as he states it as an assumption and recognizes that it is an assumption which another player may be privileged to accept or reject. The fact that any set of assumptions is permissible makes the game open to any player with a specified set of assumptions.

5. Since the inferences or generalizations of science are drawn (1) from the assumptions (which are actually inferences drawn from previous observations) and (2) from the current observations, the

inferences must be so constructed that they are consistent both with the observations and the assumptions. It is important that the subsidiary assumptions be as few as possible.

6. Qualifying adjectives must be used sparingly. In a scientific discussion, qualifying adjectives are often the clearest indications of bias. The following quotation from a letter by the Praesidium of the Academy of Medical Sciences, U.S.S.R., to Comrade Iosif Vissarionovich Stalin (from Pravda, September 15, 1948) reveals the use of adjectives characteristic of the political concept of science:

"Only the ideological defeat of the idealistic, bourgeois tendencies of Weismann and Morgan, which have found adherents among some of our Soviet scientists, with their abject servility before bourgeois science, has insured the success of our progressive Michurin science."

The American geneticist, T. H. Morgan, was an aristocrat, but there are no political implications in his scientific writings. The development of a scientific doctrine may create an atmosphere which changes political views, but when the rules of the scientific game are followed by different groups of scientists all of whom make the same assumptions (or who state all their different assumptions) and who interpret their data in the most economical way, the different scientists should all be in agreement, or should recognize that two or more interpretations are equally likely.

The Importance of the Political and Religious Beliefs of Scientists

Religious and political beliefs are basic assumptions, and it is very important to know if a biologist is a religious man. If a chemist or a mathematician believes in God, the belief might not change his procedure in the determination of a molecular weight or the solution of an algebraic equation. However, if an astronomer or a biologist believes in God, or accepts (believes) the Talmuds the Bible, Das Kapital, Mein Kampf, the Koran or any other authoritative code of ethics, the belief comprises an assumption which could affect his interpretation of his data; the same observations could result in different interpretations. Biologists are seldom free to state their religious convictions, and it must always be assumed that these are concealed. In the U.S.S.R., all scientists must profess to be atheists to hold their positions. It may very well be, however, that some of them are secretly practicing Christianity, Buddhism, or are members of some other religious organization. In the U.S.A., a scientist is supposed to have some mystical or superstitious religious conviction. A confirmed atheist in the U.S.A. usually denies his belief; otherwise he may jeopardize his opportunity for employment, especially in the educational system, where the greatest opportunities for pure research are available.

The Soviet scientist is also committed to certain political views. What is expected of him is clearly stated in a reply to Professor H. J. Muller by the Praesidium of the Academy of Science, U.S.S.R., appearing in Pravda, December 14, 1948:

We, the Soviet scientists, are convinced that the entire experience of history teaches that there does not exist and cannot exist in the world a science divorced from politics. The fundamental question is with what kind of politics science is connected, whose interests it serves -the interests of the people or the interests of the exploiters.

The verb "serves" is italicized to indicate that the above doctrine makes a prostitute of science. The pronouncement is completely false; science is a purely personal, nonpolitical activity, and creative science is an activity which is so personal and so absolutely foreign to politics that it might be almost impossible for a politician either to comprehend it or to engage in it. But it would be incorrect to assume that non-Communist politicians disagree with the political principles of the Praesidium. Most Western politicians believe that science should serve society.

"Pure" Science

Playing the scientific game is a success when it reveals new concepts, and new concepts are usually the outcome of the study of fundamental or basic problems. Hints leading to fundamental concepts are sometimes obtained unexpectedly from an effort to apply science, but in trying to solve an applied problem, one generally assumes that current concepts are adequate and then applies them to the problem at hand. Applied science involves the application of old ideas. "Pure" science involves the development of new concepts.

The creative scientist is judged by the intensity of his love for and interest in his subject; by the sincerity of his interest; by the degree of his own self-interest; by his love for intellectual pursuits

as such, rather than love for political activity; and by his varied and wide knowledge. These attitudes tend to lead to his withdrawal from the world rather than increasing his interest in it. Possible applications, either for good or evil, are a minor consideration. Intellectual integrity beyond any possible self-interest is an ideal toward which he is constantly striving. It is as pointless to ask such a man to act politically to improve the world as it would be to require that every dentist should also be able to shoe a horse.

The creative scientist is tolerated in our society only because the society has found that it can use him; society needs his findings but cannot share his interest. His place of seclusion, once the monastery, now the university, is invaded by a variety of good and evil men who are bent on exploiting his capacity to dream. He is attributed a variety of objectives by the nonscientist: to do good; to improve the world; to help mankind; to make life better. But the scientist himself is almost completely absorbed by a single interest: The search for beauty achieved by bringing order out of chaos.

Scientific Integrity

Science is a constant test of personal integrity, and, in this sense, wholly demanding and therefore wholly satisfying. It demands self-criticism of the highest order and continual and constant criticism of all others engaged in the same pursuit. The first test which one applies to another scientist is the test of integrity. One asks, "Is he primarily interested in the solution of the problem which he is studying, or in the promotion of his own interests, or in the satisfaction of his vanity? Is he capable of self-criticism, and, if so, is he too vain to disclose his own failures?" The interest and time which one spends on another man's work and the procedure which one employs in criticizing it depend first and foremost on one's opinion of the man's integrity. In other words, one judges character first, and then the work. The judgment is personal and subjective and is made in the same way that one judges an artist or a composer. But since self-interest, envy, friendship, rivalry, and a host of other factors affect the judgment of the assessor, very few judgments are unbiased.

But raising the question of scientific sincerity requires a re-evaluation of what is meant by sincerity. Scientists are shut off from the rest of the community, and, like all ghetto-dwellers, they have one ethical code inside the ghetto and another without. Scientists often fear and distrust those outside the ghetto. Generally the employers of scientists, either in industry, in the educational system, or in government, are nonscientists, and, while the scientist-employees may not want either to improve an industrial product or to instruct the young, they still want to eat. Some kind of accommodation is necessary. A scientist, without infringing on his personal ethical code, i.e., without prejudice to his scientific sincerity, may deceive his employers when questioned concerning his political or religious attitudes. But a scientist cannot retain his scientific status if he is not scrupulously honest in his dealings with fellow scientists on scientific questions. Just as the monastery was the natural refuge for intellectuals in the Middle Ages, so industry with its laboratories, the university with its superficial need for some kind of intellectual activity, and the government with its enormous research programs are the refuges of scientists today. But members of the Inquisition, whether they be Spanish Inquisitors, Congressional Committees, local Baptists, or Party members, may all expect the same servile and frightened responses to their inquiries. Heroism is not an essential or even a peripheral qualification of the scientist. That would be too much to expect. The most fantastic popular image of the scientist (even more unrealistic than the "Mad Scientist") is that of Galileo muttering to the Pope, "It still turns." Many idealists might have been happier with the picture of Galileo burning at the stake, still protesting his beliefs, but this kind of stupid sincerity is not required of the scientist. If he is wise and aware of the danger of honest intercourse with those outside the ghetto, he dodges all religious discussions or questions concerning the purpose of life, or living for the good of humanity, etc., because he is not truly an accepted member of the social community, which will always continue to look upon him as an outsider.

"Facts"

The assumptions in biology, like the axioms in geometry, are the premises upon which the inferences (scientific laws) are based. But the axioms in geometry are "self-evident truths." "Self-evident" is clearly a synonym for common sense, and we know, both from Galileo's experience with falling bodies and from Einstein's experiment with time, that common sense is not a reliable guide to a "truth." The assumptions in biology are the supposed, alleged, or obvious (depending upon the individual biologist) "facts" of experience. But nothing is more unreliable than an obvious fact. Each

new discovery adds new facts (and changes old ones). The inferences from one set of experiments become the assumptions of the next. The complexity (and the progress) of science are the result of the increasing number of assumptions which are added as the body of knowledge grows. But this procedure has one compensation. With each advance, an enormous mass of what were previously disconnected facts becomes simplified, unified, and generalized into a single scheme. Thus at each great forward step, confusing particles of information become generalized into a single simple concept. From then on, this single simplified generalization is taught. If there is an error in the generalization, an error creeps into the assumptions, and the inferences drawn from that time forward are faulty. A scientist who wishes to be satisfied with the order which he derives from chaos must make certain that the generalizations which he accepts as facts from his teachers have been critically verified. These "facts" are the assumptions from which he will draw his inferences—the inferences that are his claim to creativity. Therefore, no study is more important for biology than the study of the history of biology, especially as it concerns the philosophy of science. Only by this means can the scientist assure himself that the historical assumptions are sufficiently reliable.

Scientific Theories

In former times science was expected to supply answers to the three questions: Who am I? What am I? and Where am I? Or, it was expected to reveal the Ultimate Truth. Less is expected of a science today. The formulation of scientific theories is an intellectual exercise rather than a search for ultimate truth. There is much skepticism about the word "truth" because the truth changes, or, at least, ideas of what is true change as one learns more and more about the world around him. A theory is not said to be either right or wrong or true or false. It is no longer certain that science is a way to distinguish the true from the false. A scientific theory is a way to make sense out of the available information, which one usually calls "facts," and these "facts" depend upon what is assumed to be "true." When new information becomes available, one makes new assumptions and a new "fact" appears or the old "facts" change. The following example shows how theories change as the facts change. Burning a sheet of paper produces carbon dioxide and water. The burning also releases heat. It has been known since about 1800 that the weight of the paper plus the oxygen which is necessary to burn it is equal to the weight of the carbon dioxide and the water given off by the burning. It was also known that the energy stored in the paper was equal to the heat given off. The source of the energy stored in the paper was sunlight, and the same amount of the sun's energy which was stored in the paper was given off as heat. The common sense interpretation of this phenomenon proves three things: (1) that matter is indestructible because the weight of the paper and the oxygen is exactly equal to the weight of the water and the carbon dioxide, (2) that energy is indestructible because the amount of energy stored in the paper is exactly the same as the amount given off, (3) that matter and energy are separate and independent things and differ from each other. On a common sense basis, matter was imagined to be small, solid particles, and energy either the motion of these particles or the stress and strain in the molecule. The stress and strain in the paper molecule was released in the form of motion of molecules. This theory was very useful for a long time. Then radium was discovered. It was found that radium produced energy without any detectable chemical reaction. The theory that matter and energy were independent of each other was no longer useful and was replaced by the theory that matter could change into energy and vice versa.

A scientific theory must satisfy three requirements: (1) It must be useful, i.e., to science by making it possible to predict the results of experiments. Then the theory can be tested by whether or not its predictions are fulfilled. (2) It must be teachable; otherwise, it will perish. (3) It must be beautiful. A theory must be aesthetically satisfying by making an orderly arrangement of knowledge possible.

But no theory is complete, because no theory has yet been developed which explains all the known "facts." Although a theory may be expected to explain many of the "facts," one which attempts to explain all the facts invariably runs into contradictions. If a theory made sense out of everything, then all problems would be solved.

The peculiar nature of a scientist's attitude toward a theory determines his reaction to opposing or contradictory views. But the adjectives "true" and "false" cannot be applied to theories any more than the adjectives "black" and "white" can be applied to sounds. A theory is a tool; to say that it is false is comparable to saying that a screwdriver is false when one needs a wrench. A theory is an aesthetic delight; to say that it is false is equivalent to saying that a sunset is false and a sunrise is true. Many things may be wrong with a theory: it may lack aesthetic appeal; it may be difficult to

teach; it may have a limited range of application; but it cannot be either "true" or "false." Some theories are too complicated to be useful, and some are faulty in the contrary direction. The effectiveness of a theory depends upon the quality of the assumptions upon which it is based and upon its practitioners' cognizance of the assumptions.

The flaws of a theory never lead to its rejection. A theory is rejected only after a more satisfactory new theory is available as a substitute for the old one. This practice results from the fact that the absence of a theory would leave a totally unacceptable void in which a scientist could not work. Scientists tolerate theories that can easily be demonstrated to be inadequate. A theory, no matter how well it is established, is not an eternal verity, nor even a close approximation to the truth; it is merely a guide to assist in planning experiments. There is no point asking whether it is right or wrong; the only important question is whether it is useful.

Instruction by Indoctrination

The fastest and easiest way to acquire a point of view on a scientific question is by direct indoctrination. The preferable but more difficult procedure is to obtain acquaintance (1) with as many of the fundamental assumptions of a science as can be enumerated, (2) with the experimental verification of the assumptions, and (3) with the line of reasoning by which the doctrine was inferred from the assumptions. Conflicting points of view can only exist between scientists who have submitted to direct indoctrination. Thoughtful confusion is a healthier state than the certainty characteristic of brainwashed indoctrination, for the former may lead to a resolution of differences while the latter leads to the indefinite prolongation of conflict.

But the innovation which marks the resolution of conflict in science is usually accomplished at the cost of precision. Pirie has said that ". . . a cynic can assess roughly the eminence of a scientist by the length of time for which his theories are able to hold up the development of science after his death. . . ." The innovator in biology is a man with the courage of his convictions who ignores his inner doubts (if he has them), crushes his detractors with scorn, and denies the existence of contradictory facts when they are presented to him. A great innovation is usually achieved by oversimplification at the cost of accuracy. This is especially true in biology because the field is so enormous that no human mind can encompass all of it. The innovating specialist must operate in a limited area which at the moment assumes for him the greatest possible importance. His inferences from this limited area of study become, by extension of his thinking, the key to the total solution of most of the major problems of the science. The theory which he uses to plan his limited experiments is magnified to the dimension of an eternal verity. "Evolution is a scientific fact," "The existence of genes is a scientific fact," "It is a proven fact that acquired characters are not inherited," etc., etc. These are the affirmations of credos which different innovators struggled desperately to impose on fellow scientists. Morgan delayed the study of the instability of the gene and the autonomy of the plasmon by thirty years. Pasteur and Koch held up progress in the study of the life cycles of bacteria by more than half a century. But the blame for these delays falls not on the master, but on his uncritical, indoctrinated disciples. The progress in a science depends upon the speed with which (1) the achievements of the master are assessed and placed in proper perspective, (2) the fallacies of his theory are exposed, (3) the contradictions which he denied are brought into light, and (4) the precious gem, which has in it some reflection of reality, is integrated into the whole of the science. The opposition of the indoctrinated disciples often makes such achievement seem almost impossible. One looks with amazement at the deluded citizens of the Middle Ages as if they were a race apart because for a thousand years they accepted Aristotle's "facts" in preference to the evidence of their own senses. The scientific method is supposed to prevent similar mistakes today. But the problem of distinguishing fact from fancy is still a personal problem, and people have changed little since Aristotle.

By "believing" a theory to be "true" one loses scientific mobility and control of his thinking and becomes controlled by the theory instead of controlling the theory. Since the formulation of new theories is one of the principal goals of scientific activity, the capacity of a believer for scientific achievement becomes limited by the degree of his belief. The neophyte does not learn about the inconsistencies of the theory because he is taught the theory in its simplest form. Even after long training, a scientist may not be much more informed about the philosophical aspects of the theory than an intelligent layman is. If he is not contemplative, he may go through a long professional career without considering the inconsistencies. Indoctrination is much faster and quicker than a critical appraisal of the theory because of the many aspects which need to be considered. It is natural that one who has learned by being indoctrinated should indoctrinate his students in turn.

The Control, Support, and Application of Science

The Communist party in the U.S.S.R. conceives of the application of science as the ultimate objective of scientific activity. It was decided in Russia that the application of biological science should precede over theoretical science. Powerful forces are at work in every society to control both science and the scientist. The freedom of the old time professor who was compelled to satisfy no one except himself is almost a thing of the past, and with his passing, pure science and all other creative artistic, literary, and intellectual activity may suffer a mortal wound. In the U.S.A., at present, scientists receive support only if they present a request which has some utilitarian excuse. The governmental and nongovernmental agencies which support science are (with single exception) all users of applied science. The exception is the National Science Foundation. Almost no university in the U.S.A. uses its own funds to support scientific activity, either pure or applied. The university tells the scientist that if he wishes to carry on scientific research, he can apply to industry or to a foundation which grants funds, but that the university is unable to supply him with any funds for research. Equipment, supplies, salaries for assistants must come principally from some agency other than the university itself. The agencies—the Atomic Energy Commission, the Office of Naval Research, the Public Health Service, the Department of Agriculture—all want something useful for their money. The money is there to distribute to the scientists who can promise most in the most convincing manner. Most scientists hate to think that science is thus degraded, but to the capitalists, the communists, or the humanists, the control and direction of science toward application make sense, and they would not think of trying to change anything except to make the direction more effective. The dependence of science upon funds in the control of those who require an application of science to health, industry, defense, or agriculture is the tragedy of an unintellectual, anti-intellectual, utilitarian society.

It is ironical that the most phenomenal success in plant-breeding was achieved by a relatively unknown biologist who was saved from losing his job only by the intercession of a powerful friend. Professor Goldschmidt told the writer at the 50th anniversary of the rediscovery of Mendelism when Professor Shull was being honored for his discovery of hybrid corn, that many years before, he (Goldschmidt) had received a letter from Shull saying that the Princeton authorities had decided to discharge him because they thought he was just puttering around with inbred corn, an activity that seemed to them (the bosses at Princeton) completely pointless. The first step in production of hybrid corn is the production of inbred lines. These inbred plants get smaller and weaker-looking as inbreeding continues. Sometimes it takes ten or more years to purify the inbred plants. The Princeton executives, looking over the sorry plants that Shull had produced after his many long years of work, agreed that this was one program that should go to the junk heap. Shull's desperate appeal to Goldschmidt brought a letter from that great and famous Director of the Kaiser Wilhelm Institute which mollified the University officials, and they permitted the distraught Shull to continue the experiments which ended in the most magnificent payoff in cold cash that any single experiment has ever produced. The scientist needs the freedom to follow any leads that seem fruitful and especially to occupy himself with problems which he finds attractive.

Academic Freedom and Creative Science

Scientific controversy is the life-blood of science. Without controversy, or when controversy is suppressed, science languishes into sterile doctrine which may not be questioned. Only the freedom of the scientist to debate and question the most widely held views is compatible with creative scientific activity. It may be helpful to examine the situations under which creative science exists and the factors in a society which permit the scientist to attain freedom. In the modern world, creative science has flourished only in Northern Europe. In some continents creative science is almost completely nonexistent. In Africa and in South and Central America little scientific activity exists. In the Arabian and Semitic world, except for Israel there is little science, and Israeli science is primarily a European importation. In all of Asia creative science languishes except for isolated local imports, usually from England. Bertrand Russell says that science in Italy died with Galileo, and he places the responsibility directly at the door of the Catholic Church for its policy of degrading the scientist. In Spain, Portugal and the Balkans there is little creative science, nor, in spite of the enormous upsurge of technology, is there much evidence of creative science in communist Russia, although creative science flourished in Russia before the Revolution. In Germany, England, The Netherlands, Sweden, Denmark and France the per capita output of creative scientists is high. But in the U.S.A., with the highest standard of living in the world, there is a much lower per capita (or per dollar) output of creative science.

COLD WAR IN BIOLOGY

The U.S.A. is maintaining its scientific status principally with scientists imported from England, Sweden, The Netherlands, and above all, from Germany. It is questionable if the U.S.A. can maintain a creative scientific cadre if these sources dry up. The situation today is much like that in the Roman Empire after the fall of Greece. Throughout the period of Roman prosperity, the Greeks were always recognized as the clever and the cultured and, for several centuries after the Golden Age, Greece supplied the intellect that sparked Roman culture. In exactly the same way the U.S.A. is maintaining its scientific power by European importation.

Science flourishes in an environment in which the scientist has the fullest freedom from control by the society in which he lives. But the struggle for academic freedom in the U.S.A. against the forces of capitalist conformity is as hopeless as it was in the Rome of former days and as it is today in communist Russia. In both Russia and the U.S.A., science is wooed for the material reward, the professor is a tool of the Party, or the butt of capitalist jokes, or the lackey of the Parent Teachers Association, or the prostitute of industry, the military, or agriculture—and, to a large extent, the scientist has degraded himself by selling, or even abandoning, his birthright. In Germany, Sweden Denmark, and England, the professor is a free and haughty individualist who bows to no man, and certainly to no distraught parent or board of trustees. The German or the Swedish professor is not generally sweet-tempered, kindly, or self-effacing. He is often authoritative and arbitrary, if not just downright disagreeable. But he is a man.

The Greek intellectuals of the Golden Age were also men— independent, haughty, arbitrary, and probably pretty disagreeable to everyone except the disciples who worshipped them. Certainly they thought very little of their equally great contemporaries, for this attitude is also typical. But for two thousand years, from 500 B.C. to 1500 A.D., creative scientific activity and intellectual freedom disappeared from the face of the earth. It was no accident that, after the Dark Ages, creative science originated as a hobby of European aristocrats. If creative science disappears from the modern world, a race of superb technologists will build roads and television sets, and automobiles and jet planes with models that will be frozen for a thousand years.

Factors Limiting the Freedoms of Thought and of Expression of the Scientist

Self-Imposed. Discipline. An interesting and curious restraint is imposed upon the scientist by the background of his training and associations. He is directly limited by the limitations of the times and of his contemporaries. But there is also a very effective restraint which the scientist consciously imposes upon himself. He repeatedly encounters phenomena or performs experiments which are not consistent with the current explanations. At first, he assumes that the error lies in his method of observation or in his experimental procedure. Finally, when he is convinced that the deviation is real, he feels that it would be ridiculous to question the established ideas, or more seriously, it would make him look ridiculous to do so. He feels easier in his mind if he shoves the aberration out of his thoughts because he fears that he might be wrong or that if he published and was later found to be wrong he would suffer humiliation. He usually directs his activities into other channels and thus avoids the disturbing influence of having to contradict the theory he has been taught. "Better to be silent and be thought a fool than to speak and remove all doubt." Hence, in the scientific society, as in the social society, most of the discipline is self-imposed. Conformity is a passion and very few wish to act in opposition to the majority.

Scientific Freedom? If deviation assumes serious proportions, scientists are not above suppressing it by direct action. A typical example is revealed by an incident which occurred in 1949 during a business meeting of the American Genetic Society in New York. A group of society members proposed that a Committee for Scientific Freedom be formed to speak for the Society as a whole, in an attempt to prevent the teaching of Lysenkoism. The incident was precipitated by the fact that a young instructor at the University of Washington had attempted to teach Lysenkoism to his students but had been promptly disciplined. The committee members were apparently terrified at the prospect of the infiltration of Lysenkoists into the colleges and universities. The writer protested that he did not want to have anyone speak for him as a member of the Society, and that, if such a committee were formed, he would resign from the Society. It seemed wrong that a committee founded for the purpose of suppressing the freedom to teach whatever the teacher saw fit should call itself a committee for "Scientific Freedom" when it was exactly the opposite. Fortunately for the writer's relation with the Society, a member proposed an amendment to the motion which stipulated that the committee should remain inactive. This highly acceptable bit of parliamentary strategy was followed by the passage of

the motion as amended. Several younger members of the Society commended the writer's action and said they were heartily in favor of his stand but did not dare to express themselves openly.

Job Control. One might ask why the younger members of the Society did not dare to enter the discussion. The answer is that such an action would have marked them in the eyes of the assembled membership as deviationists and it is important to remember that deviationism is as serious a crime in the capitalist society as it is in the communist society. The control of the deviationist in the capitalist society is much more subtle and, actually, much more effective. The younger members' reluctance to express themselves openly arose from the fact that the membership of the Society included all those who controlled jobs and grants for research—the only sources of livelihood available to the younger members. To be identified as a deviationist who might not teach what was in the textbooks would be simple and deliberate career-suicide. It would be better to be completely unknown as a competitor for a job or a grant than to be recognized as a deviationist. Thus, thought control is exercised through job control. In an open society doctrine is maintained even more effectively than in a dictatorship because the movement of the disciplined worker out of the field is generally voluntary, and the opportunity for employment in other fields is not impaired by the deviationist's defection in one field.

Once a job has been secured and the holder has academic tenure he might be thought to be secure in his position. But the rules of tenure do not apply to the lower members of the academic echelon and even when the rules do apply they apply only at the discretion of the Board of Trustees. Nearly all contracts carry fine print which gives the Board authority to abrogate the rules and, even if the contracts are not so specified, Boards, nevertheless, often assume this authority. A word from a powerful leader in science or industry may influence a Board to discipline a faculty member for his purely scientific actions or for his religious or political beliefs.

The Referee System. The practice of refereeing papers for publication is one of the devices by which dissenting ideas are kept out of print in the U.S.A. To be accepted by most scientific journals, a scientific paper must meet the approval of two out of three referees. If it is a pedestrian paper confirming conventional ideas, it generally meets with approval. If it is unorthodox, the editor can assure its rejection simply by his choice of referees, who remain anonymous as far as the author is concerned.

If an editor receives a scientific communication which offends him, it is a simple matter to refer it to a hot-headed emotional colleague. The referee is protected by anonymity and the editor "regrets" that the rules will not permit him to accept the communication. The referee system is supposedly devised to prevent incompetents from publishing, but everyone agrees that scientific publications are loaded with trivial trashy papers. Actually, the referee system succeeds in excluding the "lunatic fringe" rather than the incompetents. The difficulty here is that new ideas are almost invariably labeled as "lunatic" when they are first introduced.

The referee system is not used in Germany because, in Germany, there are almost as many different dogmas as there are professors and it would be difficult to identify any particular one as either orthodox or heterodox. It would probably be so difficult to obtain general agreement that the referee system would be unworkable. Conformity in scientific thought is not demanded in Germany, and the German professor is a man of such importance in the community that it would be as inconceivable to believe that he would be afraid to express his opinions as it would be to imagine that any means of communication would be denied him.

The failure of the scientist to preserve his scientific freedoms of thought and expression in the U.S.A. is the direct result of his degradation resulting from his social and financial insecurity in the anti-intellectual environment in which he lives.

The Fundamental Problems of Biology

There are five fundamental aspects of biology which engage the attentions of different specialists:

(1) the problem of the origin of life, (2) the problem of evolution or the origin of the species, (3) the problem of the development of a fertilized egg into an adult organism, or the origin of the organs, (4) the problem of the origin of the nervous system and its *modus operandi*, and (5) the problem of the origin of the capacity for conscious perception and abstraction. Genetics, or heredity, is an integral aspect of each problem.

In studying the origin of life, one seeks to discover how life began from nonliving material.

Almost the first question one asks is how the first living jelly made more jelly. "More" jelly implies jelly like itself, and thus the question of hereditary transmission is involved. One also asks if life had one or more origins and how living and nonliving material are different.

Evolution deals with the origin of the different kinds of closely related groups of organisms, the members of which resemble each other. This resemblance is maintained by some kind of hereditary mechanism. The members of one group differ markedly from the members of the other groups of homogeneous, closely-related organisms. These differences are also due to the operation of some kind of hereditary apparatus. All horses resemble each other in a recognizable manner just as all cats do, and the most casual observer can separate them into two groups. To classify the different cats into their proper or naturally-related groups is much more difficult, and could become a never-ending task of relatively trivial importance. All cats, from lions to housecats, fall into one inclusive group, or taxum; evolution deals with the origin of the whole hierarchy of different taxa.

In studying the development of a multicellular organism from a single fertilized cell, or from a single unfertilized cell, one seeks to discover how the different organs of the adult organism had their origin (having arisen from the same original cell). What makes liver, kidney, heart, and brain so different from each other? How are their differences maintained? Thus the problem of the origin of the organs is closely related to the problem of the origin of the taxa.

The origin of conscious thought is a problem so baffling that only the bravest have dared to consider it seriously. Conscious thought and the creation of abstract concepts are true aspects of the "secret of life," and any general theory which does not include some ideas on this subject can only be considered to be incomplete, but there are, at present, no concepts concerning the mechanism of thought which have approached the solution, or even the definition, of the problem.

The Conflict in Genetics

Genetics is now engaged in a controversy between those who insist on the primary importance of the gene, and those who oppose them. The contestants have often yielded to the temptation to support an accepted doctrine rather than an orderly and systematic search for a rational explanation. Many geneticists have accepted Mendelism rather than oppose the current doctrine and find themselves unable to express a free opinion because of the strict discipline of the organization. In general, acceptance of a doctrine implies the denial, or limitation, of the privilege of examining the assumptions upon which the doctrine is based. But these assumptions are the conclusions from previous experiments, and if one is not privileged to examine the assumptions, he is not privileged to question the procedure or the conclusions of the original experiments on which the assumptions were based. Under a doctrinaire system a simple experiment receives the sanctification of authoritarian dogma.

One likes to think of science as divorced from personalities because one seeks the guidance of a principle rather than a person. Thus, the individual scientist experiences a feeling of freedom since he has the impression that he lives in a community in which the law and not the man is the ultimate arbiter. This truly democratic principle has led to the fallaciously democratic practice of determining the validity of a scientific view by finding out how many other scientists agree with it. Voting in this context is so much influenced by past training and indoctrination that it tends to reject the new and to reaffirm the old. In reality, the scientific structure is permeated with opinions which pass for valid scientific inductions and with contradictions which are disregarded because it is too painful to face the prospect of the revisions of theory which would be required to reconcile the contradictory observations with the dominant theory. The manner and the conviction with which a person propounds his views are often the determining factor in the voting which decides on the adoption of one of two alternative theories. The universally-desired objectives of divorcing personality from principle can be achieved only by critical analysis of the history of the development of an idea and by careful consideration of the different personalities involved. The scientist is obliged in evaluating each separate scientific contribution to consider the specific indoctrination and the point of view of the contributor as well as the data which he presents.

FOOTNOTES

1. N. W. Pirie, in *The British Journal for the Philosophy of Science*, Vol. 11 (Feb., 1952), 269-280.

CHAPTER 2

The Architects of Morganism-Mendelism

E. B. Wilson (1856-1939); T. H. Morgan (1866-1945); A. H. Sturtevant (1891-); C. B. Bridges (1889-1938); H. J. Muller (1890-); George W. Beadle (1903-); C. D. Darlington (1903-); J. B. S. Haldane (1892-1965); John Belling (1866-1933); Theophilus Painter (1889-); Richard Goldschmidt (1878-1958).

A review of the careers and a description of the personalities of the architects of Morganism-Mendelism is presented to introduce the reader to the important people who have erected this significant scientific movement.

E. B. Wilson (1856-1939)

There is no group which has contributed more to what is called "modern" genetics than the Morgan School: Thomas Hunt Morgan, Alfred H. Sturtevant, Calvin B. Bridges, and H. J. Muller. The Morgan School owes its origin partly to E. B. Wilson. E. B. Wilson was head of the Zoology Department of Columbia University at the turn of the century. He was one of the most honored biologists who ever lived in America. He belonged to dozens of foreign societies and was recognized as a leader in biology throughout the world. He wrote a book that is still a standard reference on the structure of the cell. He was very much interested in theories of inheritance and was familiar with Mendel's work. He was one of the discoverers of the sex chromosomes, and it was this discovery which paved the way for Morgan's demonstration that the chromosomes carried Mendelian factors. In 1904 Wilson persuaded T. H. Morgan to come to Columbia University.

T. H. Morgan (1866-1945)

Thomas Hunt Morgan was born in Lexington, Kentucky, in 1866, one year after the publication of Mendel's paper on particulate inheritance. He was an aristocrat, descended from, and related to, a long line of distinguished soldiers, statesmen, financiers, and authors. He received his doctoral degree in biology at Johns Hopkins in 1890. Throughout his life he was associated with the foremost biologists at home and abroad. He was professor of Experimental Biology at Columbia University from 1904 to 1928 and professor of Biology at Cal Tech from 1928 until his death in 1945. He received the Nobel Prize in 1933.

Morgan achieved great fame working with a small group of associates at Columbia University in a single room in which they studied the heredity of fruit flies. He had a talent for exploiting the simplest possible means. The fruit flies were raised in half-pint bottles each containing a small piece of banana. When they were mature, they were etherized and were studied under the low-power microscope. Many years later, after Morgan had moved his staff to Cal Tech, a large magnificently-equipped building was assigned to their use. In this building his staff pursued the grandest program of research ever undertaken on the heredity of fruit flies. But Morgan seemed to be more or less bored with the grand program. He experimented in his own small laboratory with house flies, or in the garden with Mariposa lilies, or at his home with homing pigeons.

A striking example of Morgan's ability to use simple means occurred in his study of hermaphroditic snails. Each snail has both male and female organs. Hermaphroditic snails are self-sterile; that is, they cannot produce offspring when grown alone because the sperm of one animal cannot fertilize its own eggs. Morgan was carrying on this work in a make-shift laboratory which Cal Tech had recently acquired on the beach at Balboa. There were only a few chemicals and practically no equipment in the shack. At luncheon one day someone suggested that a change in acidity might break the self-sterility. Morgan picked a lemon from the table and squeezed some juice into the aquarium, and the eggs were fertilized.

Morgan was not intimidated by complicated expositions, even those involving mathematics and chemistry in which his background was limited. An example of his courage is his criticism of the theory that growth is an autocatalytic reaction. This theory was based on the fact that an autocatalytic reaction taking place in a chemical flask describes an S-shaped curve. Growth (either increase in population or the increase in weight) also describes an S-shaped curve. Crozier, who was the foremost living physiologist and head of the department at Harvard, drew the inference that growth was controlled by an autocatalytic reaction. It was obvious to a biologist as acute as Morgan that the idea was arrant nonsense in spite of the fact that he knew very little chemistry. Morgan criticized Crozier's idea about the nature of growth by pointing out that an autocatalytic reaction occurs in a closed vessel while an animal grows in an open environment. The conditions that would bring a reaction to an end in the closed vessel would be very much different from those which would control the growth of an animal to which an almost limitless environment was available for intake of nutrients and disposal of wastes. Morgan did not need a knowledge of chemistry to recognize that the chemical analogy was fallacious, and it was Morgan's courage, demonstrated by his exposure of the fallacy, which made him great. He knew that he knew less chemistry than Crozier, but was not intimidated even though he realized that Crozier was familiar with his (Morgan's) limitations. Shortly after Morgan published his criticism of Crozier, Dean Burk showed that the autocatalytic reaction theory did not apply to growth. Burk's paper provided the experimental data and the mathematical analysis required for formally invalidating the autocatalytic growth rate theory.

Morgan professed to distrust what he called "speculation." He insisted that the interpretation of an experiment should not "go beyond the facts." It is certain, however, that he did not mean that a scientific report should be confined to a bald account of the facts. He meant, rather, that after one had reported the facts and had drawn a directly pertinent inference, he should not bother the reader with fantastic ideas about more complex interrelationships, or guesses about the significance of the isolated phenomenon in the grand scheme of nature. Morgan felt that there were so many possible wild ideas that each reader of a scientific article should be free to think up his own without being burdened by the ideas of the author. Morgan felt that if one had an idea, he should perform an experiment to test the idea, and then he should report the idea only after the test had been made and had shown either that the idea was or was not confirmed. (He did not follow this rule, however, in his criticism of Crozier.)

Morgan's demand for rigorous thinking did not restrain him from making, or permitting others to make, the most far-reaching generalization ever attempted in biology. The idea that the gene is the "ultimate living particle" or the "unit of life" developed from the work of Morgan and his associates. Morgan himself never claimed that the gene is the "unit of life" nor even that the gene is a "living particle." But many others who were influenced by his books were not so reticent. Morgan never reprimanded them, but he may have been trapped into silence by the enthusiasm of his sponsors. Robert A. Milliken was head of the department at Cal Tech and was instrumental in bringing Morgan to Cal Tech. Milliken sponsored Morgan's appointment because he was enamored of the idea that "life" could be conceived of as an aggregation of particles. This concept of particulate living matter was especially attractive to Milliken, since Milliken was the Nobel Prize-winning physicist who had shown that electricity is composed of particles. Although physicists and philosophers have shown enthusiasm for the idea of the "living particle," this idea has not met with complete acceptance by all the Western, non-Communist biologists, especially those who are active in fields other than genetics, and it has been rejected outright by the Russian Michurinist biologists.

A. H. Sturtevant (1891-)

Alfred H. Sturtevant was born in Jacksonville, Illinois, in 1891, and received his doctoral degree at Columbia University in 1914. He was first associated with Morgan in 1910 as an undergraduate assistant and worked closely with him for many years both at Columbia University and at Cal Tech. Although Morgan had ceased to work with the fruit fly about the time the group was transferred to Cal Tech, Sturtevant has maintained his interest in *Drosophila* research up to the present time. Sturtevant is a giant among geneticists; his contributions make him the greatest living biologist, but he has received amazingly little recognition, possibly because he has always been a laboratory research worker with no taste for administrative work. Many prominent geneticists studied with Sturtevant: Dobzhansky, Rhoades, Beadle, and Ephrussi have all profited from his teachings. His course of lectures is included in the book *Introduction to Genetics* by Sturtevant and Beadle, which, although outdated, is still the most outstanding textbook of genetics from the Mendelian point of view. Sturtevant

tends to be solitary. He writes little but always with great penetration. His interest in art, literature, or music is not brought out in casual conversation, and these things may not be especially important to him.

Sturtevant testified before the Atomic Energy Commission on the question of bomb testing. While two volumes were required to record the testimony of approximately a hundred witnesses, Sturtevant's testimony summarized the whole problem in about three pages, and his was the only testimony which dealt with the moral issue. He also had the courage to demand that the Army and the Atomic Energy Commission justify the continuation of bomb testing to the public by open discussion of the question.

C. B. Bridges (1889-1938)

Calvin Bridges was born in New York in 1889. He began his work under T. H. Morgan as an undergraduate assistant in 1910 and received his doctoral degree in 1915. He moved with Professor Morgan to Cal Tech in 1928 and died there ten years later.

Geneticists studying the heredity of *Drosophila* must propagate their breeding stocks and maintain them as "pure" cultures. Pure cultures of many hundreds of different kinds of flies were maintained at Cal Tech, and an expert was required to take care of them. The expert had to be able to recognize all the different kinds of flies to be certain that the right ones were used as parents for the next generation. All these hundreds had to be inspected and selected about once every two weeks. Bridges studied the cultures of *Drosophila* every day and spent several hours helping the stock room keeper. He knew every one of the 600 stocks. Much of the success which others besides himself achieved with *Drosophila* was the result of Bridges' skillful use of different combinations of the defects so that a breeding animal could survive which had been marked with one defect in the eyes, one in the bristles, one in the wings, etc. He knew which characteristics were compatible and which were not. He was an extraordinarily acute observer; it was his exceptional ability to observe detail that helped place *Drosophila* in the forefront of genetical experimentation. He knew how to make the fine discriminations between flies that looked almost alike but were genetically different.

As an undergraduate, Bridges washed glassware in Morgan's laboratory. Someone told him of a new discovery in the laboratory, a fly with a new eye color. He said he had seen the fly in the dirty bottles some weeks before it had been discovered in the laboratory. The point of the story is that he was looking at the dirty bottles without a microscope, and the fly is only a little bigger than a mosquito. Bridges was probably the most acute observer who ever studied *Drosophila*. But he was naive, childlike, gullible, and almost completely unsophisticated.

He was exceptionally good at sports. He was well-coordinated and was an expert at playing horseshoes. He had only a few hobbies. He loved to tinker with his sailboat and his secondhand Chevrolet. He was an indefatigable worker and often stayed in the laboratory until 2 a.m. For such a retiring person, he had a surprisingly wide acquaintance with different kinds of people. He knew Amelia Earhart, Theodore Dreiser, Alfred Korzybski, as well as a horde of motorcycle mechanics. Korzybski was a psychologist who was concerned about Bridges' intense absorption in his work. Because Korzybski advised Bridges to take up some kind of hobby, Bridges decided to invent a new kind of automobile—a teardrop design with the motor in back, very modern. In company with his motorcycling friends, who begged most of his money, he built his dream car at night in a cold garage. In this chilly nocturnal activity he contracted a heart infection that brought on his death. Dreiser was writing a novel about him which he intended to call *The Scientist* but both Bridges and Dreiser died before it was finished.

H. J. Muller (1890-)

Herman J. Muller was born in New York in 1890. He became associated with Professor Morgan as an assistant in 1912 and received his doctoral degree in 1916. He left immediately after receiving his degree but returned to Columbia for two more years, 1919-1920. He carried on genetical researches in a variety of institutions both in the U.S.A. and abroad, including one year in the U.S.S.R., and was until recently professor of zoology at the University of Indiana.

Muller is a Humanist and a Utopian. He loves mankind and wants a better life for all human beings, but he is devoted to humanity in the mass rather than to humans as individuals. He is concerned about breeding better humans and is active in attempts to improve the human race or to prevent its decadence. He is completely and single-mindedly devoted to science. He is intensely concerned about scientific priority, and his papers contain many references to this subject, but his

writings are so voluminous that his claims may be lost to posterity. Muller is a working scientist rather than an administrator. He has never left the laboratory and is even now breathlessly pursuing his most recent leads with the devotion and concentration of an undergraduate.

Muller may go down in history as a man who saved the life of the human race. He discovered that X-rays produce inherited incurable diseases in plants and animals, and he has spent much time and energy in assessing precisely the amount of damage caused by radiation. If it were not for his timely discovery, the human race might at this moment be exposed to excessive radiation with no idea that it was in the least harmful. For his work on the damaging genetic effects of x-rays Muller was awarded the Nobel Prize in 1946.

George W. Beadle (1903-)

George W. Beadle was born in Nebraska in 1903. He studied genetics at Cornell University and received his doctoral degree in 1931. That same year he went to Cal Tech and spent five or six years in Sturtevant's laboratory. After ten years elsewhere, he returned to Cal Tech as chairman of the Biology Division. He received the Nobel Prize in 1958 for developing the concept that each gene controls the production of a specific enzyme. Subsequently, he became the most powerful figure in genetics in the U.S.A. and, therefore, in the Western World.

In genetical research, Beadle has more control over money and men than any other single individual. This position of power is his, not by virtue of any specific office, either elective or appointive, but by his membership on various committees, by the wish of the membership on other committees to please him, by his control of recommendations for jobs, and by numerous other interlocking relationships impossible to specify. His approval puts any man or any group of men in this country in the forefront of research and science. He has moved swiftly and decisively from one field of scientific activity to another. His great contribution has been as a liaison man between genetics and biochemistry. Single-handedly he has made the biochemists conscious of the fundamentals of biology. His ability to effect this awareness is an enormous achievement, especially when one considers the fact that his own training in chemistry is only superficial. He inspires loyalty and confidence in his subordinates and, what is more unusual, in many of his peers. He is preeminent as an administrator and has lately abandoned scientific activity. He is presently Chancellor of the University of Chicago. His decisions appear to be made with assurance and certainty. He has neither concern for, nor recollection of, the past. He is a man of the present.

In Beadle's psychological approach to science he can ignore inconsistencies without misgivings. He does not have time to worry about discrepancies that another person might find overwhelmingly disturbing. This ability is the faculty of a compartmented mind. It is the quality of a man of action, the criterion of administrative ability which enables the executive to make the choice between the lesser of two evils. Beadle is not in search of fundamental order but merely of superficial order. He is not devoted to order because it has beauty; he only wants things to look nice.

Beadle's achievement in effecting a rapprochement between biochemistry and biology has been of tremendous advantage to science as a whole, but it has diluted his own contact with both fields, and his grasp of the situation has been diminished. Beadle has done much good, but like anyone in high position, he has also done much harm.

C. D. Darlington (1903-)

Cyril Darlington was born in England in 1903. He received his Ph.D. from Wye College. He was the director of a prominent institute, a professor at Oxford, and is now a professor at Cambridge. He is interested in the structure of the chromosomes and studied under Bateson, the great British geneticist. Darlington had written a major book in genetics before he was 30 years old. He spent some time in America, and the writer became acquainted with him while he worked for one year at Cal Tech; he was an extraordinarily self-assured young man.

Darlington said that if one does not go beyond the facts, he never truly understands the facts. But at Cal Tech, Morgan, and Sturtevant, too, insisted that one should not go beyond the facts. This attitude tends to be more or less general, though the reasons are not easy to discover. One would think that speculating about science is precisely what scientists should do and that if one confines himself only to the facts, he may never really understand the phenomenon. One reason for the objection to speculation is that a young man with nothing but an active imagination can gain a following without doing any "hard work." To a certain extent, the objection to speculation is an expression of the antag-

onism between the unimaginative and the imaginative worker. It seems that some kind of compromise should be made, because the facts are obviously valuable only if someone thinks about them.

J. B. S. Haldane (1892-1965)

John Burdon Sanderson Haldane was born in England in 1892. He exiled himself from his native land to live in India because he said he could not live in a land occupied by a foreign military power. He meant the U.S.A. He was professor of Biometry at University College, London, from 1931-1957. He was the most brilliant mathematician who ever pursued a career in biology. His influence was limited because too few biologists are competent in mathematics, and hence he did not develop a large following nor build up a school. (His political views may have limited his influence slightly, but being a Communist is not so serious a difficulty in Britain as it is in the U.S.A.) To become an influential biologist while one is still a relatively young man, one must popularize a concept that is at least twenty years old. The reason is simple. Only if the idea is old enough so that it will be easily understood by a large fraction of the biologists will it receive general approval. No idea can receive approval by a large audience unless it is an idea that the audience understands. Haldane anticipated the "one gene-one enzyme" concept at least twenty years before Beadle popularized it. *Drosophila* workers have not yet been able to apply Haldane's mathematical invention to the calculation of genetical "distance," but more and more young people are beginning to understand Haldane's ideas.

John Belling (1866-1933)

John Belling was born in England in 1866 and died in California in 1933. He received his academic training in England and worked in many different English schools and governmental agencies as a teacher and a scientific investigator. He spent eight years at the Carnegie Institute of Washington at Long Island from 1921 to 1929 where he made significant discoveries concerning the breakage and reunion of nonhomologous chromosomes. He was one of the most competent light microscopists who ever worked on the American continent. He made an intensive study of chiasmata and proposed the view that the chromomeres were identical with genes.

Theophilus Painter (1899-)

Theophilus Painter was born in Virginia in 1889. He received his doctoral degree at Yale in 1913, and in 1916, moved to the University of Texas, where he has been since that time. His interest in the cytology of *Drosophila* was due to his association with Professor Patterson. He was not directly connected with the Morgan School, but it was he who confirmed specifically the theory that the genes were located on the chromosomes by a direct microscopical demonstration of morphological differences in chromosomes corresponding to genetic or genic characteristics.

Richard Goldschmidt (1878-1958)

Richard Goldschmidt was not a member of the Morgan School and did not contribute to the principles upon which Morganism-Mendelism is founded, but he richly deserves inclusion among the architects of the structure because he was a Mendelist and a dissenter of great authority and courage who disagreed with some of the most fundamental principles of Morganism-Mendelism. He denied that the reality of the gene was demonstrable; he denied that gene-mutation was important in evolution. As a young man he had associated with all the most brilliant European biologists. He grew up in the glorious European tradition of independent anarchy, among workers whose interest was in the philosophical aspects of biology. For them, biology needed no excuse. It was an end in itself and a thing of beauty to be cherished. It was to be explored without dogmatic restrictions and to be asked every question and to be subjected to every doubt. Goldschmidt came to America as a refugee from the Nazis. He had been the director of the Kaiser Wilhelm Institute—the highest scientific position in Germany. He finally found employment at the University of California at Berkeley. Goldschmidt was truly an intellectual, with deep interests in art, literature, music, and the philosophy of science. He was a polished, courtly gentleman of the Old School and always kept his activity at the intellectual and the philosophical level.

Goldschmidt attempted an analysis of the modern concept of the gene and, concluding that the gene was a logical absurdity, he rejected it. The reaction of the Morgan School was immediate, unanimous, and reciprocal; they rejected him. This largely emotional reaction was cloaked by arguments concerning Goldschmidt's competence. An independent, Goldschmidt suffered defeat because he left a society where scientific independence was respected and tried to become established in one where it was suspect. His opposition to the arbitrary dogmatic ideas of the gene was not submitted to open debate. It is commonplace in biology to judge an offender in absentia and to ostracize him by innuendo. Goldschmidt's criticism of Mendelism will be dealt with in a subsequent chapter.

CHAPTER 3

The Principles of Morganism-Mendelism

The Cell; The Sex Cells (Sperm and Eggs); Sex Chromosomes and Autosomes; Mendelian Inheritance; The Genes are on the Chromosomes (Morgan, 1910); The Chromosomes Break and Reunite: — Crossing Over; Crossing Over and the Chiasma (Janssens, 1909); The Genes are arranged in Linear Order on the Chromosomes (Sturtevant, 1913); "The Exceptions Prove the Rule"; Non "Criss-Cross" Inheritance; Duplications of Genes (Bridges, 1919) Due to Unequal Crossing Over (Sturtevant, 1925); Chromosomal Inversion (Sturtevant, 1921); Translocation of Chromosomes (Bridges and Morgan, 1923); Chromosome Balance (Bridges); The Chromosome Theory of Heredity; The Ultimate Living Particle; One Gene—One Enzyme (Haldane and Beadle).

The Cell

When Robert Hooke first named the "cell" he meant exactly what he said—a small, cubical, closed, empty cavity—because that was exactly what he found when he sliced cork, which forms the outer bark of a certain kind of oak tree that abounds in Spain and Portugal (Fig. 1). Hooke considered the cell to be a characteristic biological structure, but he did not conceive of it as containing anything. The word "cell" persisted, however, and finally was applied to all the building blocks that comprise the tissues of higher plants and animals, in spite of the fact that these building blocks are not empty but are filled with a slimy substance. In general, "slimy" has unpleasant connotations to most people, but it has become generally recognized that slimy substances are the basis for life.¹ The Germans, with their direct use of the vernacular called the fundamental living substance "Urschleim," meaning the "original slime," while Anglo-Saxons, with their distaste for their own language, preferred to speak of it in terms of the Greek equivalent, "protoplasm."

The protoplasm was soon divided into two components—the nucleus and the cytoplasm. The nucleus was first described by Brown, an Englishman who also discovered "Brownian movement."² In a footnote Brown described the nucleus as a centrally located vesicle in the protoplasm. The nuclear vesicle contains solid bodies which can be stained more readily by aniline dyes than the rest of the protoplasm, and the residual, relatively weakly staining material outside the nucleus was called the "cytoplasm" or the "cell slime." During the latter half of the nineteenth century, after the tremendous development of the German dye industry, the solid bodies in the nucleus were studied very fruitfully by staining them and studying their behavior with the microscope. The stained bodies in the nucleus were either thread-like or tightly coiled structures, and were named the "chromosomes" or the "colored bodies" (Fig. 2). The number of chromosomes was found to be constant for any given

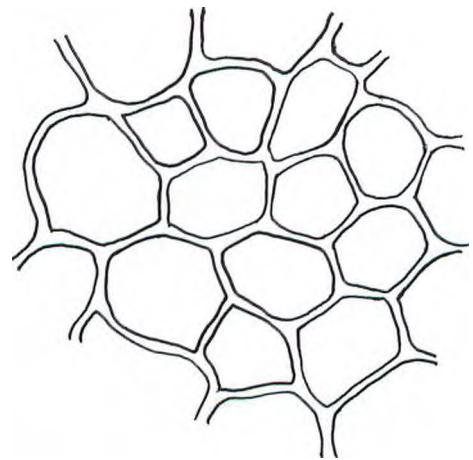


Fig. 1. The cells observed by Robert Hooke. Actually, Hook saw only the plant cell walls. Plant cells are surrounded by cell walls but animal cells do not have cell walls.

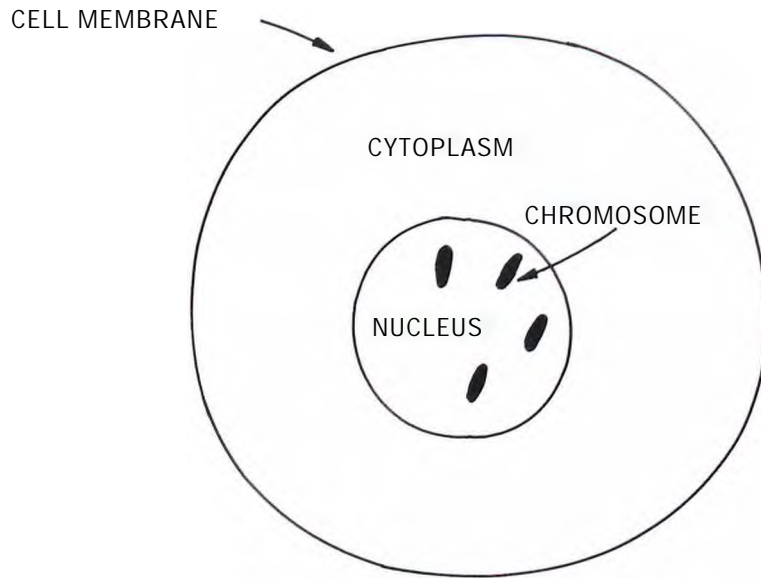


Fig. 2. An animal cell, a mass of protoplasm without a cell wall. The chromosomes are visible in the nucleus. The nucleus is surrounded by cytoplasm. The cytoplasm is enclosed in the cell membrane.

species. The behavior of the chromosomes at cell division led to the view that each thread split longitudinally at each cell division and each half was precisely partitioned to each daughter cell, or to each daughter nucleus, at each division of the cell.

The Sex Cells (Sperm and Eggs)

It was discovered that fertilization of an egg involved the fusion of two nuclei—one from the sperm of the father and the other from the egg of the mother. Weismann (before any critical, direct observations were available) made the daring prediction that sperm or eggs must always contain exactly half the number of chromosomes characteristic of the species. Otherwise, the number of chromosomes in each fertilized egg would be doubled at the beginning of each generation, and before long this increase in number would lead to a

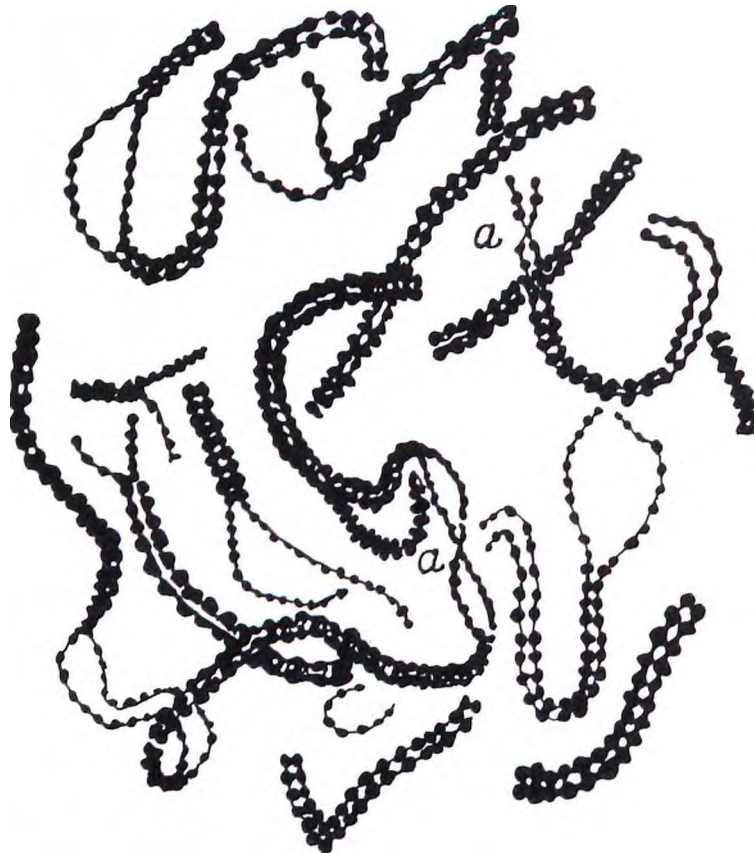


Fig. 3. Camera-lucida drawing of the chromosomes of *Allium triquetrum* copied from Belling. The homologous chromosomes are pairing with each other bead-for-bead in preparation for the formation of sex cells.

catastrophic imbalance. This daring prediction was finally confirmed, and eventually a theory affirming both the integrity of the chromosomes with regard to numbers per species and structure per chromosome, and affirming also the precision of both cell division and the reduction division, became widely accepted. In many organisms (Fig. 3) the chromosomes look like strings of beads. The homology (i.e. the structural correspondence) of the chromosomes from the father with the chromosomes from the mother was spectacularly demonstrated by the close resemblances and identical serial arrangement of those "beads" which could be morphologically identified in the chromosomes from the father and the chromosomes from the mother when "bead-by-bead" association occurred at certain stages in the life-cycle.

Sex Chromosomes and Autosomes

Further study showed that males and females in animals differed conspicuously with regard to one pair of chromosomes. This pair of chromosomes was called the sex chromosomes. Two kinds of sex chromosomes—the X-chromosomes and the Y-chromosomes were recognized. The other chromosomes, which occurred in identical, or homologous, pairs were called the "autosomes," and the autosomes seemed to be the same in both sexes. In the *Drosophila* fruit fly, which has been so widely exploited for research in heredity, each female contains two X-chromosomes and three pairs of autosomes while each male contains an X- and a Y-chromosome and three pairs of autosomes. When the number of chromosomes is reduced to produce sex cells, each egg contains a single set of three autosomes and one X-chromosome while each sperm contains a single set of three autosomes and either an X- or a Y-chromosome. When a sperm carrying an X-chromosome fertilizes an egg, a female fly is produced; the fertilization of an egg with a sperm carrying a Y-chromosome produces a male (Fig. 4).

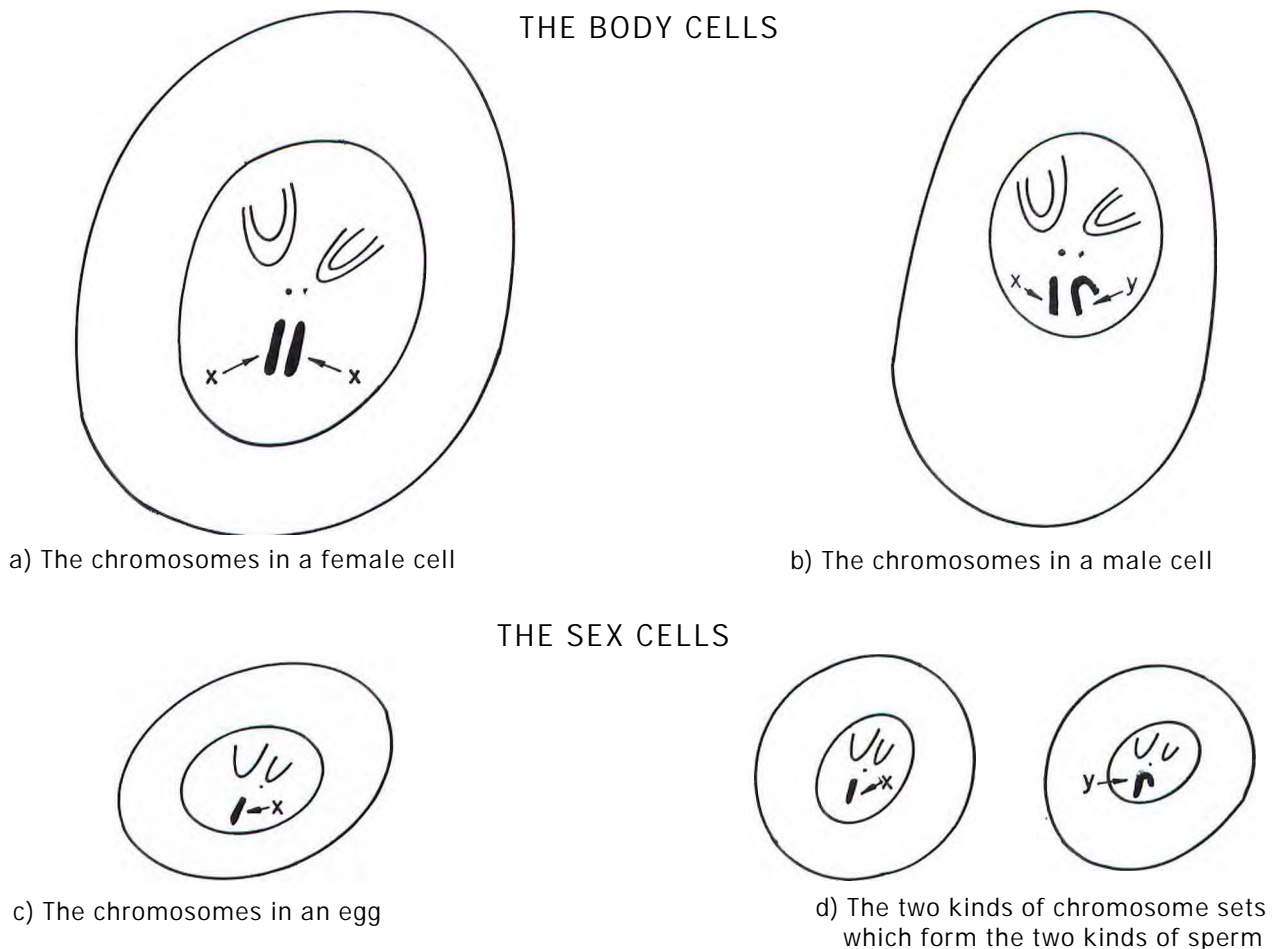


Fig. 4. The autosomes and the sex-chromosomes in *Drosophila* body cells and sex-cells.

Mendelian Inheritance

The concept of the Mendelian gene (particulate inheritance) began with Mendel. Gregor Mendel was the abbot of a small Bohemian monastery during the last century. At that time, a living organism was considered to be an entity which could only be regarded as a "whole"; in the production of hybrids, the "individualities" of parents were supposed to be "blended" in the hybrid. According to this view, one would expect the offspring of a tall man and a short woman to be of average height. Mendel was a teacher of mathematics and physics who performed experiments on the inheritance of peas in his spare time. He was interested in numbers and especially the binomial theorem which involves the pyramid of numbers shown in Figure 5. In 1865, he reported his results in the proceedings of a local society. Mendel discovered that the first-generation hybrid peas, produced by crossing tall pea plants with short pea plants, were not intermediate in size (or blended as one might have expected) but were all tall. When he inbred the tall hybrids, he found that in the next generation the offspring were tall and short, and, most surprisingly, there were no intermediate types; tallness and shortness were mutually exclusive characters. When he mated the "brothers" and "sisters" of this tall generation to each other, he discovered that the offspring were tall and short in the ratio of 3 tall to 1 short. He concluded that the factor controlling shortness was concealed (recessive) in the hybrid and reappeared in the next generation after "skipping a generation." He studied a number of other characteristics of peas such as round-seededness versus wrinkled-seededness, and green-seededness versus yellow-seededness, and found that each pair of contrasting characteristics was inherited in a manner which produced the same precise ratio which the binomial theorem predicted on the hypothesis that the different "factors" controlling the different "characters" were inherited independently of each other.

										Number of pairs of mutually exclusive characteristics	Mendelian ratio expected
1										0	0:1
1 2 1										1	1:3
1 3 3 1										2	1:7
1 4 6 4 1										3	1:15
1 5 10 10 5 1										4	1:31
1 6 15 20 15 6 1										5	1:63

Fig. 5. The Binomial Pyramid. The predicted ratios of one defective (for all the characteristics) to three normal (for one or more of the characteristics) is given in the last column.

Mendel made the following inferences from his discoveries: (1) Certain hereditary characteristics are controlled by particles. (In general, the particles fall into the two main classes of normal and defective, which are also called "dominant" and "recessive" since a single normal [dominant] particle corrects the defect when a normal and a defective particle are present in the same plant or animal.) (2) Each animal or plant carries two particles for each character, one from each parent. (Each pair may comprise two normal [dominant] particles, or two defective [recessive] particles, or one normal and one defective particle.) (3) Each sex cell contains one particle, chosen at random, from each pair of particles. (4) The particles do not interact and are not contaminated by each other when they are present together in a hybrid. (5) The two members of each pair of particles are assorted to the sex cells at random with regard to the members of every other pair or particles.

The Mendelian particles are now known as "genes." The 3:1 Mendelian ratio is the foundation upon which Morganism-Mendelism rests. It is the ratio in which normal and defective offspring appear when the first generation hybrids are inbred. Albinism in humans is caused by a defective

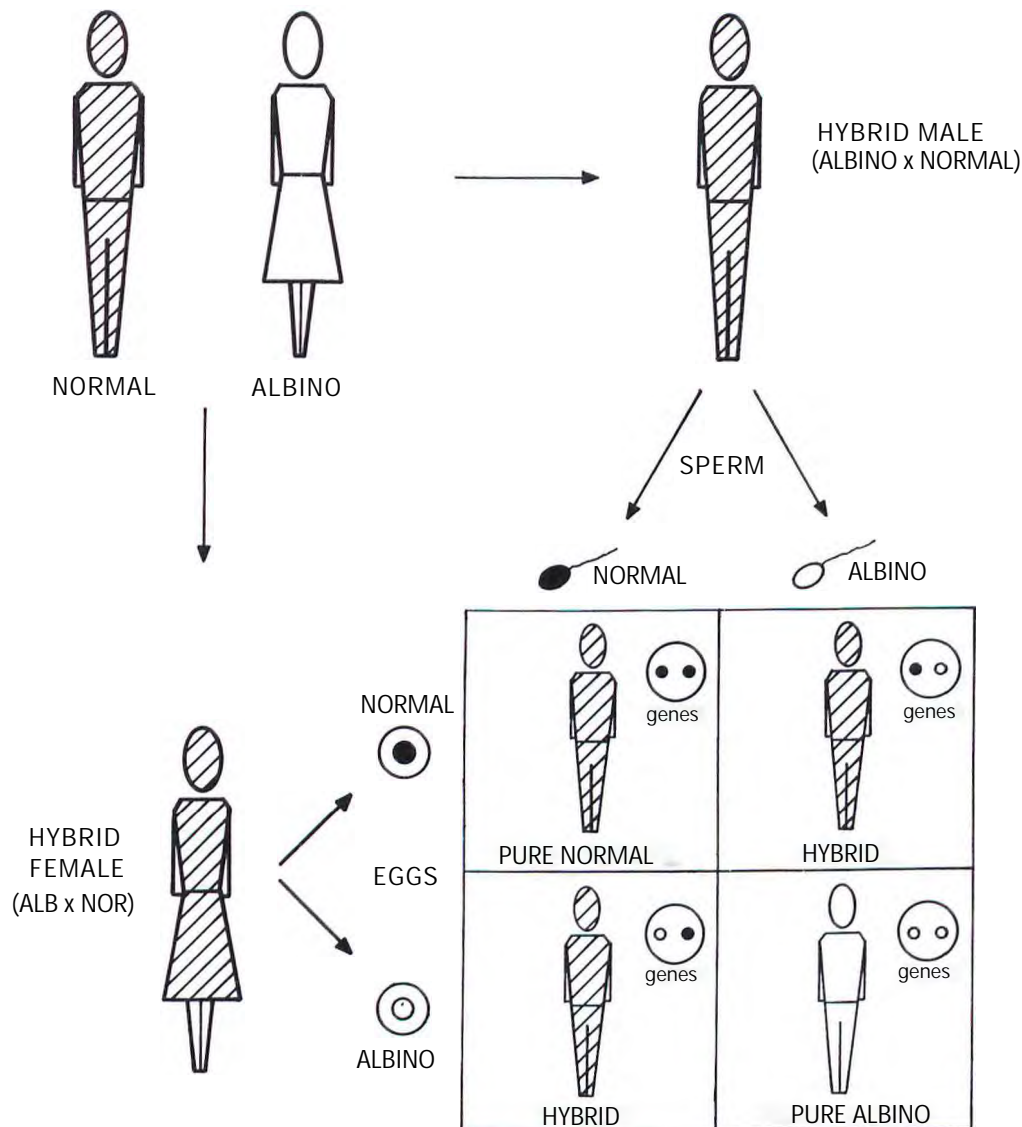


Fig. 6. Inheritance of albinism in humans.

gene. The offspring of a normal and an albino is a hybrid, but he looks normal; the defect is concealed in his hereditary apparatus. A mating of two such normal-albino hybrids produces three kinds of offspring: (1) albino-albino (pure albino), (2) normal-albino (hybrid), and (3) pure normal (Fig. 6).

One quarter of the offspring are pure albino; thus the ratio is 3/4 normal : 1/4 albino. The checker-board diagram called a "Punnett Square" describes the mechanism. Every individual produces either eggs or sperm which carry the genes transmitted to his offspring. Each normal-albino hybrid produces two types of sex cells: albino and normal. When these are mixed in all combinations, three kinds of offspring are produced in a 3:1 ratio of normal : defective.

Mendel was satisfied that he had done a very good job, and he was disappointed that his work did not receive the recognition which he thought it merited. He did not believe, however, that he had solved "the problem of life" or that the hereditary factors were the "ultimate living particles." He had no idea where the hereditary particles were located in the cell or if they were associated with each other in any way. He presented an interesting, startling, and clearcut demonstration that certain hereditary characters are controlled by particles which are transmitted from parent to offspring as unit particles, but nothing more was involved in Mendel's concept of inheritance. His paper made little real

impression on biologists, although many of those in high places at that time were acquainted with the facts which he reported.

Mendel's work was neglected for 35 years. Then in 1900, Mendelism was rediscovered simultaneously by three different scientists in three different countries—de Vries in Holland, Tschermak in Bohemia, and Correns in Germany. This sensational triple event attracted many biologists to the study of Mendelian inheritance and led to the discovery of many completely new aspects of heredity.

The Genes are on the Chromosomes (Morgan, 1910)

In 1909, Thomas Hunt Morgan began to breed the fruit fly, *Drosophila melanogaster* in search of mutations which would change one species into another. Normal fruit flies have red eyes. In his search for mutations, Morgan found an abnormal fly with white eyes. When he mated a white-eyed female to a red-eyed male he found that the sons were all white-eyed and the daughters were all red-eyed.

The experiments showed that white eyes in fruit flies (the normal eyes are red) were transmitted as if the factors were carried on the sex chromosome (Fig. 7). The Y-chromosome is a "blank" which does not carry any Mendelian factors; it passes from father to son and is found only in males. That the gene controlling white eye-color is defective, is indicated in Fig. 7 by a broken square; the normal (red-eye-color gene) is indicated by an intact square. This phenomenon was called "criss-cross" inheritance because the sons of a defective mother looked like their mother while the daughters looked like their normal father.

Morgan (1911) pointed out that color-blindness in man "follows the same scheme as does white eyes in my flies." The fact that the inheritance of a Mendelian gene could be related to the process by which sex chromosomes were transmitted to their offspring led Morgan to the conclusion that the genes are located on the chromosomes. The conclusion was generally acceptable because the red- and white-eyed genes were an obvious pair of Mendelian genes. It is important to remember that genes can only be studied when one member of a pair differs from its partner.

The Use of Chromosome Maps for the Study of Chromosome Structure

Previous to the study of *Drosophila* genetics, the behavior of the chromosomes was studied by the microscope and by use of the various stains which made the chromosomes more clearly visible than the other slimy structures in the cell. With the advent of research on the fruit fly by the Morgan School, the study of chromosomal behavior took another and a very different path. The new approach was based on the chromosome map. The Mendelian factors controlling the hereditary characteristics were found to lie in a linear order along the chromosomes, and the presence or absence of a part of a chromosome, or any change of the arrangement or distribution of the factors controlling hereditary characteristics, could be followed much more precisely by making maps of the chromosomes than by the most precise and critical microscopical observations which could be achieved by the finest optical instruments. The maps were developed in a special manner by analysis of the progeny of hybrids, and it is the development of this aspect of Morganism-Mendelism (as the Russians properly call it) that I propose to describe.

The Chromosomes Break and Reunite: —Crossing Over

In 1906, two British scientists, Bateson and Punnett, discovered a phenomenon which they called "coupling" and "repulsion." They found two different Mendelian characteristics which were transmitted in a Mendelian (3:1) ratio in separate experiments. When both genes were present in the same individual (i.e., when one parent was doubly defective and carried both defective genes, while the other parent carried the two normal genes), the offspring tended to produce progeny in which the characters remained in the same combinations in which they were present in the parents; most of the offspring were either doubly defective or completely normal; only a few showed single defects. They called this phenomenon "coupling" since the characteristics seemed "coupled." When they crossbred individuals with single defects they found that most of the progeny carried the single defects and only a few carried both defects. They called the latter phenomenon "repulsion," and said that the genes "repelled" each other. In these experiments the genes were not independently distributed as in Mendel's experiments but tended to remain either in coupling or in repulsion whatever the original state may have been. In 1911, Morgan

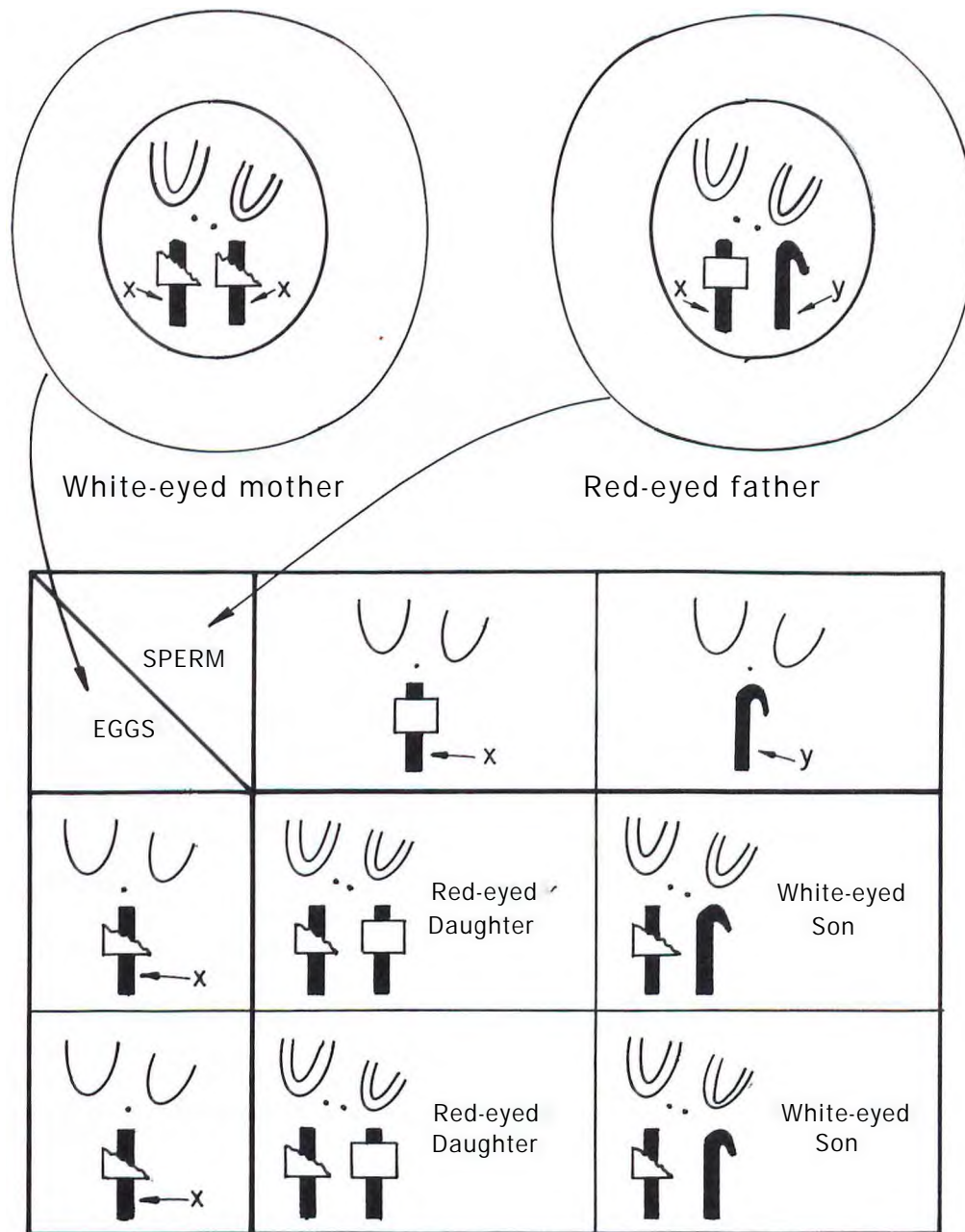


Fig. 7. White-eyed mother mated to a red-eyed father produces red-eyed daughters and white-eyed sons.

discovered a similar phenomenon in the study of inheritance of the yellow body color of flies (Fig. 8). The normal body color of the fruit fly is gray, and, hence, the yellow body color is a defective mutation, like the white eye color. When Morgan mated a male fly with yellow body and white eyes to a normal female, he produced a hybrid female which looked normal because both the defective genes were concealed in the female by two normal genes which it had received from its mother. When he studied the sons of the hybrid female, he found that over 95% of the sons were either (a) normal with regard to both eye and body color or (b) were defective with regard to both eye and body color. That is, most of the sons had red eyes and gray bodies or white eyes and yellow bodies. Only a very small fraction of the sons had (a) white eyes and gray bodies or (b) red eyes and yellow bodies. Morgan had said previously that the genes were probably on the chromosomes. When he discovered this phenomenon, which he called "linkage," he said that the chromosomes must break and reunite to produce the small

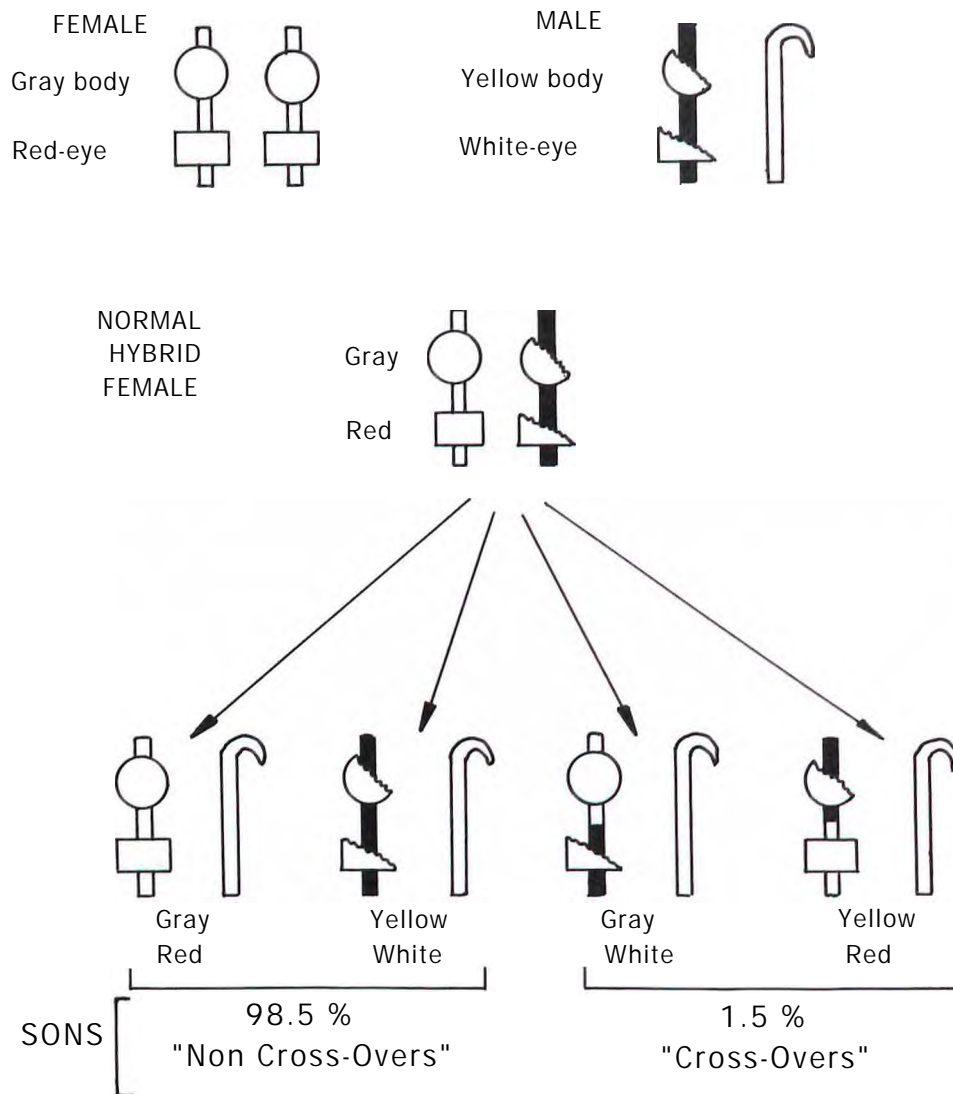


Fig. 8. An experiment by which Morgan drew the conclusion that chromosomes broke and reunited by "crossing over."

number of recombinant flies, that is, those flies in which the combinations were different from those in their parents. He concluded that the number of recombinants was few because only a few breaks occurred. Morgan's inferences from this experiment are probably the most important drawn from any single biological experiment in the twentieth century; modern genetics is founded on the inferences drawn from this experiment.

Crossing Over and the Chiasma (Janssens, 1909)

In genetical analysis the two observations on which breakage and reunion of chromosomes are inferred are: (1) the appearance of genes in new combinations (or, rather, their persistence in old combinations) by the study of the progeny of hybrids and (2) the direct observation, by the microscope, of the appearance of the chromosomes during the formation of sex cells. Chronologically the latter event occurred first. In 1909, Janssens proposed that the chromosomes might break and reunite under certain conditions. He drew this conclusion as the result of a series of microscopical observations of the chromosomes, but without any genetical evidence. Morgan cited Janssens' hypothesis when he

argued that genetic recombination of factors in the same chromosome could be achieved by breakage and reunion. What Janssens had observed were cross-shaped formations of chromosomes. The stage of the cross-shaped forms (the chiasmata) observed by Janssens occurs after the stage which Belling drew so beautifully in Figure 3. Both of these stages precede the formation of the sex cells. Janssens observed that at this time four separate strands were present, instead of the two paired chromosomes assumed by Sturtevant and Morgan. Preceding the formation of the sex cells he found one or more twists in nearly every pair of chromosomes which could be interpreted according to the diagram shown in Figure 9.



Fig. 9. A diagrammatic representation of a chiasma as described by Janssens.

The Genes are Arranged in Linear Order on the Chromosomes (Sturtevant, 1913)

In 1913, A. H. Sturtevant showed that genetical analysis of *Drosophila* hybrids could show not only that crossing-over occurred but that the invisible genes are arranged on the chromosome in a linear array corresponding to the linear order of the visible "beads" seen by the cytologist. Sturtevant arrived at his theory of the linear order of the genes by studying the progeny of a female which was hybrid for three different defects.

Name of the defect	Description of defect	Symbols	
		Normal	Defective
Crossveinless	Absence of a vein in the wing	A	a
Cut	Shortening of the wing	B	b
Vermilion	Eye color (lighter than normal)	C	c

In this famous experiment a hybrid female carrying A b C genes in one X-chromosome and a B c genes in the other was mated to a male. As shown in the preceding figures the changes which occur in the X-chromosomes of a female fly can be followed by studying her sons, irrespective of the father.

Sturtevant found that the sons were of the following types:

Nature of chromosome changes	Characteristics of Sons	Number of Sons		Interpretation of recombination in terms of kinds of chromosomes recognized
No recombination	A b C	759	1525	No exchanges between chromosomes
	a B c	766		
Recombination in Region I only	A B c	73	153	Exchange occurred between A and B (Region I)
	a b C	80		
Recombination in Region II only	A b c	140	298	Exchange occurred between B and C (Region II)
	a B C	158		
Recombinations in both regions	ABC	2	4	Exchanges occurred between both A and B and between B and C (Regions I and II)
	a b c	2		

A total of 1525 chromosomes from the hybrid female reappeared in her sons in the same combinations that were present in the mother herself. The critical category of recombinants is the class which occurred with lowest frequency, namely 4. Sturtevant assumed that recombinations occurred by chance; hence, the least abundant class was the class in which two recombinations had occurred, and this class determined the linear order.

Since the least frequent categories of recombinants were A B C (2) and a b c (2), the "real" original order must have been $\frac{A}{a} \frac{b}{B} \frac{C}{c}$ hybrid female, because only this order would have produced ABC and a b c by two simultaneous crossovers. It was on this basis and with data like these that Sturtevant established the linear order of the genes and made the first chromosome maps.

"The Exceptions Prove the Rule"

The preceding discussion shows how Bateson and Punnett's discovery of "repulsion and coupling," and Morgan's discovery of "linkage" which contradicted Mendel's theory of free assortment led eventually and naturally to the theory of the linear order. The hypothesis of the linear order met a wide general opposition and if only the first few papers which have been described above had been published, the whole idea would have soon been rejected and lost. The great and merited respect and admiration which has been showered upon the Morgan School has come not from these first ideas but from the massive effort which, against determined opposition, they exerted to extend their ideas and to support them with an incontestable volume of evidence. The famous "three-point crosses" were multiplied thousands of times and each sequence of ABC was followed by another of BCD and a third of CDE, etc., etc., until the most obdurate disputant was silenced under a flood of evidence which did not permit refutation. Thus, the minor inconsistencies of nonadditivity could not refute the reality of the linear order itself.

But in this relentless pursuit of the chromosome map, many exceptions were encountered. In some flies the order ABCDE was found to be ADCBE or ABBCDE or some other deviation. It is to the great credit of the Morgan School that they were to discover every exception to the linear order and to be able to demonstrate that these exceptions were not only not inconsistent with the original proposal but even made the original proposal more convincing than would have been the case if the exception had not been discovered.

A brief report on a few of the exceptions which follows may be interesting.

Non-"Criss-Cross" Inheritance

Mrs. Lillian Morgan (Thomas Hunt Morgan's wife) discovered exceptions to "criss-cross" inheritance in which the daughters of a defective mother looked like their defective mother while all the sons were normal. This discovery was exploited by Bridges to prove that the Mendelian particles (which Sturtevant had shown to be arranged in a linear order like beads on a string) were actually on the chromosomes. By a series of exceedingly ingenious experiments, Bridges also showed that the breakage and reunion of the strings of Mendelian beads occurred when four strands of beads were together, instead of occurring between only two strands of beads.

Duplication of Genes (Bridges, 1919) Due to Unequal Crossing Over (Sturtevant, 1925)

Crossing over does not always occur between two chromosomes at exactly homologous points, i.e., does not always produce pairs of reciprocal strands, but sometimes occurs between nonhomologous points making one chromosome longer by a duplicated section and the other shorter by a corresponding deletion. In 1919, Bridges discovered that genes in a chromosome may be duplicated over short regions. In 1925, Sturtevant found that chromosomes may pair in a nonreciprocal or nonhomologous manner and that breakage and reunion may occur between the chromosomes in the region in which they are paired nonhomologously. This event would produce one chromosome with a duplicated section (ABCBCDE), and the other chromosome with a deletion of the duplicated region (ADE). This discovery is important because of its evolutionary significance. It implies that chromosomes increase in length and, hence, in complexity. It also suggests how a species might acquire a larger number of genes by the obsolescence of one of the duplicated genes followed by the assumption of a new function. It also raised important questions concerning the nature of the gene (See Chapter 4).

Chromosomal Inversion (Sturtevant, 1921)

Sections of chromosomes can be inverted. Sturtevant discovered that if the normal arrangement of genes in a chromosome is ABCDEFG, this arrangement may become rearranged into the order ABEDCFG. Genes in an inverted region cannot pair easily with their homologous genes in a chromosome in which the normal order exists and, because crossing over depends upon the precise pairing of chromosomes, the inversion tends to inhibit crossing over. This inhibition of interchange tends to produce sections of a chromosome in which a large block of genes remain together (closely linked) and are inherited as a unit, tending to produce a new variety.

Translocation of Chromosomes (Bridges and Morgan, 1923)

Breakage and reunion may occur between two different nonhomologous chromosomes producing "translocated" chromosomes. In 1923, Bridges and Morgan discovered that chromosomes could be translocated; that is, a section of one chromosome could exchange with another different nonhomologous chromosome by breakage and reunion. The phenomenon of translocation provides another device by which varieties may arise within a species.

Chromosome Balance (Bridges)

A normal individual is the end result of a physiological balance produced by a balance between the chromosomes. Sex is the expression of a balance between the sex chromosomes and the other chromosomes. Bridges discovered that the X-chromosomes and the autosomes interact as if they were two separable units. If the ratio of the X-chromosomes to the other chromosomes in an individual is 1:1, then that individual is a female irrespective of whether the ratio is two sex chromosomes : two sets of autosomes, or three sex chromosomes : three sets of autosomes, or four sex chromosomes : four sets of autosomes. When the ratio is one X-chromosome : two sets of autosomes, the individual is a male. Bridges discovered that if the balance between maleness and femaleness were disturbed, the effect would be the production of an intersexual individual. Chromosomal imbalance has recently been found to be of great importance in producing physiological and psychological aberrations in humans. In humans the "blending" effects of hormones tend to obscure intersexual phenomena. In *Drosophila* the right side of the body may be male and the left side female, or the front end male and the rear end female. Or the leg of an obviously "female" fly may be "male." It is more than 30 years since Bridges first showed that sex-determination results from the balance of autosomes by sex chromosomes and that animals (or humans) which appear to belong to one sex may actually be basically intermediate or may even "belong" to the opposite category. Research on the human chromosomes has very recently amply confirmed Bridges' researches and has shown that many unfortunate humans are condemned at birth to life-long conflicts between the sex to which their appearance has assigned them and the sex to which their genetical composition has fated them. This is not to deny the fact that irregular sexual behavior may not often be due to environmental influence but it does mean that in many instances the tragedy is typically Greek in that the Gods of chance have predetermined it at birth.

The Chromosome Theory of Heredity

The work of Morgan, Sturtevant, Bridges and Muller demonstrated that the Mendelian particles are carried on the chromosomes and that they are arranged on the chromosomes in a linear order. Both of these brilliant concepts are clearly and undeniably the products of the Morgan School. These were new concepts not suspected by Mendel in 1865 nor by the three men who rediscovered Mendelism 35 years later. The "hypothesis" that genes are on chromosomes was anathema to William Bateson, the leader of the British Mendelists, who had discovered that genes were associated in heredity, a fact which had evaded Mendel. But Bateson denied that this association was due to the fact that genes were carried on chromosomes, and he refused to accept scientific papers discussing this "hypothesis" in the journal which he edited. Many years after the discoveries of the Morgan School had been generally accepted, Professor Theophilus Painter of the University of Texas verified the concept by direct observation of the chromosomes. Balbioni, an Italian microscopist, had discovered that certain cells in the fruit fly contained giant chromosomes and that these giant chromosomes were marked with cross bands. Professor Painter followed up Balbioni's discovery by showing that the cross bands on the

chromosomes were distinguishable from each other. Later a more or less direct relation of one band to one gene was established. Painter's demonstration made the theory that genes are carried on the chromosomes in a linear arrangement one of the fundamental facts of biology and confirmed this fundamental inference of the Morgan School.

Painter's original paper was followed up by a final and definitive study by Bridges carried out with his usual zeal and his enormous capacity for precise observation and painstaking and unceasing persistence. He produced a composite drawing of the bands of the salivary chromosomes which is one of the great scientific monuments to an almost limitless endurance and pertinacity. He summarized the correspondences of bands to genes, and carefully stretched chromosomes in critical regions to catch every tiny detail. These drawings and this immense effort have no parallel in biological research; there may have been lonely astronomers who have expended comparable finesse in their solitary watches at the telescope, but I am not sufficiently acquainted with research in that distant field to know about it. It is safe to say that no one in the present generation of biologists will duplicate Bridges' original effort, although it may be corrected in minor details.

His discoveries indicate that the chromosomes have certainly become longer by unequal crossing over. ABC — ABBC — AABBC — AAABBBBC — etc. A study of his pictures suggests that this process may reveal events which occurred long before flies emerged as biological entities in evolution and that flies carry in their chromosomes residual effects of events which occurred even before animals were invented, just as the light which comes to earth from the stars may be the effect of events which occurred millions of years earlier than the time the light actually reaches earth.

The Ultimate Living Particles

The study of the heredity of fruit flies expanded enormously during the 20's and the 30's until most American and many foreign universities had set up laboratories engaged in analyzing the heredity of the fruit fly. Under the aegis of the Morgan School, the specialists engaged in studying heredity developed the concept that Mendel's particle, now called the gene, controls heredity, and by extension metabolism, appearance, behavior, and nearly every other characteristic of the living organism. This view is called "Morganism-Mendelism" by the Russians in recognition of the part the Morgan School played in the origination of the idea. The doctrine of Morganism-Mendelism holds that the nucleus, which carries the chromosomes and contains the genes, carries the positive agents which control and direct all vital activity. In their enthusiasm over genes, many proponents of Morganism-Mendelism proposed that the genes are responsible for all vital activity and that the gene is actually the "ultimate living particle." This view over-emphasizes the importance of the genes and the nucleus and minimizes the importance of the cytoplasm in which the nucleus carrying the genes is embedded. The evidence that the genes in the nucleus control certain hereditary characteristics led to the unwarranted inference that the cytoplasmic jelly does not control any hereditary characteristics, to the doctrine that the cytoplasm is less important than the nucleus, and, finally, to the view that "life" could be understood if one understood the gene. This sweeping generalization is disputed by the Russian-Michurinists and by many Western biologists.

One Gene — One Enzyme (Haldane and Beadle)

Each gene produces a single specific initial effect by the production of a single specific enzyme. This dictum is of major importance—one of the great links between heredity and biochemistry. It is principally responsible for the enormously successful activity in biochemistry which has already yielded a plethora of Nobel prizes and is almost certain to yield even more. The enzyme is the key to biological activity. It is the substance which enables living organisms to defeat time because it increases the speed of biochemical activity enormously compared to the speed in the absence of the enzyme. It also directs the chemical activity toward a specific end result. This is because the enzyme is a biological substance which acts as a platform or a vise on which or in which a chemical reaction occurs. The proteinaceous enzyme has an active site which has an attraction for the bonds which link two or more biological molecules such as sugars, amino acids, alcohols, or other such substances typically "biological," and which can break these bonds to disassemble the large molecules into smaller individual units. There are about 20 amino acids which are capable of combining with each other in different sequences and in different numbers. All living organisms produce proteins which exist only in their own individual species, i.e., are species-specific. This fact is presumably related to the fact that each species has its own species-specific genes. When a human eats beef, his digestive system produces

enzymes which break down or disassemble the beef protein into its individual amino acids and these basic units are then reassembled in the human cells into the proteins characteristic of the human cells. There are certain co-enzymes, most of which are vitamins, which collaborate in the process. Thus enzymes make it possible for different species to coexist by preying upon each other or by supplying the complex aggregates which contain the basic units required by all. They are the links which combine species to species into one great society and which make each species capable of producing the substances which give it its own singularity.

At the first stages of genetical analyses the characteristics were not directly relatable to chemical reactions. Characteristics such as curly or straight hair, long or short wings, or different morphological types of fungi, cannot be related directly to chemical events, although the underlying concept is that some chemical event must have produced them. Later certain characters were discovered which were directly related to single chemical events. The most conspicuous of these is color in flowers. The different kinds of red and yellow pigments are closely related chemical substances, and the ability to produce these pigments is generally under the direct control of Mendelian genes. Pigmentation in flowers was studied in 1920 by Haldane and Scott-Moncreiff, who showed that a red flower was transformed into a yellow flower by a single gene and, hence, that a single gene must have controlled the chemical reaction which transformed the red pigment into the yellow pigment. This concept was enormously extended by George Beadle and Edward Tatum in 1942, when they showed that a transformation of one amino acid into another was controlled by a single gene. Beadle's "one gene - one enzyme" slogan has received wide acceptance, and this principle is the most recent basic concept developed from Morganism-Mendelism.

The basic principles of Morganism-Mendelism were developed during the 40 years from 1910 to 1950, changing the study of inheritance from a descriptive, anecdotal relation of what happened when different kinds of hybrids were made to a mathematical, statistical analysis of precisely predictable data by which it was possible to associate certain landmarks of an observable structure (the chromosome) with the inheritance of a specific biochemical capacity (an enzyme).

FOOTNOTES

1. The most viscous (the "slimiest") biological substances known is probably deoxyribonucleic acid, now known to the man-of-the-street by the initials DNA and described by some over-enthusiastic professional biologists as "the living molecule."
2. Brownian movement is the jiggling of microscopic particles, which is visible at low magnification, due to the bombardment of visible particles by invisible molecules in the ambient liquid.

CHAPTER 4

The Indescribable, Indefinite, Undefined Gene

The Problem of the Gene; Johannsen's Invention of the Word "Gene"; Conceptual vs. Operational Views of the Gene; The Changes in Points of View From One Generation to the Next; Morgan and The Theory of the Gene; Parallelism Between Chromomeres and Genes (Belling); Sturtevant and Beadle on the Primacy of the Gene; Muller's Concept - tion of the Gene as "Living"; Sturtevant's Pragmatic Definition of the Gene; The Gene as the "Unit of Life"; Goldschmidt's Rejection of the Concept of the Particulate Gene; Stadler on the Operational Versus the Hypothetical (Conceptual) Gene; More Than one Gene at the Same Place; Nucleic Acids; The Nucleic Acid Molecule and the Gene; The Cistron; Diffusion and Interaction of Gene-Products; The Virus-Genes Concept; Accessory Chromosomes; The Concept of the Gene as a Biological Entity.

The Problem of the Gene

Many years ago at Cal Tech, Calvin Bridges wrote a paper which was published in Science in which he discussed the hierarchy of particles from electrons and atoms to genes and viruses. I mentioned Bridges' article in the course of a discussion with the famous astrophysicist, Fritz Zwicky, who is almost as emotional as he is widely-respected in his field. He was very upset because Bridges had ascribed specific dimensions to atoms and electrons and said that physicists actually had no idea what either of them were nor even vague ideas of their dimensions. He complained that the only people who thought they understood atoms and electrons were those who knew nothing about them. Laymen and physicists who speak glibly about genes may be surprised to discover that professional geneticists are as confused about the concept of the gene as the physicists were 40 years ago about atoms and electrons. In this chapter I shall attempt to relate some of the highlights of the history of the gene.

Johannsen's Invention of the Word "Gene"

The word "gene" means so many different things to different people that it may be helpful to consider its origin: in coining the word, Johannsen said:

. . . It is a well-established fact that language is not only our servant, when we wish to express—or even to conceal—our thoughts, but that it may also be our master, overpowering us by means of the notions attached to the current words. This fact is the reason why it is desirable to create a new terminology in all cases where new or revised conceptions are being developed. Old terms are mostly comprised by their application in antiquated or erroneous theories and systems from which they carry splinters of inadequate ideas, not always harmless to the developing insight.

Therefore, I have proposed the terms "gene" and "genotype" and some further terms, as "phenotype" and "biotype" to be used in the science of genetics. The "gene" is nothing but a very applicable little word, easily combined with others, and hence it may be useful as an expression for the "unit-factors," "elements," or "allelomorphs" in the gametes, demonstrated by modern Mendelian researches

As to the nature of the "genes" it is as yet of no value to propose any hypothesis; but that the notion "gene" covers a reality is evident from Mendelism. The Mendelian workers have the great merit of being prudent in their speculations.¹

Although Johannsen made the claim that "the notion . . . covers a reality," he did not present a formal definition of the "gene." His admiration of Mendelists because they are "prudent in their speculations" suggests that he equated speculations with critical inquiry into basic assumptions. But

his substitution of the short word for a longer one did nothing to clarify one's understanding of the situation.

Conceptual Versus Operational Views of the Gene

Two opposing tendencies which separate some theorists when they discuss the gene may be distinguished as the conceptual and the operational. The conceptual point of view is characteristic of those who would like to define the gene from the broadest possible point of view, trying at once to conceive of the function of the gene in the organism, its place in evolution, the manner of its origin, its phylogenetical significance and as many other aspects as possible. The operational point of view is characteristic of those who prefer to define the gene only in terms of the experimental operations by which the existence of genes may be demonstrated.

The conceptual attitude is characteristic of the romantic, imaginative, exploratory thinkers who feel that one must consider every possibility and whose interests are speculative and wide ranging. In the extreme, the conceptual scientists may be considered to be "fuzzy-minded" and imprecise. In scientific disciplines there are fashions (which change with the times) concerning how much speculation is permissible by the leaders of a particular scientific community who control job opportunities, the avenues of publication and the distribution of research grants to the members of the lower echelon of that particular community. But no matter what conservative scientists may think or say about the possibility that speculation may mislead or confuse the scientific community, or the necessity to protect new-comers into the science from the imprecision to which extremism in this direction may lead, one must admit that, without any speculation, science would die, just as certainly as it would suffer severely if speculation were to run rife, completely uncontrolled by experiment.

The operationalist prefers to confine himself exclusively to precise, pragmatic, undebatable, conclusions which rest only on abundantly confirmed experimentation and which would yield a definition in which no speculative, unsubstantiated concepts were involved. But any definition based on "facts" would be subject to the limitations already discussed in Chapter 1. An operational definition would not tell the reader what the scientist who made it thinks of the gene's place in nature, its significance to the organism, its phylogeny or its origin. And certainly no student of the problem is without some thoughts on these matters which could be interesting or helpful to others with similar interests.

It would seem, therefore, that a balance or a compromise between the "fuzzy-mindedness" of the speculative (conceptual) extremist and the unimaginative sterility of the operational extremist would be desirable. The uncommitted worker could consider both points of view and exploit either, as the appropriate occasion arises; he should not place his faith in either as a final choice. He should try to avoid the vagueness of one extreme and the sterility of the contrary extreme and keep an open mind to the opportunities for ultimate understanding that each view affords.

The Changes in Points of View from One Generation to the Next

If one were to divide the geneticists into different generations, one would place the following names (without regard to respective rank) in the first generation:

E. B. Wilson, Morgan, Richard Goldschmidt, Correns, deVries, William Bateson, John Belling, Johannsen, Boveri.

In the second generation: Sturtevant, Bridges, Muller, J. B. S. Haldane, Vavilov, Darlington, Stadler.

In the third generation: Beadle, Ephrussi, Sonneborn, Karpechenko, Catcheside, Dobzhansky, Auerbach, McClintock.

In the fourth generation: Crick, Hershey, Benzer, Lederberg, Pontecorvo, Meselson.

The first generation, in general, had broader conceptual views of the gene than those which prevail today. The second generation was about equally divided in attitude but a "biological" as opposed to a "biochemical" point of view still prevailed, i.e., problems of the species, of phylogeny, of evolution, etc., were considered important; the same catholicity prevailed generally in the third generation.

The present fourth generation has been overwhelmed by the mass of precisely-detailed and revolutionary discoveries of biochemistry, and has been completely unable to consider the biological problem in its broadest aspects hence, an operational, almost purely pragmatic, point of view prevails among the current geneticists. In a conversation with Meselson, I recall that he said, "Biology is now reduced to a study of the chemistry of nucleic acids." Morgan, Bateson, Belling and Darlington continued

in Mendel's foot steps with the concept of a discrete particulate gene, but this view has been rejected in toto by the current generation. This chapter will attempt to present the views of the different theorists and the steady evolution from a conceptual to an operational attitude toward the gene.

Morgan and The Theory of the Gene

In formulating his theory of the gene, Morgan (1928) stated (a) that "the characters of the individual are referable to paired elements, genes, in the germinal materials," and he concluded a discussion of theories of heredity by saying (b) that "most of the facts concerning heredity known to us at present can be accounted for by the theory as it stands." These two quotations taken together may be interpreted to mean that the totality of the characteristics of the individual are transmitted by the genes and controlled by the genes, and that the cytoplasm plays a subsidiary role. Except for this statement, Morgan did not discuss cytoplasmic inheritance in *The Theory of the Gene*. In dealing with the question of acquired characters, Morgan states:

Weismann in 1883 challenged the entire transport theory, [that is, the theory of pangenesis developed by Darwin] and convinced many, but not all, biologists that the evidence for the transmission of acquired characters was inadequate.²

Morgan's attitude toward the gene was pragmatic and operational. He related the gene to the hereditary character; in fact, he related genes to all the hereditary characters, but, aside from the manner of its transmission, he did not further specify the characteristics of the gene. The following quotation, in which his complete theory is formulated, describes only the transmission of the gene and does not attempt to define the gene conceptually nor in any way relate the gene to the character which it controls.

The theory states that the characters of the individual are referable to paired elements (genes) in the germinal material that are held together in a definite number of linkage groups; it states that the members of each pair of genes separate when the germ cells mature in accordance with Mendel's first law, and in consequence each germ cell comes to contain one set only; it states that the members belonging to different linkage groups assort independently in accordance with Mendel's second law; it states that an orderly interchange—crossing-over—also takes place, at times, between the elements in corresponding linkage groups; and it states that the frequency of crossing-over furnishes evidence of the linear order of the elements in each linkage group and of the relative position of the elements with respect to each other.³

Parallelism Between Chromomeres and Genes (Belling)

Although many biologists, even before 1900, had favored the view that the chromosomes carried the hereditary materials it was not until 1928 (after the Mendelian particles had been identified as genes) that John Belling proposed that each of the chromomeres, that is, each of the separate, visible particles (the "beads") on the chromosome, actually was a separate gene. He was an extremely expert observer and especially interested in the large chromosomes of liliaceous plants. Belling (1928) proposed the following hypothesis:

Correct scientific procedure, in the writer's opinion, demands the adoption, as a working hypothesis until a better one appears, of the assumption that chromioles and chromomeres are genes, doubtless with more or less of an envelope.

CHROMOMERES (AND CHROMIOLES)

Chromomeres are in a linear series in the chromosome at pachyphase.

Chromomeres are formed of two pairs of chromioles at pachyphase.

Chromomeres are of markedly different sizes.

The chromomeres of different sizes have the same order in the two homologous threads at pachyphase.

GENES

Genes are in a linear series in the genetic chromosome.

Genes are divided into two pairs at pachyphase.

Genes are of markedly different qualities.

The genes of different qualities have the same order in the two homologous genetic chromosomes.

CHROMOMERES (AND CHROMIOLES)
(continued)

Only homologous chromomeres of the same sizes are paired at pachyphase.

In rare cases, the two chromioles of one homologue seem smaller than those of the other.

Homologous chromomeres attract one another and are joined by thin threads.

All the chromioles divide at the same rate.

The number of ultimate chromomeres has been shown, in four plants, to be probably between 1500 and 2500.

GENES
(continued)

Only genes of identical qualities are paired in homozygotes.

Rarely the homologous genes differ in quality, being allelomorphic.

Homologous genes attract one another and pair.

All the genes divide at the same rate.

The number of genes has not yet apparently been shown to be outside these limits.⁴

Belling was also of the opinion that the individual genes were actually visible under the microscope as he indicates in the legend of the drawing (Fig. 10), but in spite of his inner conviction that he had seen genes, his writings give no specific definition of the term.

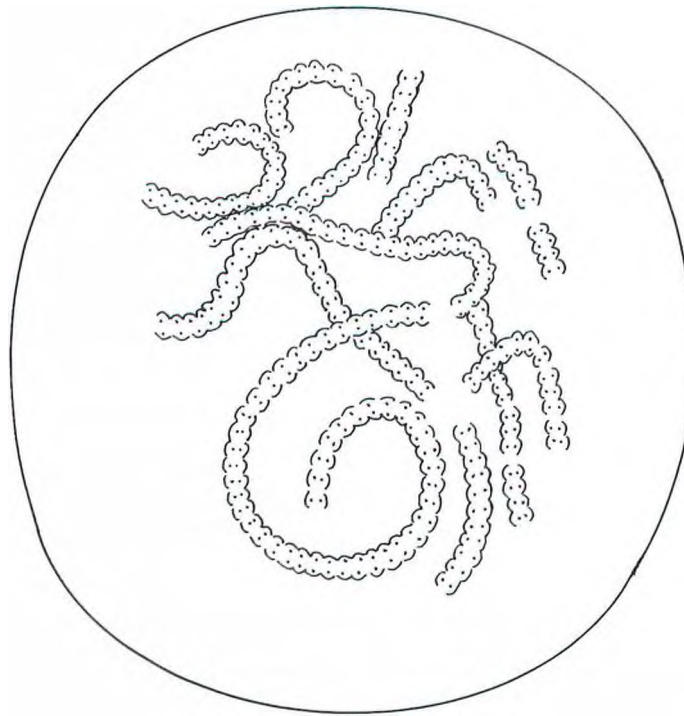


Fig. 10. Chromosomes of *Allium triquetrum* copied from Belling. In describing this drawing, Belling said, "The chromomere cores (or genes) were visible as minute (probably submicroscopic) dots, one in each chromomere."

Sturtevant and Beadle on the Primacy of the Gene

Sturtevant and Beadle in *An Introduction to Genetics*, 1939, elaborated upon the theory of the gene, especially as it concerns the primacy of the gene in the determination of hereditary characters, or conversely, the neutrality, or the lack of significance, of the cytoplasm in the control of heredity:

The question may be asked: Is all heredity due to genes carried in chromosomes, or are other bodies also to be taken into account? . . .

There can be no doubt that in seed plants . . . the plastids . . . have permanent properties that are maintained without regard to the genes.

. . . Animals do not have plastids, and one may ask: Do they furnish evidence for the existence of any permanent autonomous elements outside the chromosomes?

. . . experiments [on animals] demonstrate that the cytoplasm of the egg contains the potentialities of early development; but they do not demonstrate that this property is due to self-perpetuating elements in the cytoplasm. It is probable that the genes in the chromosomes of the mother are ultimately responsible for all the specific properties of the cytoplasm, as can be shown in certain instances.

One may not conclude that the cytoplasm is of no importance in development. It is obvious that, if it were possible to dissect out a complete set of genes and place them in a vacuum, they would not produce an organism. [Actually there is no known nutrient medium except cytoplasm in which genes can function.] The cytoplasm is not only a necessary medium for the growth of genes and for the production of their specific effects; it is itself specific. There is abundant evidence that the cytoplasm of different species, and even of different individuals, has a highly specific composition. The question at issue, however, is; Is the specificity of the cytoplasm to be referred back to the specificity of the genes, or is it a permanent property that reproduces itself regardless of the genes present? That is, do the genes modify the nature of the cytoplasm, and, given time, mould it into a specificity determined by their own properties? At present the most probable answer to these questions is: Only the chloroplasts are known to have permanent properties independent of the genes in the chromosomes.⁵

Hence, Sturtevant and Beadle (in 1939), as well as Morgan (in 1928), affirmed the primacy of the gene and denied the existence of any concrete evidence by which the autonomy of the cytoplasm had been demonstrated. It is important to point out that Sturtevant and Beadle recognized, and admitted, that their affirmation would not have been acceptable to Boveri, to Conklin, or to Jacques Loeb, who held that the cytoplasm played a much more active role than Sturtevant and Beadle proposed for it.

It is an interesting historical sidelight that Sturtevant and Beadle, in *An Introduction to Genetics*, did not define the gene, and, furthermore, that after the book was completed they discovered that each of them had different concepts of the gene. Sturtevant was inclined to define the gene in terms of its location on the chromosomes, that is, operationally as the end product of genetical analysis, while Beadle was inclined to define the gene idealistically, in terms of its function. From Beadle's work on the physiology of the gene, he stated his concept of the gene by the aphorism, one gene-one enzyme. Both of these workers, at least at this early date, agreed with Mendel who specified that the gene was a hereditary particle producing a "factor" which controlled a "character." Even Sturtevant speaks of gene-products as if the gene were active in the control of a hereditary characteristic. Hence, ever since Mendel, the concept of the gene has suggested the idea of a particle or a region of a chromosome active in the production of a factor now generally assumed to be an enzyme.

Muller's Conception of the Gene as "Living"

Muller is as different from Sturtevant as two completely dedicated, skillful and competent scientists who have spent their entire lives in the same field can possibly be; Muller describing in terms of his concept of its activity and function.

The major actor in this great drama of evolution by natural selection has proved to be gene, a particle too tiny to be seen under the microscope but immense by inorganic standards. . . . Although the genes form only a small part of the cell's bulk, they control through their diverse products, primary, secondary, and more remote, the composition and the arrangement of most or all of the other materials in the cell and, therefore, in the entire body

Recent evidence indicates that the gene consists of a substance known as nucleic acid, in the form of a much coiled chain, or double chain, composed of a great number (thousands) of links. . . .

The most remarkable thing about the gene is that each huge chain-molecule has the faculty of capturing, by some specialized sort of affinity peculiar to its links, chemical groups in its vicinity which in some way correspond to these links. The captured groups thereby become matched up alongside the gene's links in an arrangement similar to that in the gene itself, and they are enabled to become bound together, just as the gene's own links are. As a result, they finally constitute another gene essentially like the original one. Thus the gene reproduces itself.

. . . in the origination of life the gene arose first, and . . . protoplasm came into existence later, very gradually, in the form of a series of products of the chemical action of aggregates of genes that had mutated in such ways as to be able to give rise to these products. Protoplasm would thus consist of substances accessory to and produced by the genes.

[Muller suggests that the protoplasm came into existence due to the action of genes, but when one considers the fact that genes cannot exist in the absence of cytoplasm, Muller's statement is an assertion of faith rather than a solution of the problem of the origin of either genes or cytoplasm.]

Its [the cytoplasm's] existence would be due to the fact that those mutant genes had been naturally selected whose products happened to afford chemical tools, such as enzymes, that are useful for the survival and multiplication of these genes themselves.

. . . Life's essence lies in the capability of undergoing such evolution, and this capability is in-

herent in the gene, by virtue of its property of duplicating its variations.

It is not surprising that, in the remote past, the gene itself should have come into existence. For conditions were such, in the envelope of the primitive earth, that the accidental encounters of substances, together with the absorption of energetic radiation, continued during many millions of years, must have provided a tremendous accumulation of ever more complicated organic compounds, including many of those occurring today within cells. And if, among the myriad types of molecules thereby produced, genes were included (only one successful gene being required!), then the component parts also would already have been formed, out of which these genes could manufacture duplicates of themselves. Moreover, there would also be numerous other ready-made constituents present, which were capable of being utilized as accessory substances after mutations implementing such utilization had occurred in the descendant genes.⁶

The reason that, in the first place, the effect of a single gene is so inordinately amplified in an organism and that, in the second place, gene changes become accumulated in such a way as . . . to give increasing organization that in turn results in the perpetuation and spread of the organized material at the expense of the rest, is because of the very property that makes a gene a gene: that is, its ability to duplicate not merely itself but its own variations (mutations), and to do so to an unlimited degree. It is this that, in its various expressions, makes possible growth, heredity, and evolution from the simplest of beginnings to the most complex; and it is this, therefore, that causes the great present-day gap between the animate and the inanimate and so justifies us in separating these two categories of nature from one another. In other words, it is this property that forms the basis of life itself. The most fundamental problem of life, then, is to discover what it is in the structure and workings of the gene and its companion materials which renders it able to do this.⁷

Muller has emphasized the primary significance of the gene (1) in its control of heredity and (2) in the origin of life. Although he considers himself to be a mechanist, he justifies the separation of animate from inanimate into two specifically different categories. This follows from his specification that the gene is living material and hence that nongenic material must be nonliving material. Muller is able to make this discrimination because he looks upon the gene as possessing the property which forms the basis of life itself. This dangerously approaches the statement so frequently made in elementary courses in genetics, that the gene is the "unit of life." But to call the gene "living" is equal to calling the other components of the living state "nonliving." This attitude smacks more of mysticism than of mechanism.

Sturtevant's Pragmatic Definition of the Gene

Sturtevant's definition of the gene is a masterpiece of clarity; it states precisely what is known about the gene and no more. It is devoid of mysticism, but it does not present the basis for a theory which one might test to bring about further understanding. Sturtevant's definition may be the essence of what is desirable in a definition; no matter what else may be discovered about the gene, Sturtevant's definition will always be correct. His definition brings one squarely face-to-face with the known essentials, revealing the basic limitations of concrete knowledge on the subject. Sturtevant said:

There is no escape from the conclusions that the chromosomes are regionally differentiated, physiologically as well as visibly under the microscope; that particular and identifiable regions are necessary for particular reactions in the organism; and finally that these particular regions behave as units in heredity—specifically in crossing over.⁸

This is an operational definition stating the facts derived from experiments without revealing its author's concept of the nature of the gene.

The Gene as the "Unit of Life"

It is not easy to discover where the concept of the gene as the "unit of life" originated. Physicists are more readily inclined to accept the view than biologists. The physicist, Schroedinger, wrote a small book entitled *What Is Life?* and in this volume he is revealed as the most extreme proponent of the view that the gene is the "unit of life."

The idea that the gene is the "unit of life" resembles more a religious revelation of the nature of life than a scientific conception of the phenomenon of life. The difference between religious knowledge and scientific knowledge is that religious knowledge is revealed without the necessity for understanding its basis in fact; actually the demand is made that religious knowledge be accepted on faith.

Furthermore, the terms in which the revelation is stated are not defined. For example, in the several statements "God is good"; "God is love"; "God is truth"; it is not considered necessary to define "God," or "goodness," or "love," or "truth." In fact, each of the terms is defined in the others. In spite of the fact that every attempt is made to avoid such situations in science, they are constantly encountered in areas where they are least expected. The purpose of a definition is to explain the defined object in terms which are already understood. But scientists are not agreed on a definition of life, and to equate the gene with life is to equate a term to be defined with one which is not understood. It seems perfectly clear that the definition does not add to one's understanding of life. It is difficult to comprehend the meaning of "unit" in this connection. Are many "units" needed before life can be achieved, or does one "unit" by itself constitute "life?" It seems obvious that this definition of the gene is nonsensical, or, at the best, mystical. Any mechanical concept, however complicated or speculative, in which the gene is represented as a functional structure, is preferable to nonsense or mysticism.

Goldschmidt's Rejection of the Concept of the Particulate Gene

Morgan's concept of the gene reflected Mendel's concept of the particle, but Goldschmidt proposed a contradictory concept: the gene is not in itself a reality but is merely the expression of a disturbance in the relationship of the components of a continuum, a position-effect.

The following quotations amplify his theory:

Optimistic observers more than once have claimed to have seen the genes. About twenty years ago Belling, a brilliant observer and a keen thinker, took me with solemn ceremony to his microscope to show me the gene. He had succeeded in staining distinctly within some big chromosomes a tiny but visible central dot which he considered to be the gene finally made visible. The number of geneticists is not small who talk of the bands in the salivary chromosomes as genes and obviously are convinced that these are the real, visible genes of classic Mendelism, though numerous facts already mentioned or still to be mentioned are opposed to such oversimplification. Recently much smaller structures have been seen in the bands with the electron microscope and have been hailed as the real genes.⁹

It is clear that Goldschmidt thought Belling's ideas were ridiculous. It is important to realize that both Belling and Goldschmidt were great scientists of the highest order of intelligence, both were friendly and tolerant men who lived near enough to communicate frequently and freely with each other, and each had a real understanding and a great respect for the other's accomplishments. Belling was relatively introverted, but Goldschmidt was urbane, worldly and the ultimate in the polished continental gentleman. One must ask, again and again, why—with all these opportunities—did they not achieve agreement?

The theory of the genes goes back to the desire, visible in all pre-Mendelian speculations of the epigenetic type, to explain hereditary corpuscles in the cells which could be moved around in the proper way to meet the needs of the respective theory. With the discovery of mitosis these corpuscles were put in linear order into the chromosomes (Roux, 1883), and Mendelian genetics revived them as genes (Johannsen's term). The experimental underpinning of these speculations begins with Boveri-Sutton's proof that Mendelian segregation and recombination is the consequence of the location of Mendelizing factors within a pair of homologous chromosomes. It reaches its climax with the crossing-over studies of the Morgan group, which proved the exact order, linear arrangement, and localization of Mendelizing alleles in the chromosomes; and it ends with the proof (Painter) that the visible arrangement of structures of the salivary gland chromosomes agrees exactly with the results of genetic localization. In the minds of geneticists and nongeneticists alike, this established the gene as the unit of heredity, even the unit of life, being corpuscular, individual, independent, self-duplicating, but capable of mutational change, beadlike, as in a string of beads and imbedded in the chromosome.

Though this was and is clearly the idea of a gene, its definition, as derived from experiments by the Morgan group, was less concrete. By definition the gene was the smallest section of a chromosome within which no crossover break can occur. But this definition does not make much sense, for is based upon a criterion which cannot be stated in absolute terms. The distance between two genes is measured by the percentage incidence of a crossover break between them. The smaller the distance the more improbable a break and the larger the number of individuals needed to discover a break. It is well known that a number of apparently unitary loci have been separated by breaks when sufficiently large numbers were used and the tendency for crossover breaks increased by proper experimentation. Where is the limit for this? Since this question cannot be answered, the crossover definition of the gene is not possible. It is important to realize this fact because this very definition has frequently been used to avoid the consequence of modern discoveries for the classic theory of the gene.

... we cannot define a gene, even assuming the correctness of the classic idea of the particulate gene, by the breakability of the chromosome (crossover). The definition must contain the characterization of the gene itself, and that is its ability to mutate into one or more alleles.⁹

It is important to note that Sturtevant's definition of the gene does not satisfy Goldschmidt's requirement. Both Sturtevant and Goldschmidt defined the gene in terms of the chromosome rather than on the basis of the "characterization of the gene itself," which Goldschmidt required.

Goldschmidt argues that no one has ever demonstrated that mutagenic agents like X-rays or nitrogen mustard can produce mutations in what are supposed to be "genes" rather than rearrangements of materials in the chromosome. Goldschmidt suggests that nothing in the chromosome has been changed except the arrangement of the hereditary materials.

. . . A gene mutation or point mutant in such experiments means, of course, a mutant which with the best available methods does not show cytological rearrangement. But not all mutants can be checked cytologically. In the salivary chromosomes some regions are more favorable than others. In favorable regions a deficiency, down to a single band, can be checked easily; in others it is more difficult. Small inversions are even more difficult. Inversions of a few bands may or may not be detected without a very detailed study, which usually cannot be made in connection with large-scale quantitative work. If an inversion of a single band should occur, which Goldschmidt and Hannah (1944) claim to have demonstrated, it will hardly ever be noticed. The so-called gene mutations will include many small rearrangements in the best material, *Drosophila*, and many more in other material where radiation effects are studied quantitatively. In the next best material, maize, the best preparation of pachytene chromosomes, where the most reliable check is made, does not permit more than one-tenth the chance of discovering small rearrangements that the salivary chromosomes allow. Thus any conclusion on mutation drawn from the number of gene mutations versus rearrangements rests upon a very slender base and is, in the best of cases, weighted in favor of point mutants. Even in the salivary chromosomes the cytological evidence may be deceiving. Kodani (1947) has shown that chromosome tips may contract and a single thicker band be formed out of a series of distinctive bands. This shows that some bands may be compound, and a break within them almost impossible to detect. If we look dispassionately at the cytological facts, we realize that rearrangements might be of any size from almost the whole length of a chromosome to a single band, and even smaller than this in the salivary chromosome containing up to 1,000 bands. Hence, the separation of gene mutation from rearrangement by cytological criteria is completely gratuitous and is only an indication of the limitations of our methods. The problem of whether there is a difference between a radiation-induced mutant and a chromosome break cannot be solved by the direct cytological method. It has to be solved indirectly, from evidence derived from radiation effects.¹⁰

Ernst Caspari in an obituary of Goldschmidt summarized Goldschmidt's views:

. . . In his interpretation of the importance of the position effect, Goldschmidt went much farther than other geneticists of that time since he realized that it made the distinction between gene mutations and chromosomal rearrangements operationally impossible. He abandoned, therefore, the concept of corpuscular genes, ultimate well-defined units of heredity situated in the chromosomes, and substituted for it a pattern of hierarchically arranged series of fields without definite borders inside the chromosomes. These ideas were generally rejected by geneticists at the time but proved to be instrumental in the re-evaluation of the gene concept which started in the late 1940's and is still proceeding.¹¹

The "re-evaluation" of the gene concept to which Caspari refers involves the definition of the gene in terms of a nucleic acid continuum, a concept which is particularly attractive to the new school of biochemists, biophysicists, and viral and bacterial geneticists.

Stadler on the Operational Versus the Hypothetical (Conceptual) Gene

Stadler, in an attempt to resolve the difference separating Goldschmidt and Sturtevant, pointed out the difference between the "operational" and the "hypothetical" gene. He says:

Operationally, the gene can be defined only as the smallest segment of the gene-string that can be shown to be consistently associated with the occurrence of a specific genetic effect. It cannot be defined as a single molecule, because we have no experimental operations that can be applied in actual cases to determine whether or not a given gene is a single molecule. It cannot be defined as an indivisible unit, because, although our definition provides that we will recognize as separate genes any determiners actually separated by crossing over or translocation, there is no experimental operation that can prove that further separation is impossible. For similar reasons, it cannot be defined as the unit of reproduction or the unit of action of the gene-string, nor can it be shown to be delimited from neighboring genes by definite boundaries.

. . . The inferences from this evidence provide a tentative model of the hypothetical gene, a model that will be somewhat different in the minds of different students of the problem and will be further modified in the light of further investigation.

The term gene as used in current genetic literature means sometimes the operational gene and

sometimes the hypothetical gene, and, sometimes, it must be confessed, a curious conglomeration of the two. The resulting confusion may be strikingly illustrated in seemingly contradictory statements by two such gifted and clear-sighted geneticists as Richard Goldschmidt and A. H. Sturtevant. Goldschmidt, after reviewing the evidence on position effect, states that genes do not exist, or at any rate that the classical theory of the corpuscular gene must be discarded. Sturtevant, citing the evidence that chromosomes are regionally differentiated, that particular regions are necessary for particular reactions in the organism, and that these particular regions behave as units in crossing over, states "These propositions . . . prove the existence of genes."

Goldschmidt is essentially correct if, by the gene, we mean the hypothetical gene, and the particular hypothetical gene that he has in mind. His positive conclusion that the gene does not exist is prone to mis-interpretation but apparently means only that this hypothetical gene does not exist. His contention that the properties commonly ascribed to "the classical, corpuscular gene" go far beyond the evidence is, I think, fully justified.

Sturtevant is correct if, by the gene, we mean the gene of the operational definition, since this implies no unproved properties. If it were true that there are no discrete units in the gene-string, Sturtevant points out, the most direct way of establishing the fact experimentally would still be by studying the properties and interrelationships of these distinguishable regions. These are the genes of the operational definition.

[Stadler, like Goldschmidt, has considered seriously some of the difficulties involved in attempting to establish that a gene is actually an indivisible unit. He says:]

A second assumption, or group of assumptions, is concerned with the possibility of distinguishing gene mutation from gene loss. It was originally supposed that induced recessive "visibles" could safely be considered gene mutations, on the assumption that all genes were essential to survival. This was contradicted by various instances of cytologically demonstrable deficiencies viable in haploid tissue or in hemizygous individuals, or viable as homozygotes in diploid individuals. Such cases were relatively few, but since both the cytological and the genetic criterions of deficiency approach the limit of their range of effective application as the deficient segment becomes smaller, there is reason to suspect that physical loss may be responsible for observed mutations also in cases in which deficiency cannot be demonstrated. As we have become better acquainted with individual genes and their functions, the assumption that genes, as a rule, are individually essential to life has lost its plausibility.

Mutation to an intermediate allele is sometimes considered evidence against loss mutation. This involves another assumption, that of the unitary nature of the gene—an assumption made consciously and with careful consideration in the early development of gene theory, but one that must be seriously questioned in the light of later evidence. It is only on the hypothesis that multiple alleles are variant forms of a single unit that we may exclude the possibility of their occurrence by loss mutation. On the hypothesis that they represent different mutations in a complex of closely linked genes, we could account for mutation to different levels by the loss of different segments of the chain.

The "compound gene" is in a sense a contradiction in terms, for the hypothetical gene is unitary by definition. But the genes identified in our experiments cannot be made unitary by definition. . . . there might be many cases in which the segment of the gene-string identified experimentally as a single gene might actually be a cluster of genes of identical or similar effect.

The notion of the compound gene, or some equivalent unit, may prove to have significance, since there may be special relationships among the clustered elements that mark them off as a group from adjoining unrelated elements. One of these may be interrelationships in gene action between the clustered elements which could lead to the occurrence of position effects when members of the cluster are separated by crossing over or translocation. This may be a basic factor in the explanation of position effect in general.¹²

Stadler could find no clarifying concept nor any method for dealing with the "complex gene." Stadler represented the older generation of geneticists who thought of the gene as a discrete particle. But the geneticists of the younger generation, who think of the gene as a nucleic acid continuum have ignored Stadler's injunction that an operational definition is critically important. They begin with the assumption (which they consider to be a self-evident fact) that the gene is a segment of a nucleic acid molecule in which adjacent genes may or may not overlap. But I think this basic assumption is invalid because it includes the implicit assumption that "genes" in viruses and in higher organisms are homologous.

More Than One Gene at the Same Place

The "white-eye" gene (p. 24) is located at a "distance" 1.5 crossover units from "yellow. There are more than 10, nearly 20, different eye color genes located at the same distance from yellow. It is assumed that they are all at the same "place." This phenomenon is inferred to mean that there are a large number of different kinds of defects all of which can lead to the failure of the gene to produce the normal eye color. This view is supported by the experimental fact that a hybrid carrying two different defects located at the "same" place on the chromosome produces defective and not normal eyes. If both defects were at different places, only separated by an immeasurably small distance, then each

defect should be corrected by the normal gene or the other and the hybrid should be a normal individual. But the doubly defective hybrid is defective like the parents. We have seen that Goldschmidt has argued with great cogency that one may not be able to demonstrate that a given gene is the "ultimate" gene. Morgan argued that the multiple-defect-of-one-gene phenomenon could be proved to be the result of a change in only one gene, but Stadler showed that Morgan's arguments were fallacious. The phenomenon of multiple-defects-at-one-place is called "multiple allelism" and is currently the most important problem in genetics. The new generation of biochemists believe that they have a solution to this question on a biochemical basis. I do not concur in this belief because my own work contradicts their views; I will present my arguments later (p. 81). But first it will be instructive to consider the views of the gene based on the very recent biochemical studies of nucleic acid.

Nucleic Acids

Stadler belonged to the generation of geneticists who thought of the gene as a discrete, possibly a protein, particle. But many geneticists of this generation think of the gene as a nucleic acid continuum and begin with the assumption that the gene is a nucleic acid molecule. Chromosomes contain proteins and two different kinds of nucleic acids, DNA and RNA. RNA exists in small concentrations in the chromosome and in much larger quantities in the cytoplasm. But DNA synthesis and chromosome replication are closely connected, and many biochemists, biophysicists, and viral and bacterial geneticists believe that the DNA in the chromosomes is the nucleic acid which is primarily concerned with the transfer of hereditary information from one generation to the next.

DNA is a duplex molecule; the two halves of the long molecule are complements of each other. The union of the two complementary halves along the center line is fragile and the molecule can be split along this center line. The split produces two nonidentical complementary halves. Each half can serve as a pattern upon which the original double strand can be reconstituted. The components of nucleic acids are called "nucleotides." The nucleotides of each half can attract a set of complementary nucleotides from the milieu to reconstitute two new double-stranded nucleic acid molecules.

This precise and completely unexpected mechanism which made it possible to produce two "new" (daughter) individual molecules by longitudinal splitting from one "old" (parental) molecule has seemed to many scientists so precisely identical to the phenomenon of reproduction of chromosomes that the DNA molecule has been called the "unit-of-life"—the "living-molecule," etc., and has therefore been considered to be parallel to the gene which had also been called the "unit of life" or the "living particle."

Proponents of the nucleic acid concept of the gene propose that the chromosome is a linear continuum of DNA. They hold that crossing over occurs only between any two adjacent components of the nucleic acid—"the nucleotides." On this theory the arrangement of nucleotides in the nucleic acid comprises a "code" which carries the hereditary "information"; the only "particle" is the nucleotide.

The Nucleic Acid Molecule and the Gene

Morgan said the gene was probably a particle about 0.2 microns in diameter made up of protein. The disdain in which this view is held by biochemists is nowhere more clearly shown than in Pontecorvo's writings. He holds that the gene is a nucleic acid. The concept of the nucleic acid gene is stated by him with exceptional clarity:

The most obvious wrong idea on its way out is that of the particulate gene, i.e., of the genetic material as beads on a string in which each bead is an ultimate unit of crossing over, of mutation and of specific activity. This picture was not merely crude: it was wrong because it implied an unnecessary, and almost certainly nonexistent, structural differentiation between the beads and the string. . . . What has replaced it is the picture of a nonrepetitive linear sequence of building blocks of only a few different kinds, the unique grouping of which determine unique functions. Each of these functions we now call a "cistron."

The analogy of the genetic material with a written message is a useful commonplace. The important change is that we now think of the message as being in handwritten English rather than in Chinese. The words are no longer units of structure, of function, and of copying, like the ideographic Chinese characters, but only units of function emerging from characteristic groupings of linearly arranged letters. Miscopying has now become misspelling: a mistake in letters or in their order, not usually a mistake in words. In this analogy, letters correspond to mutational sites exchangeable by crossing over, words correspond to cistrons, and misspellings to mutations. When the confusion of the present transitional period will be over and when knowledge about the primary functions of the genetic material will be sounder, we may be able to use again the term gene without danger, both for the group of mutational sites, the function of which is to determine the amino-acid sequence of a protein, and for the function itself.¹³

This statement tells us what the gene is not and suggests that the gene is related to mutational sites and proteins, but follows the general trend in failing to provide a specific, quotable definition.

The Cistron

A new nomenclature has been developed to apply the concept of the gene to nucleic acid. Readers of scientific work outside their specialty usually accept new words uncritically, especially if the author says that the word specifies some kind of "unit." A scientist not skilled in physics may have a vague idea of the basis for assuming that the electron is the "unit of electricity"; therefore, when physicists speak about "protons," "mesons," "photons," etc., he assumes that they are speaking about terms which can be demonstrated experimentally and which have some meaningful relation to reality, although he may have no idea how the demonstration was achieved. Physicists and philosophers have accepted the gene, postulated by biologists, in this uncritical manner. As a result of his study of the inheritance of viruses, Seymour Benzer has invented several new words for the "gene" and its components: the "cistron," the "recon" and the "muton." Benzer has defined the "muton" as the smallest "unit" of mutation and the "recon" as the smallest "unit" of recombination, on the hypothesis that the gene is composed only of nucleic acid. Benzer's new words have been accepted with the readiness in which most workers accept technical terms which they do not understand. Caspari has implied that this new approach is consistent with Goldschmidt's ideas of genetic structures, but there is a significant difference between Benzer's and Goldschmidt's concepts: Benzer's units are smaller than the Mendelian gene, while Goldschmidt argued that any "unit" of heredity must be larger than the Mendelian gene. Goldschmidt considered the whole chromosome to be an individual, integrated, indivisible unit.

The cistron of a virus comprises a particular region of the nucleic acid of the virus which renders the total virus nonfunctional if a loss or defect occurs in the region. A cistron comprises one continuous region within which overlapping defects or losses produce the same defect in any one of a group of closely related, "sister," viruses. The test for the identification of a cistron is operationally indistinguishable from the test by which *Drosophila* workers identify more than 15 different genes which control a variety of different eye-colors and which numerical analyses show to be located at the "same place" on the chromosome. The test resembles the test for allelomorphism of genes, but this operational similarity does not equate genes and cistrons.

Pontecorvo stated that the genome is a "nonrepetitive linear sequence of building blocks of only a few different kinds, the unique grouping of which determine unique functions. Each of these functions we now call a 'cistron.' " It would seem better to call the region controlling the function a cistron. The concept derived from bacteriophage genetics has been applied more or less uncritically to the concept of the gene of higher organisms; unfortunately, genes of higher organisms are now called "cistrons" by many workers, but this careless interchange of terms is particularly deplorable since neither term has been adequately defined. The basic confusion in concepts is that the "gene" of Benzer is a divisible unit while the gene of Morgan and Sturtevant is an indivisible unit. Some workers feel that the change in attitude is comparable to the change from the concept of the atom as unsplittable to the modern concept of nuclear physics.

Diffusion and Interaction of Gene-Products

Benzer's definition of the cistron is based on the observation that certain hereditary particles can only produce a normal organism if one or more of them are in "tandem" in a single strand. Sturtevant discovered that interactions often occur between the different adjacent genes which appear to control a specific function as the result of the diffusion of gene-products from one gene to its adjacent partner in the same strand. Demerec and Hartman discovered a series of linked genes which effect an assembly-line synthesis and this phenomenon is most easily understood if one considers the interaction to involve the diffusion of gene-products from one locus to the next. Benzer defined a "cistron" as a region of a virus in which hereditary factors located near or adjacent to each other are involved intimately in a single function and which are nonfunctional if communication between them is broken. It is difficult logically to separate Benzer's definition of the cistron from the phenomenon in which two specific genes in *Drosophila* interact only when they are in the same chromosome. Benzer would have called two such genes one single cistron in spite of the fact that the *Drosophila* genes are actually two separate "genes" and even occupy different bands on the chromosome. Because the word "cistron" is based on interactions between hereditary units, "cistron," whatever it means, should not be substituted for "gene." It is difficult to see how one can logically use the phenomenon of interaction as a basis

for defining any hereditary unit because functional interaction occurs not only between different genes but also between adjacent components of the chromosome which may be either genic or nongenic. Heterochromatin is a kind of nongenic substance on a chromosome, but when it is placed in juxtaposition with a gene of known activity, heterochromatin may produce a marked change in the activity of the gene. Thus, a piece of heterochromatin and its adjacent gene would have to be called a cistron according to Benzer's definition and the concept of the cistron would then include both genic and nongenic components. If a cistron is defined as a unit which controls a specific function by the interaction of separable parts, then the concept could apply equally to separable sections of the chromosome, or even to the entire chromosome (or the entire genome) as Goldschmidt would certainly insist.

The Virus-Gene Concept

The early history of virology was marked with acrimonious dispute concerning the question of whether a virus, like a bacteriophage, was "living" or merely a by-product of biological activity. Recently the pendulum has swung to the opposite extreme and many biologists have identified viruses with genes. In fact, the bacteriophage virus is now believed by many to contain in excess of 20 separate genes. An intense and extraordinarily popular program aimed at describing the "fine structure of the gene" is based on the hypothesis that the virus is a gene-containing parasite operating in the cell by a mechanism indistinguishable from the mechanism of gene-action and diverting the metabolism of the host to its own uses by a positive act of enzyme synthesis.

This hypothesis of the "genic" nature of viruses was the natural outcome of the current conventional view held by many Mendelists that the gene is the only living material and, hence, that only genes are "self-duplicating." It has been proposed (1) that the nucleic acid in the virus is the homolog of a chromosome carrying genes, (2) that since the parasitic virus "chromosome" contains only nucleic acid, genes in higher organisms are composed only of nucleic acid, and hence, (3) that a knowledge of the structure of the nucleic acid in a virus would be knowledge of the "structure" of the gene.

Pirie has suggested that viruses "(1). . . can be the extreme form of degeneration of micro-organisms so that, from merely being able to multiply in a host, they have become totally parasitic and dependent on the host's synthetic systems. (2) They can arise in a cell when, as a result of an aberration in metabolism, it produces a structure robust enough to withstand normal scavenging processes, and able to act as a model for further synthesis. (3) They can be structures with qualities similar to those needed in possibility (2) but coming into the cell from outside—from another species, for example.

"Of these three possibilities (1) and (3) are probably the most generally accepted. The possibility that anything similar to the viruses we now study was a stage in the evolution of more elaborate organisms, though often touted, need not be taken seriously. Present-day viruses demand so much from an environment before they can multiply in it that they are improbably components of the pre-biotic world."¹⁴ Pirie's pronouncement that substances like viruses need not be considered seriously by those interested in the origin of life must have been made with his tongue in his cheek, because he is only too well aware of the fact that the basic hypothesis which directs the scientific activities of most of the foremost geneticists and biochemists of the present time is founded on precisely that assumption.

Accessory Chromosomes

An important indication that the gene is much more complicated than a simple nucleic acid is supplied by the B-chromosome of maize. The B-chromosome is conventional in appearance and contains nucleic acid like a normal chromosome but carries no genes. It is probably not a maize chromosome but one which drifted into the cell by an illegitimate pollination. Once established in the cell, it was duplicated synchronously with the other chromosomes because the cell supplied all the necessary components for its reconstruction as well as the enzymes which assemble them into the chromosome. The B-chromosome, like all chromosomes of higher organisms, in contrast to the virus, is more than a strand of nucleic acid; it contains a great variety of other materials, including at least two kinds of proteins and at least three kinds of nucleic acids—one kind of DNA comprising what is called the "heterochromatin" and another kind making up the "euchromatin," as well as the nucleic acid called RNA. The B-chromosome also contains other conventional localized structures necessary for its transmission from cell to cell.

There is a prevailing conviction that the "fine structure of the gene" may be revealed by genetical

and biochemical analysis of the viruses, but a complete analysis of the organization of the nucleotides in the euchromatin of the B-chromosome could not yield any information concerning the structure of genes because it contains no genes.

The Concept of the Gene as a Biological Entity

The gene was first recognized by Mendel as a particle transmitted to the offspring by the sex cells, but he also suggested that it came to expression by a factor which led to the production of a character. Although it is often said that a factor or a character is transmitted to the offspring critical use of the terminology should be more restrictive; it is the Mendelian particle which is transmitted and neither the factor nor the character; the latter appears as a result of the presence of the particle. With the advent of biochemistry the purely biological aspects of the problem have been more clearly specified, and it is now generally thought that each gene or Mendelian particle produces its specific character because it controls a capacity which leads to the production of a specific enzyme; hence, the "factor" of Mendel has become the enzyme of present-day biochemistry.

The gene, like the species, is a biological entity which the practical working biologist recognizes without difficulty in living material with which he is familiar. But the gene and the species have both evaded definition by biological theoreticians for the same fundamental reason: A species of yeast (or bacterium) is clearly not equivalent (as a species) to a species of, for example, *Oenothera* or *Drosophila*. There is a hierarchy of different kinds of species and although each species is clearly enough differentiated with regard to its immediate relatives, it is difficult, if not impossible, to equate a species in one genus to a species in a widely different genus. It seems reasonable to suppose that the hereditary genetical particles distributed among the different living organisms from viruses to man also exist in a wide hierarchy of categories, and that a "gene" of one phylum is quite different from a "gene" of another phylum or the "gene" of a virus.

This view would presume that genes in cellular organisms are much more complex than the hereditary apparatuses of viruses. The locus, the factor and the phenotype in higher organisms involve a mechanism so complex that it might better be called a gene-system than a gene. Even within a single species (see above) there are fundamental philosophical difficulties in defining a gene. Practically no textbook of genetics, and only a few geneticists, have attempted to define a gene, and in those instances in which definition has been attempted, the author has usually found himself hopelessly involved in the difficulties of distinguishing the gene as a conceptual or an operational object. The attempts at conceptual definitions have led implacably to frustration and the operational definitions have produced only philosophically sterile repetitions of the experimental procedures.

Morgan proposed that the gene was a large protein molecule which could undergo alteration but which could not be changed by crossing over. Hence, Morgan's particulate gene was a structure, sensitive to mutagenic agents, but not divisible by crossing over. Goldschmidt criticized this view as illogical and incapable of being specified. Goldschmidt held that the phenomenon identified as gene mutation did not result from changes in the "genes" but from changes in the arrangement of what one might call "hereditary" materials. The proponents of the nucleic acid gene disagree with Goldschmidt's view because the present theory suggests that the interaction between the different gene products is probably not a major factor in effecting changes in the genome. The nucleic acid chemists, like the proponents of the particulate gene, believe that the differences in the enzymes which are controlled by the gene is the principal item which distinguishes the different genotypes; but they agree with Goldschmidt in considering the chromosome to be a continuum separable at almost any point by crossing over.

It seems probable that the difficulties involved in discussing genes may derive from the possibilities (a) that the genes in higher organisms may involve many more elements than the primary particles which were first envisioned, (b) the hereditary gene-like apparatuses, especially those in viruses which have been used as models, may represent only fragments of the extremely complex genes of higher organisms. Most of the recent speculations concerning the nature of genes have derived from the biochemical studies of nucleic acids and the genetical analysis of viruses. Attempts to apply concepts of hereditary particles in viruses to more complex organisms have led to the proposal of an extremely involved, and generally untestable, hypothesis concerning the mechanism of gene-action.

For more than half a century, biologists have groped for a concept of heredity by concentrating on attempts to understand the nature of Mendelian hereditary particles. Recent biochemical advances have indicated a direct relation of hereditary particles to enzymes and have made great advances in the approach to a biochemically specific concept, but many difficulties still stand in the way of achieving the final object,—an acceptable definition.

FOOTNOTES

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The Autonomy and Interaction of Genome and Plasmone

The Universal Cytoplasm; Unlike Reciprocal Hybrids in Flowering Plants; Cytoplasmic Autonomy in Mushrooms; Autonomy of Plasmone in Mosses and Mosquitoes; The Inter-Action of Genome and Plasmone; Heritable Changes in Nuclei Induced During the Development of a Multi-Cellular Animal; Differentiation into Germinal and Somatic Nuclei Effected by the Cytoplasm; The Dilemma of a Mendelist in Dealing with Cytoplasmic Inheritance; Graft Hybrids in Paramecium; Goldschmidt's Reaction to Boveri's Experiments with *Ascaris*; The Acquisition of New Characters by Infections of Various Kinds; Went's Theory of Asexual Introgression.

The Universal Cytoplasm

The cytoplasm is a clear, limpid fluid, the composition of which is completely unknown; it contains many particulate structures, which can be separated by centrifugation and which are currently the subject of intensive study, but the clear fluid in which these bodies are suspended is still one of the major biological mysteries. The nucleus is suspended in the cytoplasm together with a variety of other cell organs, or organelles, such as mitochondria, chloroplasts and microsomes. But biological activity does not occur in the absence of cytoplasm; cytoplasm, and cytoplasm alone, is the *sine qua non* of life. Although some theorists favor the view that genes or nucleic acids are the prime movers in biological processes, neither genes nor nucleic acids can carry on any biological process in the absence of cytoplasm. Cytoplasm is to the biological universe what space is to the physical universe. It is the all-pervading, essential background against which all living activities are manifested. It is so universally present that many biologists have ignored it, just as many physicists ignored physical space before Einstein. It is principally the German geneticists, led by Correns, Renner, Harder, Michaelis, von Wettstein, and Oehlkers, who have studied the inheritance of cytoplasmic characters. The Germans make a clear distinction between the genome (the totality of the genes in an organism) and the plasmone (the totality of the cytoplasmic components of an organism) and they have demonstrated the autonomy and interactions of both of these major components of the protoplast in many experiments.

Unlike Reciprocal Hybrids in Flowering Plants

The 3:1 ratio is the device for identifying different genes in a family; the principal device used to identify different cytoplasms is the production of nonidentical reciprocal hybrids. If the egg of one hybrid comes from species A and the sperm from species B, while the egg of the corresponding hybrid comes from species B and the sperm from species A, the two hybrids are said to be "reciprocal." For example, the ordinary mule is the offspring of a mare (female horse) and jackass (male ass). The reciprocal hybrid, the offspring of a female ass and a stallion is rare, first, because the mule is a work animal and the gestation in the small jenny (female ass) means that a smaller animal will be produced, and secondly, because size relations between the two animals make both mating and delivery difficult. In reciprocal hybrids made between individuals of different species, most of the cytoplasm in the hybrid comes from the mother because the sperm (or pollen) from the father transmits almost no cytoplasm. Hence, although each of the interspecific reciprocal hybrids contains the same chromosomes, i.e., half are from one species and half from the other species, the cytoplasm of the species is that of the maternal parent. The working mule carries horse cytoplasm.

Peter Michaelis studied the reciprocal hybrids between two species of flowering plants, *Epilobium hirsutum* and *Epilobium parviflorum* (Fig. 11). When a female parent is *hirsutum*, that is, when the hybrid nucleus grows in *hirsutum* cytoplasm, the plant is only a few centimeters tall. In the reciprocal hybrid, the same hybrid nucleus (carrying the same genes, half *hirsutum* and half *parviflorum*), lives in

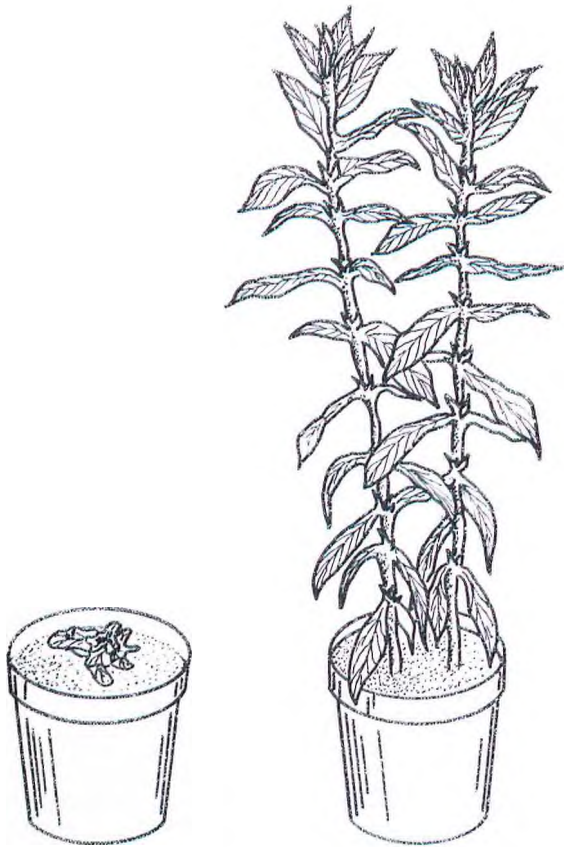


Fig. 11. Two of Michaelis's nonidentical reciprocal hybrids. In the left pot the hybrid nuclei are growing in *hirsutum* cytoplasm; in the right pot the identical hybrid nuclei are growing in *parviflorum* cytoplasm. The same genes produce different plants depending upon which cytoplasm is used.

parviflorum cytoplasm and produces a plant 50 centimeters tall. Thus, the reciprocal hybrid proves that *hirsutum* cytoplasm is different from *parviflorum* cytoplasm. It is important to remember that the nucleus is the same in both hybrids. That is, both hybrids receive the same genes but these genes are carried in different cytoplasms. The persistence of the different effects of the unlike cytoplasms in the cells of the unlike reciprocal hybrids for the hundreds of cell-generations necessary to produce a mature plant shows that the cytoplasm carries autonomous (so-called self-replicating) hereditary factors.

Mendelian theory holds that if reciprocal hybrids are different, the differences are due to a delay in the dilution of gene products present in the maternal egg cytoplasm. Sturtevant has proposed that unlike reciprocal hybrids in which the maternal cytoplasm seems to play a dominant role in differentiation of two types like those described by Michaelis, are due to a delay in the expression of the genic characters of the father. Such a proposal might explain unlike hybrids in which the difference disappears after a few generations, but this hypothesis does not explain Michaelis's demonstration that some differences in the cytoplasm persist for more than ten generations when the hybrids are back-crossed to the male parent—a condition in which the maternal cytoplasm maintained itself in all succeeding generations without "diluting out." Generally, reciprocal hybrids appear to be nearly identical, but this may be because hybrids can usually be made only if the differences between the cytoplasms are minimal. Where the differences between the cytoplasms are really great, as they probably are between different genera or different families, no hybrids can be made and, hence, no data are available. The kinds of reciprocal hybrid which produce two viable and fertile offspring like those studied by Michaelis, are relatively rare.

Cytoplasmic Autonomy in Mushrooms

Richard Harder carried out some experiments in which he made mixtures of different cytoplasms without really making hybrids. In Harder's experiment, one haploid culture "acquired" a new character by introduction of a different cytoplasm. Harder studied two different cultures of a mushroom; (1) one culture comprised an A nucleus living in A cytoplasm and (2) the other comprised a B nucleus living in B cytoplasm. When mushrooms fuse to form hybrids, the fusion of the cytoplasms occurs first and the fusion of the nuclei is delayed until many cell generations after fusion of the cytoplasms. The first step in hybridization produces a structure which contains one separate A nucleus and one separate B nucleus in a mixture of A and B cytoplasms. In this species of mushrooms, both parents contribute equal amounts of cytoplasm. The A and B nuclei remain separate; the nuclei do not fuse to form a single hybrid nucleus as they did in Michaelis's experiments with flowering plants. Harder removed one of the two separate nuclei by microsurgery. This operation can be performed simply with the mushrooms by cutting out the next to the last cell at a time when one of a pair of nuclei is in the "clamp" (Fig. 12). This operation produces either A nuclei in A + B cytoplasm or B nuclei in A + B cytoplasm. The only viable cultures which were recovered were those which carried the B nucleus. Apparently the A nucleus could not survive alone in the mixture of A and B cytoplasm, or only the A nucleus went into the clamp. A and B nuclei in A + B cytoplasm produced a viable culture. When the A nucleus was removed the culture was still viable: in this culture a B nucleus was present in the mixed (A + B) cytoplasms. This made it possible to compare the organism produced by a B nucleus living in A and B cytoplasms with the original B

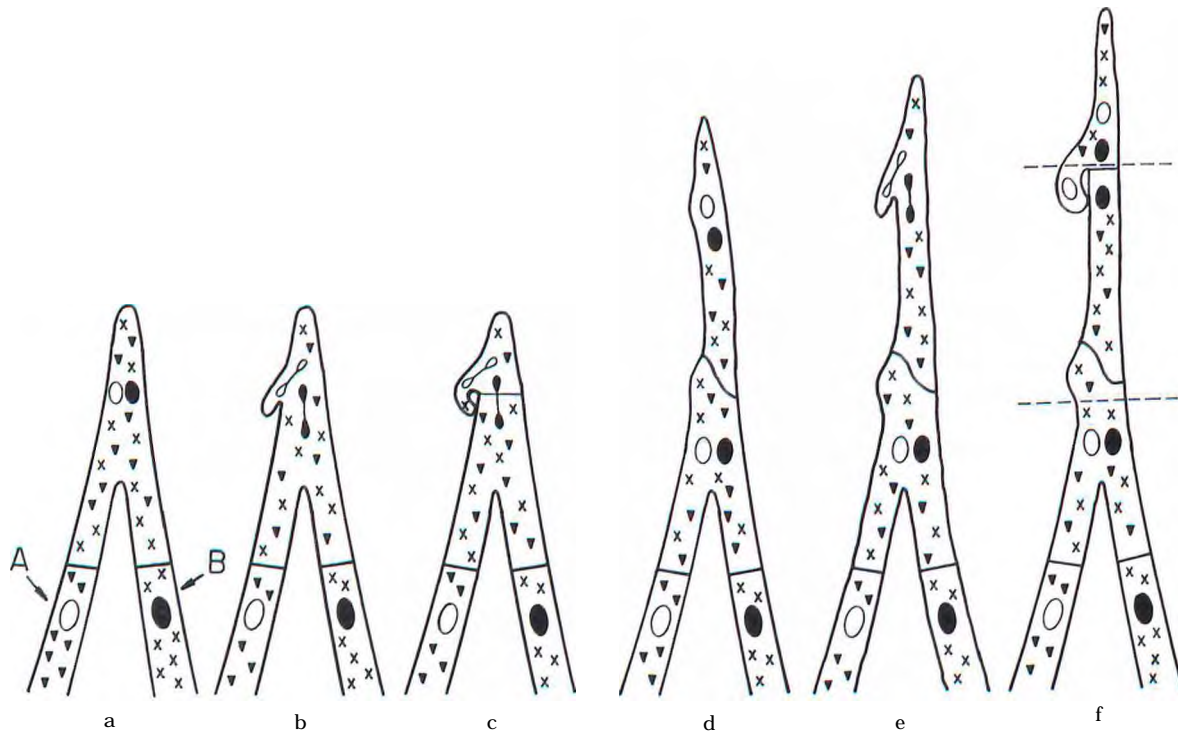


Fig. 12. Harder's experiment with mushrooms. In mushrooms, two different nuclei are associated in each tissue cell instead of a single fused nucleus as in the cells of higher plants. The different nuclei are indicated as white and black, and are designated A and B, respectively. The association is maintained by conjugate nuclear divisions coordinated with wall formation. The total phenomenon is called the "clamp connection." The original gametes may come from widely different sources; the A (white) nucleus and the B (black) nucleus may have been separated for millennia, since one may be collected from Asia and the other from Canada. Even if the separation is not geographical the lines may be very different. Harder tested for differences in the cytoplasm by allowing culture A (with its A cytoplasm, indicated by solid triangles) to fuse with culture B (with its B cytoplasm, indicated by x's). After the fusion was complete and the clamp of the conjugated division was growing out, Harder cut the fungus, shown in f, at the places indicated by the dotted lines. This isolated a single cell containing only one of the two nuclei but containing a mixture of the two different cytoplasm. The experiment made it possible to compare the original culture containing a B nucleus in B cytoplasm with the culture produced by the operation in which the B nucleus was present in A + B cytoplasm. These two cultures were different and the difference was permanent, proving that the A and B cytoplasm differed from each other by a difference which was not controlled by genes.

strain, in which a B nucleus lived in pure B cytoplasm without any admixture of A cytoplasm. These two organisms were different and remained different for years without reversion; thus a permanent, stable, transmissible, hereditary factor had been "acquired" by placing cytoplasm from culture A in a B culture containing a B nucleus and Bcytoplasm.

Autonomy of the Plasmone in Mosses and Mosquitoes

One of the early students of cytoplasmic inheritance, Fritz von Wettstein, worked with mosses. He demonstrated that the plasmone had characteristics which could not be altered by genes from another genus. He inferred (from a series of backcrosses of a hybrid, between two different genera of mosses, to the male parent) that the plasmone of the mother contained autonomous components which were not appreciably affected by exposure to the chromosomes brought into the hybrid from the foreign father. The two species of mosses were indicated as "Pi" and "Hy" respectively. The parents differed in eleven clear-cut characters, and the proportion of the Pi and Hy characters could be followed in the hybrids. The autonomy of Pi-plasmone was tested by backcrossing a hybrid of a Pi (mother) by an Hy (father) to the Hy father for five generations. As the backcrossing continued the hybrid should eventually contain only maternal cytoplasm and only paternal genes. But most of the hybrids retained a majority of the maternal Pi-characteristics through five generations of backcrossing. The genes of the Hy father were incapable of converting the Pi plasmone into an Hy plasmone. In view of the long exposure of the mother's

cytoplasm to the father's genes, it is difficult to ascribe the persistence of the female characters to a "delay" in the expression of the genes from the male. It is more reasonable to assume that the mother's plasmon exerted a positive effect due to autonomous cytoplasmic maternal entities comparable to those in the genome.

An even more impressive example of the persistence of an autonomous component in the maternal cytoplasm of mosquitoes has been provided by Laven. When an Ha (mosquito) mother is mated to an Og mosquito father, 80 to 90 per cent of the eggs are fertile. The reciprocal mating (Og mother x Ha father) produced only sterile eggs. In a series of 52 backcrosses to the father in which the genes of the progeny would be expected to be identical with the parental Og race of mosquitoes, the offspring still behaved like the original maternal Ha race because the progeny were unable to produce fertile hybrids when a male hybrid was mated to a female Og mosquito. The Ha maternal cytoplasm must contain some factor which is transmitted through the cytoplasm of the egg but which could be modified by the paternal genes; this cytoplasmic factor controls fertility between the sperm of Ha and the eggs of Og.

Since the Ha-inhibiting material could persist for 52 generations in the absence of Ha genes, the inhibitor must have been as "self-perpetuating" as the chromosomes themselves. Laven thought that the cytoplasmic factor from Ha might affect the middle-piece of the sperm so that the latter would contain a substance giving an incompatibility reaction with the egg of the other race (Og), but he ignored the possibility that the sojourn of the Og chromosomes in the Ha cytoplasm might have changed the Og chromosomes. At any event it is clear that a Ha cytoplasm carries autonomous components and that delayed action of the Ha genome can be excluded as an explanation.

The Inter-Action of Genome and Plasmon

In summarizing his long study of cytoplasmic inheritance, Michaelis states:

The cell is the unit of life, in which nucleus and cytoplasm form a self-perpetuating reaction system. . . . The first task of the genetic investigator is. . . to differentiate between the various self-perpetuating particles of the cell. . . . During the last sixty years geneticists have analyzed nuclear genes by comparing the Mendelian behavior of certain characteristics with the behavior of nucleus and chromosomes. The field of cytoplasmic inheritance is far less fully explored. In the last few decades it has been possible to demonstrate an independent cytoplasmic inheritance by investigating non-Mendelian characteristics and reciprocally different hybrids. . . . If we now consider the interactions between nucleus and cytoplasm, we can only contrast the nuclear genes with the sum of all cytoplasmic constituents. This sum is designated: plasmon.

Thus, Michaelis contrasts the autonomous genome with the autonomous plasmon, giving each unit an equivalent self-sufficiency. He defines life in terms of the interaction between these two different "reaction-systems." This point of view is clearly a departure from the views of the American Mendelists, Sturtevant, Beadle and Morgan, and equally far from the views of the Russian Michurinists (See Chapter 6) who affirm the autonomy of the cytoplasm and claim that the nucleus can be generated by the cytoplasm. Neither the Russian Michurinists nor the American Morganist-Mendelists quote the German, Peter Michaelis. In his research on the plasmon, Michaelis compared reciprocal hybrids, both with the same genes, one carrying the cytoplasm of one species, the other carrying the cytoplasm of a different species. Since the egg transmits all, or nearly all, the cytoplasm, it is possible to compare different cytoplasms with each other because both reciprocal hybrids produce the same hybrid set of genes in different cytoplasms. Michaelis also investigated the differences between different specific plasmons. He collected a great variety of different species and crossed them with individuals of known nuclear composition. He continues:

. . . In all cases in which the nuclear component of the cell has been varied by introducing different nuclei, these nuclei also changed the extent of reciprocal differences. It therefore appears that all the genetic components of the cell induce independent primary reactions, but that the most essential reaction-chains of the cell arise through interaction of nucleus and cytoplasm.

. . . during the systematic search in the collection several species-hybrids were found with a remarkable instability of the plasmon. Cytoplasms which had been absolutely constant in other crosses for more than 20 years, and 20 backcross-generations produced in these species crosses numerous cytoplasmic alterations by plasmon-segregation. [Michaelis has inferred that the instability of the plasmon is due to the irregularities of multiplication of the organelles of the plasmon]. . . . As a working hypothesis I assume that in normal genome-plasmon combinations (1) the multiplying of plasma-genes and plasma organelles is correlated with the multiplying of nuclear genes and cell division and that (2) the distribution of cytoplasmic units during cell division proceeds in an orderly fashion. In other genome-plasmon combinations this coordination is apparently broken and a segregation of plasma units is possible by irregular uncoordinated multiplication by an irregular distribution.!

Similar inferences have been made in the study of the cytoplasmic organelles in yeast which supply the cell with biological energy by consuming oxygen. Under some circumstances, these particles multiply at different rates from the nuclei. If the temperature is either too high or too low, the coordination between the process of division of the cell and the division of the respiratory organelles may result in the loss of the respiratory organelles. Michaelis assumes that the irregular distributions of the plasmonal organelles led to the variability of the plasmone in the highly variable hybrids. He has also made the interesting observation that changes in gene action and genic characters may occur under the influence of foreign cytoplasm. Therefore, he says that the activity of the gene depends as much on the cytoplasm in which it is found as on the gene itself. [See the B-chromosomes, Chapter 4 p. 41.]

Heritable Changes in Nuclei Induced During the Development of a Multi-Cellular Animal

After an egg is fertilized, the fertilized cell divides to produce an embryo containing thousands of cells. It has long been known that after the first division both cells are equivalent or totipotent, since separation at this point will produce identical twins. Briggs and King, at the University of Indiana, performed a number of experiments in which they planted single nuclei, extracted from the cells of developing frog embryos, into single unfertilized eggs after they had removed the nucleus coming from the mother. Their objective was to discover if a nucleus produced by fusion of a sperm and egg nucleus could initiate a new animal in a denucleated egg and, secondly, if the nuclei, as they divided to produce thousands of new cells, undergo heritable change during the process of growth and differentiation of the embryo. They found that the first hundred cells or so, produced by seven or eight consecutive divisions, were equivalent, since the nuclei could be transplanted into denucleated eggs and produce identical "twins (?)." But after more divisions, they found that the nuclei taken from specifically determined regions and transplanted into denucleated eggs could not produce normal embryos. The later the stage of development of the embryo which supplied the nucleus, the fewer denucleated eggs that received these "differentiated" nuclei developed normally. Briggs and King concluded that the nuclei in different cells of the embryonic frog, in different kinds of tissues, become persistently differentiated, in spite of the fact that these nuclei possess indistinguishable chromosomes. The differentiation of the nuclei was expressed by the limitation of the capacity of the transplanted nuclei for carrying out the processes which the nucleus, produced at the first fusion, was fully competent to accomplish. Only one difficulty is involved in this interpretation; it is not possible to exclude the possibility that some cytoplasm in which an inhibitory substance had developed had been transferred with the nucleus. A control would require the demonstration that the cytoplasm from a cell did not inhibit the normal development of the fertilized egg.

Differentiation into Germinal and Somatic Nuclei Effected by the Cytoplasm

Paramecium is a microscopic animal which has often been called a "single-celled" animal. It would be better to call it "acellular" because it is highly differentiated and the differentiation of different regions is related to differences in the density of the cytoplasm. The cortical cytoplasm, just inside the outer membrane, is viscous while the internal cytoplasm is fluid. Each organism contains two nuclei: the macronucleus and the micronucleus; the former is the somatic nucleus; the latter is the germinal nucleus which produces the sexual nuclei preceding sexual fusion between two paramecia. Somatic gene-controlled characteristics of Paramecium are under the influence of the genes in the macronucleus. After fertilization, two identical fusion nuclei are formed in the animal; one is near the anterior end of the cell, and one is near the posterior end. It is the cytoplasm in which the nuclei come to rest at this stage in the life cycle which determines whether they will become somatic or germinal nuclei. Sonneborn disturbed the relative positions of the nuclei in the cell by centrifugation and found that the fate of the nuclei could be changed by changing their positions. But once a nucleus has become either germinal or somatic by the exposure to the cytoplasmic environment, this changed characteristic is thereafter inherited through all subsequent cell divisions. This is a demonstration of an environmentally acquired character which persists indefinitely through vegetative multiplication.

The Dilemma of a Mendelist in Dealing with Cytoplasmic Inheritance

Dr. Tracy M. Sonneborn of Indiana University is a dedicated biologist who has spent his entire career in extraordinarily productive research on the protozoan Paramecium. He is an extremely active

biologist with a large staff and spends a full working day at the bench. There are few, if any, biologists with a better knowledge of, a deeper devotion to, or a greater enthusiasm for the organism which they have chosen to study. Sonneborn is also a deeply indoctrinated Mendelist. It is inevitable that a worker as familiar with a living organism as Sonneborn is with *Paramecium* should encounter many cases of cytoplasmic inheritance. Hence, it is interesting to observe his reaction to these phenomena. Indoctrinated Mendelists, less well-acquainted with their material than Sonneborn, usually ignore cytoplasmic inheritance when they encounter it, considering it an experimental deviation of minor importance. Sonneborn has not disregarded the phenomena but has attempted, at the sacrifice of logic, to fit them into the Mendelian concept. The extent to which he has gone to reconcile experimental facts to the theory of the gene is demonstrated by his attitude toward what he calls "nucleo-cytoplasmic integration." In *Paramecium*, two animals fuse and finally form two zygotes, which, like Michaelis's hybrids, comprise two different animals with precisely identical nuclei. The animals fuse because their cytoplasms are different. One cytoplasm is called type VII; the other is called type VIII, but the nuclei, after sexual fusion, which are embedded in the different cytoplasms were originally exactly identical, being descended from identical parental nuclei.

Usually cytoplasm is not exchanged during fusion, only nuclei are exchanged, but if the fusion is prolonged, some cytoplasm passes into the type VII cell from the type VIII cell; then the descendants of the originally type VII cell become type VIII cells. If cytoplasmic exchange does not occur, the conjugated cells separate and each remains, respectively, type VII and type VIII and produces type VII and type VIII descendants. Since the two nuclei were originally identical, this is clear proof that the cytoplasm determines the change from type VII to type VIII. But if the vegetative somatic nucleus disintegrates in a cell which has been changed by cytoplasmic transfer from type VII to type VIII, a new vegetative somatic nucleus will be formed; then the descendant cells revert from type VIII to become type VII again.

Sonneborn begins by saying, ". . . if the type of cytoplasm is not autonomous, but is under nuclear control" [but this first premise is obviously fallacious because it is clear that the cytoplasm could not be under nuclear control, because both nuclei were originally identical], "the type VIII cytoplasm should be replaced by type VII cytoplasm in the presence of type VII nuclei" [but there is no such thing as a "type VII nucleus"; the nuclei in both type VII and type VIII cells were originally identical. One might speak of a nucleus which had resided in type VII cytoplasm, but not of a "type VII" nucleus] "and the new macronuclei formed after autogamy should be determined for type VII." [But there is no evidence that the macronuclei are "determined for" either type VII or type VIII. The macronuclei are all identical. All that happened is that a cell which had been changed by the addition of some type VIII cytoplasm from type VII to type VIII became type VII again after an extensive nuclear reorganization. Although type VIII cytoplasm entered the zygote, there is no evidence that all the type VII cytoplasm had either left the cell or disintegrated. During the period of reorganization some particles of autonomous type VII cytoplasm, which had been swamped out by the type VIII influx, multiplied rapidly enough, in its own special cytoplasmic background cytoplasm, to overcome the preponderance of type VIII cytoplasm which had entered from the type VIII cell. It should be kept in mind throughout this discussion that what Sonneborn mistakenly calls "type VII and type VIII nuclei" cannot be so designated since they are identical.]

Sonneborn continues: "The latter regularly happens. The type VII animals produce type VII progeny after reorganization of the nuclei. . . . The originally present type VIII cytoplasm has apparently been replaced by type VII cytoplasm. The cytoplasmic component in the system of mating type determination is thus ultimately under nuclear control."² This final inference is obviously invalid, since there is not the slightest evidence of nuclear control, but only of almost complete control of the cytoplasm over the nucleus.

Sonneborn's example does not pose the dilemma that he implies. It is not a question of "Which came first, the chicken or the egg?" but a clear case of cytoplasmic autonomy and control of differentiation of the nucleus. That the egg came first is perfectly obvious to any biologist, although it might be a confusing problem for a poultryman engrossed in the day to day minutiae of dealing with eggs and chickens. The residual type VII cytoplasm which was temporarily dominated by the type VIII cytoplasm fared better during nuclear reorganization than the type VIII cytoplasm and replaced the type VIII cytoplasm with type VII cytoplasm.

Graft Hybrids in *Paramecium*

If there is some question (as there obviously is in Sonneborn's mind) about the autonomy of the mating type specificity carried in the fluid cytoplasm of *Paramecium*, this should be completely dis-

pelled by the evidence of the autonomy of the solid (cortical) cytoplasm which he discovered in his sensational graft hybrids of *Paramecium*. The cytoplasm in *Paramecium* is divided into (a) solid cortical cytoplasm that is polarized and precisely oriented and that imbeds and stabilizes certain units which are organized into larger organelles, such as the gullet and (b) the fluid cytoplasm which is in the center of the organism. In the process of sexual fusion, two entire individual *paramecia* (each of which is a complete, acellular, integrated organism, differentiated into characteristic, functional regions) use with each other. Each is called a conjugant. When the sexual act has been completed the two conjugants normally separate cleanly and precisely along the line joining the surfaces (the mouth surfaces) which had just previously been fused and each becomes an exconjugant. This technical term is applied equally to each participant in the sexual act. Each exconjugant is now a hybrid in terms of the nuclear apparatus but there is normally no exchange of solid cortical cytoplasm and very little, if any, of the fluid central cytoplasm. But if one of the conjugants had been treated with antiserum previous to fusion, the union is much firmer and the separation is not always so precise. When the two exconjugates separate, sometimes one carries with it a piece of the cortical cytoplasm belonging to the other. The bit of cytoplasm comes from a functional part of the body (soma) of the other conjugant and is grafted onto the partner by the serum. Thus, one exconjugant is short of some of its essential operating equipment while its expartner is doubly equipped with the corresponding part. Since the copulation is mouth-to-mouth, a part of the mouth region is involved in this mutual loss and gain. When an exchange of cortical cytoplasm occurs the first division of the winner (the loser is now out of the picture) is delayed, apparently to adapt to the added load of new material, and instead of taking place within 12 hours, requires two days. But then it becomes apparent that the winner is the recipient of a graft which has provided it with an extra mouth and an extra gullet, both of which develop side-by-side. In fact all the structures on that side of the body are present twice. In addition, the characteristic arrangements of the rows of cilia, immediately to the left and right of the duplicated section, are also present to the immediate left and right of both duplicated sections. The rest of the body is single, and on the opposite side of the body there is but one set of organelles. The small transplant of cortical cytoplasm has led to the development of a complete double set of organelles on one side of the body with all of the normally associated structures. The new type of animal reproduces true to type. These experiments prove conclusively that the cortical cytoplasm of *Paramecium* is autonomous and support the argument that the fluid endoplasm which was capable of modifying the nuclei (see the previous section) is likewise autonomous. In discussing cytoplasmic inheritance, Sonneborn says:

. . . the question of whether the cytoplasm contains any self-perpetuating properties. . . has been long debated. . . . It has had its ups and . . . downs. On the whole the downs have been predominant. . . . This possibility should now be taken seriously in all such cases in the light of our new work on *Paramecium*. . . . We seem to have to reckon here with a previously overlooked aspect of cell heredity.

Sonneborn's statement is unbelievably naive but is characteristic of the shocked surprise of an indoctrinated Mendelist at a demonstration of cytoplasmic integrity in his own material. His frank amazement demonstrates the insularity, the isolation, and the lack of communication between him and the great German School which repeatedly demonstrated the autonomy of the cytoplasm since Boveri's first epochal paper in 1887. All previous demonstrations are belittled by Sonneborn to the level of "debates" and the demonstration which he has seen with his own eyes is so unbelievable to him that it is surprisingly described as "a previously overlooked agent of cell heredity." It seems to him that for the first time the subject can "now be taken seriously in the light of our new work on *Paramecium*." It is ironic that Sonneborn, who was a member of the Committee for Scientific Freedom which opposed the teaching of Lysenkoism (see p. 61), should have demonstrated an authentic graft hybrid, thus confirming Lysenko and refuting Winkler's (see p. 61) argument that graft hybrids cannot be produced.

Goldschmidt's Reaction to Boveri's Experiments with *Ascaris*

Back in the horse-and-buggy days, when everyone was familiar with the fact that horses suffered from intestinal parasites, the horse-worm, *Ascaris*, was one of the principal objects of cytological research. In 1887, Th. Boveri wrote a monumental paper on *Ascaris* in which he showed that the germinal cells carried two large, deeply-stained chromosomes. These chromosomes broke up into many smaller chromosomes in the somatic cells, and much of the deeply-staining chromatin simply dissolved in the cytoplasm. Goldschmidt and Lin, in 1947, showed that the chromatin which dissolved

was heterochromatin. Sturtevant remarked that Boveri's work on the autonomy of the cytoplasm did not succeed in influencing Morgan, and it is clear that even Goldschmidt, who repeated Boveri's observations with the help of Lin, did not interpret the phenomenon in terms of the autonomy of the cytoplasm. In other instances, Goldschmidt did accept evidence of cytoplasmic autonomy, indicating that his uncertainty concerning Boveri's work was not due completely to indoctrination. The discussion of Boveri's work is quoted directly from Goldschmidt's classical treatise, *Theoretical Genetics*.

Cytoplasmic influence upon chromosomal behavior is well known since Boveri's work on chromatin diminution. Here the location of the nucleus in one or another kind of cytoplasm, visibly differentiated during oogenesis, determines whether or not the chromosomes will undergo diminution (p. 290).

... If we take examples like *Ascaris* diminution or the germ-track cells of insects, discussed earlier, there can be no doubt that the differentiation of the oöplasm (egg cytoplasm), which controls nuclear features, has been brought about by processes taking place during oogenesis under the influence of the nucleus (p. 239).

It is Goldschmidt's phrase "under the influence of the nucleus" which implies (as Sonneborn also insists) that it is the nucleus which first changes the cytoplasm and the changed cytoplasm which then alters the nucleus. It is simpler to assume the autonomy of the cytoplasm; Goldschmidt's choice of the alternative is improper and due only to his indoctrination which ascribes all transmissible change to changes in genes.

The repetition and extension of Boveri's classical observations by Goldschmidt and his associates did not change his opinion: In the horseworm the chromosomes in the cells of the sex-organs are completely different from the chromosomes in the cells of the rest of the body, i.e., in those of the soma. The sex-organs contain only two chromosomes per cell, one of maternal and one of paternal origin. Each of these apparently single chromosomes is actually a multiple chromosome composed of many small chromosomes joined end-to-end. It is important to emphasize here that in every *Ascaris* that has ever existed as an *Ascaris* one must infer that the kind of chromosomal organization has persisted in an unbroken germ-track lineage, ever since it was first established, for many millenia and over countless *Ascaris* generations. It seems possible that the germ track may have become isolated in animals because (1) the germ track is sensitive to change by viral infection and transformation and (2) the integration and balance of animals is so extremely delicate that protection of the germ track is required for survival. This view is related to Goldschmidt's proposal that the genome has changed but little over long periods of time in the total number of genes but has been altered more by rearrangement than by addition or subtraction. Each end of the long sex-organ chromosomes is composed of an enormous mass of heterochromatin, i.e., genically inert chromatin. After sexual fusion is complete, the cells which go to the body lose the heterochromatinic ends of the chromosomes and the rest of the chromosome breaks up into a number of smaller chromosomes, each of which has its own centromere. (But the cells assigned to the sex organs do not change at all.) The heterochromatinic segments are lost in the body cells because they have no centromeres but the small chromosomes, each with its centromere, are now transmitted from cell-to-cell in the body sans heterochromatin. The isolation of the germ track, and its differentiation from the soma, is nowhere more clearly exemplified. The interesting aspect of Goldschmidt's interpretation of this phenomenon, with which he was so completely familiar, is his inference that it could only be explained by assuming that the changes produced in the chromosomes were under gene control.

... In a number of animals (*Diptera*, *Copepoda*, *Sagitta*, *Ascaris*) the part of the egg cytoplasm which will later supply the cytoplasm of the germ-track cells is already visibly different in the unfertilized egg (predetermined). It may be safely assumed, though it cannot be proved, that this differentiation, which takes place during oogenesis, and all other predeterminations found by experimental embryology are under genic control just as in maternal inheritance. Actually, here the cytoplasmic conditioning becomes visible in the production of stainable substances, the "germ-track determiners" which stay strictly within the future germ-track cells in subsequent development. From Boveri's classic work on chromatin diminution in *Ascaris* we know that the conditioned cytoplasm in this organism even affects the behavior of the chromosomes. ... Thus we have a lasting cytoplasmic function of a determinative nature, once the cytoplasmic difference is established (p. 199).⁴

Goldschmidt says "once the cytoplasmic difference is established" and implies that the difference is established by the nucleus. But there is no evidence that the nucleus has been implicated, and it is simpler to assume an adjustment in the cytoplasm of autonomous organelles to each other.

There is no difference between the phenomenon which Boveri reported in 1887 and that which Sonneborn described 73 years later, in 1960, as a "previously overlooked agent of cell heredity."

The Acquisition of New Characters by Infections of Various Kinds

The Aggrandizement of the Genome by Viral Infection. Those who are interested in religious debate often argue that pain is a capacity of humans and other animals that God should not have created. But it is clear to any biologist that the capacity to feel pain is a biological capacity essential to survival, since only by pain can an organism with capacity for movement avoid the stimuli which would otherwise prove fatal. One might suggest that infectious viral disease is also a mechanism essential to the long-term survival and adaptation of the species since it provides a means of aggrandizing the genome. In a viral infection the parasite lives inside the cytoplasm (or inside the nucleus) of the host cell. (In bacterial infections like tuberculosis, or scarlet-fever the bacteria live between the cells and cause disturbances by growth or by the production of by-products.)

Viruses that are relatively slightly virulent and that produce long-lasting chronic infections (sometimes transmissible through the sex-cells) are occasionally difficult to distinguish from bona fide cellular organelles. And the strange and unexpected phenomenon of transduction has lent another dimension to the importance of viral disease. Viruses may actually pick up a gene from one host and transmit it to a second host. Hence, since both humans and weasels are susceptible to influenza, the possibility of transferring weasel genes to humans and vice versa must be considered seriously; the hybridizing of weasels with humans is actually conceivable, and the number and variety of genes in both species may be increased by the genetic communication established by a common viral infection.

One might suppose that the survival value of susceptibility to viral infection might be the biological basis for the abundance of virus diseases current among plants and animals today. This is the Age of Virus Plagues comparable to the Ages of Mitochondrial, Chloroplastal, and Ribosomal Plagues of about a billion years ago.

The Aggrandizement of the Genome by Transformation. Bacterial geneticists have shown that genes can be altered by treatment with what is supposedly purified nucleic acids. This concept is exceptionally important, since it suggests that hereditary genic materials may be transferred from one organism to another, and from one species to another, in a state of nature by the disintegration of the cells of a donor species in the neighborhood of a recipient cell of a different species. This makes it possible for one to conceive of the widest possible kind of hybridizations as well as the rapid transfer or acquisition of hereditary characteristics to or from the most diverse kinds of living organisms. Among the lower, and possibly higher, organisms the disintegration of a cell may produce a material which could act like a sperm to produce a new kind of hybrid.

The Aggrandizement of the Plasmone by Viral Infection. There are two kinds of viruses characterized, respectively, by the nuclear (DNA) and the cytoplasmic (RNA) nucleic acids. The phenomenon of transduction is induced by a living virus containing DNA; the phenomenon of transformation is induced by chemically pure DNA. The cytoplasm contains a number of organelles called ribosomes which contain cytoplasmic nucleic acid (RNA). It seems reasonable to suppose that the cytoplasmic organelles had their origin as infections of the cytoplasm and eventually became integrated components of the plasmone essential to the survival of the organism. Professor Jean Brachet, of Brussels, has recently demonstrated the initiation of the neural fold in amphibians following the inoculation of the embryos with tobacco mosaic virus. This startling experiment shows that a plant virus containing cytoplasmic nucleic acid may be able to initiate differentiation in an animal embryo and suggests that viral infection might have been a factor in the heredity of complex organisms. Dr. Brachet has briefly summarized his discovery in a recent letter which the writer is privileged to quote:

. . . the tobacco mosaic virus work in which you are interested. . . was published in the Bulletin de l'Académie royale des Sciences de Belgique 29, 707, 1945. All I can say is that I grafted crystalline tobacco mosaic virus in the blastocoele cavity of amphibian gastrulae and that it gave rise to neural induction in 70% of the cases (26 out of 37). If the virus was denatured by ethanol and then treated with pancreatic ribonuclease in order to remove RNA, the inducing activity became negligible.

The propagation of a plant virus, which is a coacervate of plant nucleic acid and protein, within the cells of a vertebrate, with the effect of inducing a differentiation, which an experienced embryologist found indistinguishable from the structure characteristic of the initiation of the nervous system, suggests that some of the autonomous cytoplasmic organelles may have been acquired by an infective process. If a cytoplasmic component of plant origin can be added to an amphibian plasmone, then Lysenko's theory of graft hybrids appears to be a very reasonable one.

The Effect on Heredity of Cytoplasmic Parasites. It may be possible that the plasmone is often altered by viral infection and that additions by infection, and subtraction (by the equivalent of recovery from infection), have produced major changes, especially in animals, and are major factors in evolution. One recalls the virus in *Drosophila* which is carried in the cytoplasm and renders the fly hypersensitive

to CO₂ and the Dauermodifikation which Jollos and Goldschmidt discovered, which was induced by heat treatment to change the shape of the wing and was transmitted through the cytoplasm.

Sonneborn discovered a cytoplasmic character which was acquired by infection. The kappa character in the protozoan *Paramecium* is produced by a parasite which renders an infected organism poisonous to noninfected ones, thus giving the infected organism a competitive advantage. The kappa character is transmitted in the cytoplasm from generation to generation (not by the nucleus) and is certainly inherited, although not on a Mendelian basis, i.e., it will not yield 3:1 ratios. Kappa resembles an extrinsic parasite (a virus) more than an intrinsic organelle (like a chloroplast). The difference between intrinsic and extrinsic organelles becomes vague and unclear, however, when we consider them from an evolutionary point of view. Chloroplasts (which are not essential to green plants) must at one time have been extrinsic, but the association of host and parasite was so advantageous to both that it has persisted and flourished. The differences in the cytoplasms described by Michaelis could be due to parasites specific for certain species which have finally become integral components of their species. These various examples are only slightly different and show that stable autonomous structures are present in the cytoplasm and are capable of transmitting "acquired characters." They suggest that it is difficult to distinguish an intrinsic or a true component of the cytoplasm from an extrinsic parasite. Sonneborn's kappa, Michaelis's unequal reciprocal hybrids, von Wettstein's work with mosses and Harder's experiments with mushrooms prove that autonomous hereditary factors capable of effecting changes in character exist in the cytoplasm outside the nucleus.

Went's Theory of Asexual Introgression

Dr. Fritz Went, Director of the Missouri Botanical Gardens, is a man widely travelled and experienced in plant geography and ecology. He is a cultured scientist, trained in the Netherlands in the great tradition of the continental-European academic philosophy. The writer is deeply indebted to Dr. Went for the following direct quotation of his unpublished theory of asexual introgression:

Similarity, or convergence, in leaf and stem characters, anatomical structure, and life form, of many plants native to a particular area, regardless of family or order, has often been observed and recorded. This convergence is usually attributed to selective pressure of the environment, which is supposed to result in the survival of certain specific characters. It is assumed that these convergent characters arose by chance, and being adaptive, were selected for. If these assumptions are correct, then everywhere in the world areas with similar climates should contain plants with similar characters and life forms. This is partly true: chaparral, macchia and mallee vegetations in coastal California, the Mediterranean and Australia occur in similar climates (wet cool winters, hot dry summers), and are physiognomically similar. Thorn shrub vegetation in semi-arid regions is found in Mexico, Brazil and India.

But if we take a closer look at convergence, then we see that as far as morphological and anatomical characters are concerned, there is more a geographical than a climatic correlation. Or in other words: certain characters occur much more frequently in geographically distinct areas. Examples of this phenomenon are: 1) the Eucalyptus-type of leaf (long, elliptical, sickle-shaped, bilaterally symmetrical, xeromorph) is essentially restricted to Australia, where it occurs not only among Myrtaceae (*Eucalyptus*, *Angophora*), but in *Acacia*, *Loranthaceae*, *Proteaceae* and *Bignoniaceae*, whereas these same genera or families in other areas with similar climates do not have Eucalyptus-type leaves. 2) the "divaricato" shrub of New Zealand does not occur anywhere else, and is found there in at least a dozen families (such as *Compositae*, *Leguminosae*, *Pittosporaceae*, *Rubiaceae* and *Violaceae*). With its intricately intertwined branches, long internodes and small suborbiculate leaves it is a most distinctive type of shrub. 3) the rosemary-type of leaf is common among macchia plants of the Western Mediterranean area, whereas the holly-type leaf is common in the Southern California chaparral. These geographically restricted convergent characters are so typical that very often one can guess in which part of the world a particular plant originated.

Since these convergent characters are neither climate-nor family-restricted, the conclusion is inescapable that evolution does not produce different forms in response to climate, but according to the proximity of other plants with similar characters. If sexual gene exchange is possible, introgression (Edgar Anderson) occurs; its frequency is determined by the fertility of sexual hybrids. The numerous cases in which similar characters occur in different genera or families, between which no sexual exchange of genetic material is possible, argues for a non-sexual exchange of genetic material, an asexual introgression.

Went's theory tends to support the Michurinist practice of mixed plantings and inseminations. It indicates that plants grown together, no matter how different they may be, may become similar by asexual hybridization comparable to that described by Harder.

FOOTNOTES

1. P. Michaelis, "The Genetical Interactions between Nucleus and Cytoplasm in *Epilobium*," *Experimental Cell Research*, Suppl. G, 23G-251 (1958).
2. T. M. Sonneborn, "Patterns of Nucleocytoplasmic Integration in *Paramecium*," *Caryologia*, Vol. suppl., 307-325 (1954).
3. T. M. Sonneborn, Nucleo-Cytoplasmic Interrelations, an address to Ninth Poultry Breeders Roundtable, C Me ago (April 30, 1961).
4. R. B. Goldschmidt, *Theoretical Genetics*, University of California Press (Berkeley and Los Angeles, 1955).

CHAPTER 6

Michurinism As A Biological Philosophy

The Current Conflict in Russia; Michurinism; The Optimistic Idealism Inherent in Dialectical Materialism and Its Effect on Biological Theory; Lysenko's Scholastic Attack on Mendelism; The Rivalry Between Breeders and Geneticists; The Use of Grafts to Preserve a Commercial Variety; Lysenko's Experiments with Graft Hybrids; Sinoto's Experiments with Graft Hybrids; The Significance of Michurinism as a Biological Philosophy.

The Current Conflict in Russia

The dispute between Michurinists and Mendelists in Russia had its origin in the struggle for power in which Lysenko, a disciple of the Russian horticulturist, Michurin, ousted Vavilov, a Morganist-Mendelist, who had previously directed all genetical and horticultural research in Russia. The removal of Vavilov and his tragic death in Siberia led to a highly emotional reaction against Lysenko in which much of the emphasis, especially in the U.S.A., was placed upon the "rightness" of Mendelism and the "wrongness" of Michurinism rather than upon the "wrongness" of using political procedures to liquidate a scientific opponent. An attempt will be made to examine various aspects of the controversy without undue consideration of the emotional complications, to clarify the pronouncements which have been made on Michurinism by the Russians, and to consider their significance both in relation to the conflicts between the Michurinists and Mendelists in Russia and to the conflicts between the proponents of nuclear heredity and the proponents of cytoplasmic heredity in the Western World. Lysenko appears recently to have lost most of his power, not because of disapproval of his methods either scientific or political, but simply because the younger generation of Western biochemical geneticists has managed to open up lines of communication with the younger Russian biochemists and has achieved a rapport in viewpoint that excludes all "old-fashioned" attitudes.

Michurinism

The fundamental principles of the dominant American concept of nuclear heredity (Morganism-Mendelism) have been considered in considerable detail in Chapter 3, and in Chapter 5 the theories of cytoplasmic heredity originating in the Western World have been examined. The principles of Michurinism, or Russian genetics, favor the theory of cytoplasmic inheritance, but Michurinism has not been so clearly defined as the Western theories of either nuclear or cytoplasmic heredity and Russian genetics has not considered at all the enormous amount of data accumulated by non-Russian biologists which favors theories of cytoplasmic inheritance.

Michurin was a plant breeder, a contemporary of Stalin, who participated in Bolshevik revolutionary activities and became an official hero of the Revolution because of his attempts to improve horticulture in the Soviet Union. His philosophy of plant breeding was the philosophy common to all plant breeders before the advent of Mendelism. He believed that a plant grown under favorable conditions grows well and transmits to its seedlings the ability to grow even better, hence that the size, for example, due to increased fertility of the soil, controlled by the gardener, would lead to a change in the seeds which would enable the seeds from a plant grown under conditions which produced a large plant to continue to produce large plants.

The principles of Michurinism were enunciated by T. D. Lysenko in an address delivered July 31, 1948, but it is difficult from Lysenko's address to extract principles much more precise than those in the preceding paragraph.

The following excerpts are from Lysenko's address:

We, . . . contend that the inheritance of characters acquired by plants and animals in the process of their development is possible and necessary. [Neither here nor elsewhere are "inheritance," "acquired," or "characters" defined and these omissions give the concept a vagueness which has not been

subsequently rectified. It is difficult to understand what is meant by "necessary" and no explanation was offered.] Michurin's teaching, expounded in his works, shows every biologist the way to regulating the nature of plant and animal organisms, the way of altering it in a direction required for practical purposes by regulating the conditions of life, i.e., by physiological means.

[This direct claim made in 1949 (more than sixteen years ago) states that the experimental breeder can accomplish anything he proposes to do. Since it is obvious that the Michurinists would want at least to quadruple the yield of Soviet agriculture and since they have obviously not attained this end it seems clear that Lysenko expected more than he could deliver.)

His studies and investigations led I. V. Michurin to the following and important conclusion: "It is possible, with man's intervention, to force any form of animal or plant to change more quickly and in a direction desirable to man. There opens before man a broad field of activity most useful for him."

[This claim is repeatedly made, but generally without other specifications, and usually without examples.

For example, the increased yield of hybrid corn over the pure bred stocks can be specified in bushels per acre. Or the increased size of a mule over the mare and the ass that produced it can be specified.

But such data are never given.] . . . changed germs of newly generated organisms always occur only as the result of changes in the body of the parent organism, as the result of direct or indirect action of the conditions of life upon the development of the organism or its separate parts, among them the sexual or vegetative germs. [This statement seems to say that no organism shows any change unless there has been a change in the soma of the parental organism due to an effect of the environment. In other words, the only kind of an effect that can be transmitted is one that has already occurred. But it is an unusually vague statement and characteristic of the generally flowery and indefinite language used in the pronouncement.] Once we know how the heredity of an organism is built up, we can change it in a definite direction by creating definite conditions at a definite moment in the development of the organism. [This is a direct and unambiguous claim. It states that one can direct the heredity of an organism in a predetermined manner. That is, one may specify an increased yield of one hundred or four hundred percent and achieve this objective. It is clear that Lysenko has failed to make good this claim.]

. . . In the union of plants by means of grafting, the product is a single organism with varying strains, that of the stock and that of the scion. By planting the seeds from the stock or the scion it is possible to obtain offspring, individual representatives of which will possess the characteristics not only of the strain from which the seed has been taken, but also of the other, with which it has been united by grafting.

Obviously, the scion and the stock could not have exchanged chromosomes of the cell nuclei; yet inherited characters have been transmitted from stock to scion and vice versa. [He means 'by the cytoplasm alone."] Consequently, the plastic substances produced by the stock and the scion, just as the chromosomes, and just as any particle of the living body, possess the characters of the strain, are endowed with definite heredity.

[This claim states that graft hybrids have been produced. It is of interest because it is the only claim supported by data and will be examined in detail later. But it is clear that it does not exclude Mendelism because it states that the "plastic substances" act "in the same way as chromosomes."]

Any characteristic can be transmitted from one variety to another by means of grafting as well as by means of sex. [This sentence is completely false because nuclear (sexual) transmission is certainly a thousand fold easier to demonstrate than transmission by grafting.]

Lysenko also says:

The nature of a vegetable organism may be shaken: (1) By grafting, i.e., by uniting the tissues of plants of different varieties; (2) By bringing external conditions to bear upon them at definite moments, when the organism undergoes this or that process of its development; (3) By cross-breeding, particularly of forms sharply differing in habitat or origin.

By regulating external conditions, the conditions of life, of vegetable organisms, we can change strains in a definite direction and create strains with desirable heredity.¹

This statement makes available to the Michurinist all the techniques available to the Mendelist since it permits other techniques of hybridization. Now, although all breeders of plants and animals, both Russian and American, use hybridization procedures, the breeders never trouble themselves about the purity of the cytoplasm. Hence, effects achieved by hybridization by breeders may involve nuclear hybridizations or may involve cytoplasmic hybridization. Mendelists would insist that only the nuclear hybridizations would yield permanent effects but the evidence of Michaelis and other students of the plasmone makes debate on this subject possible.

Lysenko's statements reveal that Michurinism is a simple, naked, intuitive credo—a belief based on faith and optimism, a hope of what may be achieved rather than the summation of a series of verified experiments. Michurinism is more like a religious revelation of the glorious future than a scientific theory. It is optimism rampant—harmoniously in tune with the Soviet spirit. But the naivete of Michurinism is no deterrent to its use as a basis for experiments. A scientist can pick out each testable proposition and struggle to make order out of the chaos. The scientist's integrity is secure as long as he escapes indoctrination. But it is clear from the tenor of his declaration that Lysenko and the Communist Party demand indoctrination.

If Michurinism actually were a productive hypothesis, that is, if "improvement" by breeding were as easy to achieve as Michurinism claims, one would expect to see evidence of actual, specified accomplishments. Since none has been proclaimed specifically, one is justified if he infers that the proponents of the theory have failed to demonstrate its utility during the past sixteen years that it has presumably been under test.

The Michurinist credo, enunciated by Lysenko, states:

"Knowing the course of construction of the heredity of an organism, it is possible to vary it directly by means of the production of specific conditions at a specific moment of the development of an organism."

One gains the impression that the confidence of the Michurinist in the verity of this credo encourages him to search at random for the "right" combination "of specific conditions at a specific moment" which will produce the desired event. The Michurinist objective of achieving an end result "in a direction desirable by man" is more important to him than the mechanism of heredity itself. But considerable experience in efforts of this kind suggests that more time would be saved by attempting to work out basic principles than by trying random combinations of procedures in hopes of quick success.

In a final summation of his beliefs, Lysenko says:

"Heredity is the effect of the concentration of the action of external conditions assimilated by the organism in a series of preceding generations

This amazing statement is of special interest because it is a perfect translation of the famous statement, made more than fifty years before, by Luther Burbank:

"Heredity is the sum of all past environments."

No mention of Burbank has ever been made by Lysenko although the comparison of the two statements makes it clear that the philosophies of both workers are identical.

The Optimistic Idealism Inherent in Dialectical Materialism and Its Effect on Biological Theory

Dialectical materialism is the Marxian system of logic based primarily on Marx's extreme abhorrence of religious mysticism. It means understanding things just as they are (materialism) in their actual interconnection and movement (dialectics). Marx developed his system in an effort to reduce the mysticism and idealism that constantly threatens to subvert science but both he and Engels had an unconcealed and unjustified optimism in the efficacy of the scientific method which reappears in most Communists' insistence that science can achieve all things. One can almost hear Marx say, in Michurin's own words, "It is possible with human intervention to bring about change in every form of animal or plant. .

Lenin, in his turn, added considerably to the optimism inherent in the concepts of Marx and Engels until modern Communism has begun to assume most of the aspects of a religious philosophy, a concept that Marx would certainly consider highly objectionable. Lenin seemed to have been certain (a) that science could solve all problems, (b) that truth, as such, was attainable, and (c) that reality could be understood by the human mind. When one considers the cynicism of public men and politicians, one may not neglect the possibility that Lenin, unlike Marx and Engels, might not have been sincere in his optimism. He might have been using the dialectic, in its excessively optimistic form, to inspire his followers with the hope and assurance which he may have considered essential to achieve victory. The Communistic politicians and scientists, who accept Lenin's philosophy, are unusually confident that the rules of the dialectic will suffice to make it possible for them to achieve success both in politics and science. Nevertheless, one must admit, when one examines dialectical materialism as originally proposed by Marx and Engels, that many of the strictures against empiricism, mysticism, vitalism, teleology and idealism deserve the most careful consideration of the working scientist. However, the optimistic confidence in the efficacy of its rules, as displayed by present-day Communists, has reduced the capacity of Communists for self-criticism in spite of the paradoxical fact that they continually stress the necessity for self-criticism. The self-criticism practiced by Communists concentrates on the discovery of deviations from the dialectic when only criticism of the dialectic itself will be fruitful. But such criticism is precisely that which is forbidden. It is essential that a scientist have a philosophy to guide him, but the optimism, and the confidence in rules, together with the implied perfection of the dialectic that is characteristic of present-day Communists, comprises a source of mystical and idealistic error more serious than any that Marx sought to avoid; this optimism has limited the objectivity of Soviet science.

A comparison of Mendelism and Michurinism might lead one to conclude that the Mendelists are too empirical and mechanistic and do not rely sufficiently on a generalized philosophy—that they tend to narrowness and a sterile "operational" attitude toward science. By contrast, the Michurinists display a naive optimism, both in the future and in the efficacy of the dialectic to protect them from error, which strongly resembles religious faith. Their unquestioning (or disciplined) acceptance may have led them into a position which may make creative scientific achievement as difficult as it was under the Inquisition. They have continued to follow an armchair genetical hypothesis which has failed to yield the predicted results without any apparent evidence of developing a healthy doubt and without proposing a substitute hypothesis.

Webster's Unabridged Dictionary states that, "Dialectic was defined by Aristotle to be the method of arguing with probability on any given problem and of defending a tenet without inconsistency." Marx repeated the word used by Aristotle, although Marx applied the term to scientific procedures rather than argument. Aristotle's concept of seeking always to avoid, or at least to limit, inconsistency, and his recognition of the limitation of perception, by his accent on probability, provide as useful a set of rules as a scientist could ask for. Aristotle's principles make it possible to avoid the difficulties inherent in dialectical materialism that lead the Communists to speak confidently of "truth" and "reality" and force them to abjure indeterminacy in any form. It is amazing to think that Aristotle's message should be so acceptable after more than two millennia during which long periods of darkness have prevailed.

Lysenko's Scholastic Attack on Mendelism

Lysenko says "It is clear to us that the foundation principles of Mendelism-Morganism are false," and he quotes T. H. Morgan:

"The germ-cells become later the essential parts of the ovary and testis respectively. In origin, therefore, they are independent of the rest of the body and have never been a constituent part of it. . . . Evolution is germinal in origin and not somatic as had been earlier taught. This idea of the origin of new characters is held almost universally today by biologists. (My emphasis.—T. L.)"

Lysenko then quotes W. E. Castle:

"In reality the parent does not produce the child nor even the reproductive cell which functions in its origin. The parent is himself merely a by-product of the fertilized egg (or zygote) out of which he arose. The direct product of the zygote is other reproductive cells, similar to those from which it arose. . . . Hence heredity (that is, the resemblance between parent and child) depends upon the close connection between the reproductive cells which formed the parent and those which formed the child, one being the immediate and direct product of the other. This principle of the 'continuity of the germinal substance' (reproductive cell material) is one of the foundation principles of genetics. It shows why body changes produced in a parent by environmental influence are not inherited by the offspring. It is because offspring are not the product of the parent's body but only of the germinal substance which that body harbors. . . . To August Weismann belongs the credit for first making this clear. He may thus be regarded as one of the founders of genetics."²

These two statements by Morgan and Castle arise from the fact pointed out first by Weismann that shortly after the egg of an animal is fertilized by the sperm, cells are set aside from which the sex organs arise. This reservation of specific cells and their function as the producers of the sex cells tends to isolate the sexual mechanism from the effects of the environment, and this phenomenon is known as the isolation of the germ track. Both Morgan and Castle were primarily zoologists, and, although the germ track is isolated in animals, it is not similarly isolated in plants, and it is clear that Morgan and Castle were both thinking, as Weismann obviously was, of the situation in most animals rather than the situation in plants. In plants the sex cells are not separated from the soma. A vegetative cutting, grown by simply putting a twig into the ground, can produce flowers and seeds, hence the soma can produce sex cells. Lysenko was primarily a botanist and well acquainted with this phenomenon. Morgan and Castle committed a serious error in making the isolation of the germ track in animals an essential component of the theory of the nuclear control of heredity. A very different situation occurs in plants, and even in animals the germ track is not always isolated. But the phenomena of Mendelism are as obvious and clearcut in plants as in animals and the fact that the germ track is protected to a considerable extent from environmental influence in animals and not in plants does not change significantly the phenomena of Mendelism as exhibited in plants and animals, respectively. Hence, Mendelism is a reality independent of the isolation of the germ track. Lysenko, however, bases his refutation of Mendelism completely on two things (1) the importance which Morgan and Castle had mistakenly placed on Weismann's principle of the isolation of the germ track in animals, and (2) his

(Lysenko's) success in the production of graft hybrids in plants. Lysenko makes the following statement:

Michurin's teaching completely repudiates the fundamental position of Mendelism-Morganism, the position that there is complete separation of the hereditary characteristics of plants and animals from environmental influences. [But the germ track in plants (and even in animals) is not "separated from environmental influences," and it is clear that this difference has no effect on the formulation of Morganism-Mendelism.] Lysenko continues: Michurin's teaching does not recognize the existence in an organism of an hereditary substance separate from the body of the organism. . . . A change in the living body takes place as a result of a deviation from the normal type of assimilation and dissimilation, and of a change or departure from the normal type of metabolism.

It is quite clear to us that the fundamental concepts of Mendelism-Morganism are false. They do not reflect the reality of living nature and represent an example of metaphysics and idealism.

The chromosome theory of heredity may seem systematic and perhaps in some degree true, only if we ignore the fundamental ideas of Mendelism-Morganism, and people not acquainted in detail with the life and development of plants and animals may be deceived by it. To refute it, we have only to assume as an absolutely true and well-known fact that the sex cells or rudiments of new organisms are produced by the organism itself, by its body and not by the sex cells from which the mature parental organism arose.

This completely uproots at one stroke all of the systematic chromosome theory.³

Lysenko says that the sex cells arise directly from the soma and quite correctly refutes Morgan and Castle's statement that they never arise directly from the soma. Lysenko is thinking of the "well-known fact" that the sex cells in plants arise directly from the soma. He says that the isolation of the germ track is "the fundamental idea of Mendelism-Morganism," but I have pointed out that this statement is not correct.

It is interesting that Conway Zirkle should select this particular paragraph for the following comment:

Perhaps no paragraph illustrates better than the preceding Lysenko's complete ignorance of scientific methods and his utter lack of intellectual standards. To refute an unwanted theory (the chromosome theory of heredity) he finds it only necessary "to assume" a competing hypothesis "as an absolutely true and well-known fact." QED The hypothesis he accepts is our ancient friend "pangenesis."⁴

But Lysenko is not invoking pangenesis nor is he making an "assumption"; he is merely stating the fact that in plants the sex cells arise directly from the body of the plant itself. In spite of Lysenko's confusing oratorical style, his statement is correct but his argument does not refute Mendelism nor is his the first refutation of the idea that the isolation of the germ track is a general phenomenon since Mendelists themselves had pointed this out long before it had come to Lysenko's attention.

The Rivalry Between Breeders and Geneticists

Relations between the self-trained inventor and the academically-trained scientist have never been good. Edison was usually belittled by physicists and Ford despised college-trained engineers. The reasons for these differences and difficulties are fairly obvious: Academic training, by itself, confers prestige without necessarily guaranteeing merit, and the holder of automatically acquired prestige becomes uneasy in the presence of a self-trained expert who has demonstrated his merit and, thus, challenges the academician at the point of greatest sensitivity. The self-trained expert, painfully conscious of his own deficiencies, usually resents the honor conferred upon his academic competitors; he often looks upon the academically-trained as social parasites. In biology, the plant and animal breeders are often self-trained, but even those who are academically-trained are distrustful and resentful of the prestige, and especially of the sophistication, of the academically-trained geneticist.

The principal reason for the deep antipathy that exists between the breeder and the geneticist is in their different objectives. The breeder tries to "improve" cultivated plants and animals. He selects the "best" he can find and interbreeds in his attempt to produce "better" or more desirable kinds. Although he has a definite objective, he usually has no specific program. He deals exclusively with healthy, vigorous plants and animals and he will have nothing, absolutely nothing, to do with defective plants or animals. Geneticists, by contrast, are interested in the study of inherited defects; purebred defective individuals are mated to other purebred defective individuals. The treasured purebred *Drosophila* are eyeless, of abnormal abdomen, vestigial wing, bar eye, are crossveinless, singed, etc. Geneticists save exactly what the plant or animal breeders destroy or discard.

Although he is contemptuous of the defective plants or animals of the geneticist, the breeder is often intimidated by the sophisticated language of the geneticist. The geneticist, in turn, feels guilty

in the presence of someone who has really improved a cultivated plant, or says he has. It was from (a) the differences which always divide the self-trained and the academically-trained and (b) the dispute concerning the inheritance of acquired characters that the conflict in Russia had its origin.

The Michurinists, like many Western plant and animal breeders, believe that improved nutrition produces offspring more vigorous than their parents; but they have not demonstrated that any changes of this kind are permanent. Lysenko, more than twelve years after he pointed out how easy it was to improve milk production, was still engaged in attempts to increase milk production of cattle by conditioning the mother, hoping to transmit the character to the calves. But other experimenters in Russia have failed to support his view, and this disagreement is freely discussed by the Russians themselves, including Lysenko. The Michurinist attitude is that this kind of experimentation ought to work. The Michurinists are not too interested in the theory; they have set for themselves the limited objective of improving domesticated plants and animals. This accent on practical application is the principal weakness of the Russian approach to biology. Many Russian scientists are seeking for the chance discovery of some application or treatment which will produce an inherited change that will make it possible to improve plants and animals faster than can be achieved with present methods. Mendelian breeders affirm, however, that the only change which will be transmitted through many generations is one produced by genetic modification. They believe that stable changes are only produced by mutations of genes and they concentrate all their activities on changes of this type, usually selecting from already established stocks that have some desirable character and attempting to breed the desirable character into the culture. It was this program which Vavilov was pursuing when he was replaced by Lysenko.

But most gene mutations are defects; for example, albinism is a permanent genetic modification; in albinism the capacity to produce color in the skin is completely lost. Other gene mutations, like the mutation from normal color to albinism, generally involve some kind of loss. A list of the gene mutations in the fruit fly indicates that each mutant is traceable directly to the loss of ability of the fly to produce a structure which had some value to the organism as it existed in nature.

In the newer genetics of bacteria and bacteriophage (bacterial virus), Mendelian research concentrates on defects also. In bacteria and in the fungi the changes which are exploited for genetical analysis usually involve the loss of a specific enzyme which served the organism for the synthesis of an amino acid or vitamin. Thus the history of genetical research involves a long series of losses of capacities which organisms possessed in the wild state and which enabled them to produce a plant or an animal or a bacterium with full vigor and capacity to compete successfully in a state of nature. Even the achievement by a bacterium of resistance to a bacterial virus (which is a common laboratory mutation) involves the loss of a receptor by which the parasite attaches itself to its host. In this instance the apparent increase in vigor exemplified by resistance to disease is not a gain but the loss of ability to synthesize a receptor. One is faced with the paradox that geneticists who affirm that all improvements of plants and animals are due to mutation of genes provide as examples, mutations that decrease the ability of the organism to carry out its normal functions.

Furthermore the "improvement" of plants and animals under domestication often involves the accumulation of defects. For example, a cow which produces an enormous amount of milk is obviously a defective animal by comparison with the normal animal. The increased amount of milk is in excess of the requirements of the single calf that the cow can produce and thus is truly a handicap. Anyone who observes a milk cow, especially one of some age, needs only to note her clumsy awkward appearance and the slow and painful manner in which she drags the enormous udder behind her to realize that her emaciated condition is due to the excessive overgrowth of the udder and the outpouring of most of her metabolic capacity into the production of milk, with a corresponding sacrifice of all the characteristics which would make it possible for her to survive in a state of nature. She cannot jump a fence, or run, or protect herself in any way. Similarly, Indian corn, whose origin as a cultivated plant has been lost in the distant past, is practically unable to grow in a state of nature and can only be maintained because man cultivates it in fields and continually saves and plants the seed himself. If no more plantings were to occur, Indian corn would disappear within a few years. Michurinist "improvements" need to be studied from a philosophical and semantic point of view before the objectives can be clearly defined.

The Use of Grafts to Preserve a Commercial Variety

Lysenko claimed that he had been able to disprove Mendelism and justify the liquidation of Vavilov by his demonstration of graft hybrids in tomatoes. But the discussions of plasmonal heredity in Chapter 5 indicate that Mendelian inheritance and plasmonal inheritance can exist side by side, and

the demonstration of one considered disproof of the other. Lysenko is not consistent because he says in his enunciation of Michurinism that grafting is "as good as," rather than "better than," sex as a means of hybridization. Many Mendelists have argued against the validity of Lysenko's

demonstration of plasmonal heredity and it may be important to consider his experiments in detail. In making grafts a small tree or plant is cut off and a cutting from another plant or tree of the same species, but usually of a different variety, is inserted into the cut surface. For example, all Delicious apples are grafted onto seedlings of some other variety. The plant which carries the roots is called the stock, and that which has been inserted and tied in place, and later grows in that place, is called the scion. Both stock and scion usually preserve their varietal specificity without being affected by the graft.

There is much evidence which suggests that grafts can be made without changing the character of either scion or stock. Red Delicious apples all originated from a single seed. All the red Delicious apples that are grown were produced by grafting direct vegetative cuttings, descended from an original seedling (by cuttings, not by seed) onto any kind of apple stock. No matter what stock is used, the apples on the Delicious scion are Delicious and do not resemble the apples that would have been produced by the stock. If the apples differ, they differ from orchard to orchard as the result of environmental conditions in the orchard and not because of differences in the stocks that are used. Millions of stocks bearing red Delicious scions have been grown. Only by grafting is it possible to preserve the characteristics of the Delicious apple. Plants grown from the seeds in a Delicious apple would not produce the Delicious apples because the chromosomes are reassorted during the formation of the seeds, and the seeds from Delicious apples would produce a very different kind of apple. The same is true of oranges. All navel seedless oranges are the vegetative descendants (since no seeds are produced, propagation has to be by cutting) from a single branch that appeared on a single tree in Brazil. It appeared only once. Millions of scions, descended from this branch, have been grafted onto millions different stocks, and the results are always the same. The navel orange is practically uniform except for conditions that affect the whole orchard. And the same is true of peaches, apricots, plums, grapes, and all the different kinds of apples—Jonathans, russets, McIntosh, etc. The view that no exchange occurs between scion and stock which affects the heredity of either has the support of Winkler, who made a long study of the subject of graft hybrids in 1912 and stated:

It has been proved in a single case that graft symbiosis can change the specific character of either partner in the slightest. No success has been achieved in demonstrating such specific influence through grafting. In other words, modification- or influence-graft hybrids are not possible. This means that the genotypic basis of the organism, the specific structure of its protoplasm, forms a unit of extraordinary stable, unshakeable structure against external factors, even those to which it is exposed by grafting. In the widest sense, the nutrition is powerless to change this basic structure. Neither organic nor inorganic substances of any land are able to penetrate the living cell in suitable amounts.⁵

Although Winkler's generalization was widely held in 1912, there are many experiments, especially with microorganisms (transduction and transformation p. 52) which indicate that the genotype can be changed by substances which "penetrate the cell," (see also Went's theory of Introgressive Hybridization, Chapter 5)

Lysenko's Experiments with Graft Hybrids

Lysenko claimed that he could produce new and improved hybrid plants by grafting one variety onto another. This Procedure was approved by Michurin and conformed with the Communist doctrine that acquired characters can be inherited. Michurin had affirmed that changing the nutrition could change the heredity. He had assumed that one way of changing the nutrition was by grafting. In Lysenko's experiments, he grafted a scion that produced yellow round tomatoes and pinnate leaves onto a stock that produced red ellipsoidal tomatoes and entire leaves. His results are shown in Figure 13. Some seeds from the red tomato-entire leaf stock produced plants that resembled the scion (pinnate leaves and yellow tomatoes). According to Mendelian theory, the stock should only produce seed which would produce red tomatoes. The Mendelists said that Lysenko had not produced a graft hybrid, but that the scion had grown down inside the stock and that some seed had been produced by cells originating from the yellow scion. The Mendelists did not believe that the change in nutrition had changed red tomato cells into yellow tomato cells, but that yellow tomato cells had actually grown down into the stock and produced what they would produce any place—yellow tomatoes. The generally adverse opinion of Lysenko's claims was intensified by the rumor that a British scientist who had visited Lysenko's laboratory claimed that he had detected a fraud in a demonstra-

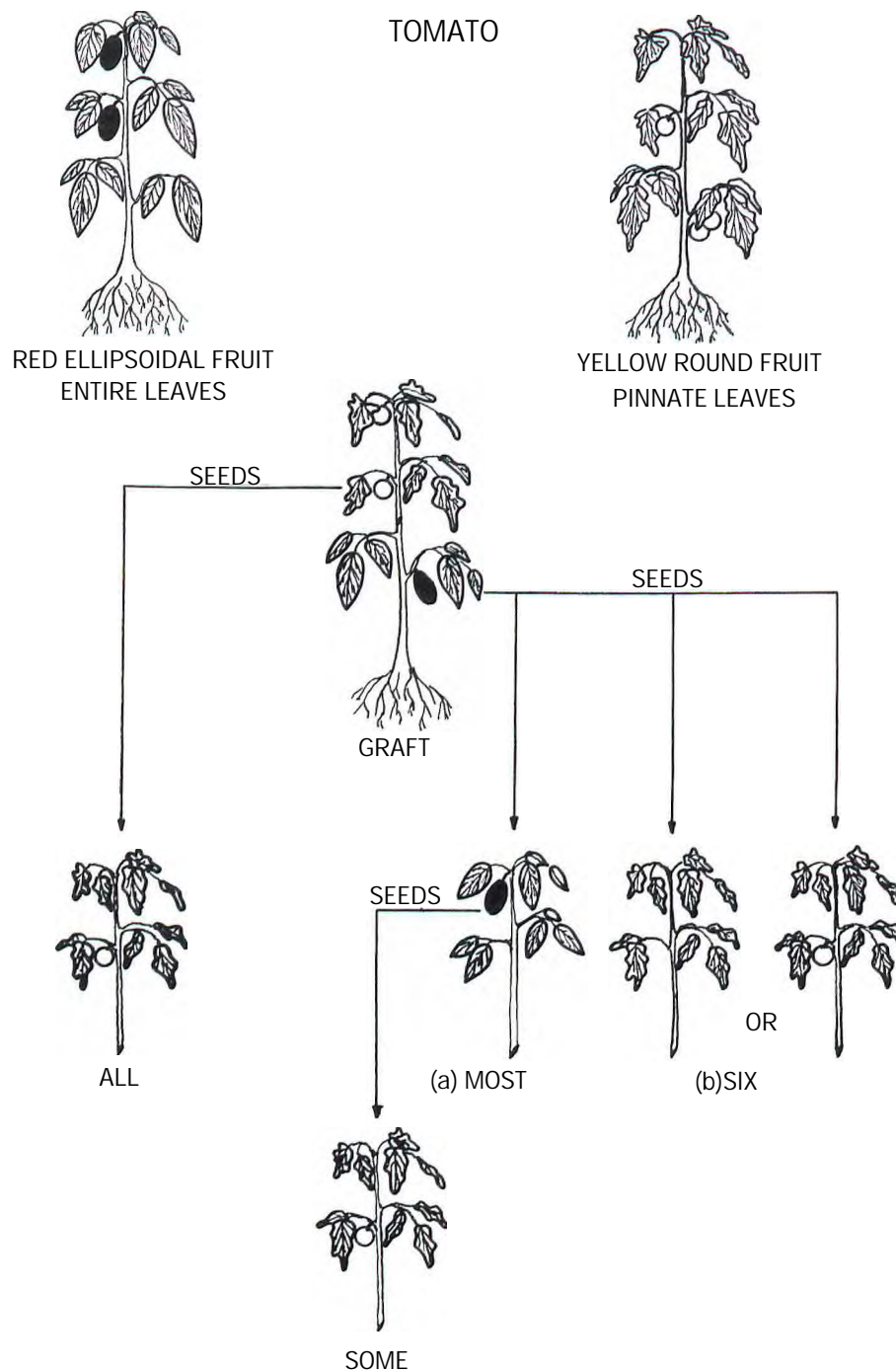


Fig. 13. Lysenko's experiments with graft hybrids in tomatoes.

tion made for his benefit. This event raised many doubts. Lysenko's naivete, his fanaticism, and the fact that so many Mendelists had suffered deeply because of his actions made him the natural butt of the resentment of Mendelists.

When one considers the charge of fraud, one might suppose that fraud could have occurred. Frauds are not too uncommon in science teaching. If one has to demonstrate a complex experiment to students in which the only observable result is the change of a red to a blue color, one can imagine an instructor manipulating the result. But fraud is almost never practiced between two scientists.

Demonstrations often go wrong, but such failures are almost never taken seriously, because experiments have a way of going wrong. It is difficult to imagine Lysenko perpetrating a fraud; it would be so much simpler for him to say that it was not convenient to make the demonstration. Fraud is very rare in science because it is understood that each experiment should be repeatable if the conditions are properly controlled. Critical experiments are repeated and confirmed or rejected by others. If the attempt to repeat an experiment fails, the first reporter is not charged with fraud, but rather with incompetence or over-zealousness.

There were not many attempts to confirm Lysenko's tomato experiments. It was rumored that one prominent American had tried and failed, but a negative experiment generally proves nothing and the American was not a man who had demonstrated an exceptional capacity for experiment. Most indoctrinated Mendelists simply said that graft hybrids cannot be produced and let it go at that. Leo Sachs of Israel also attempted to repeat Lysenko's tomato experiments and failed. If mixtures of two kinds of cells had produced Lysenko's results, as Winkler's experiments suggested, the mixtures were not easy to make. Lysenko's first experiments were reported in 1935, but the American audience was not generally receptive. In general, scientists read a man's work only if they are convinced that the author is a man of integrity, and Lysenko had not then, nor has he yet, convinced the American audience of his integrity. The reaction to Lysenko is based (1) on his political views and (2) on the obvious emotional and political content of his arguments as presented in *The State of Biology in the Soviet Union*. An American might conceivably write a paper and state that he had prayed to God for proper insight into the problem without losing his audience completely, but the remark would certainly prejudice his case in the eyes of most American scientists. If he said that he had relied on George Washington's writings or Abraham Lincoln's speeches for insight, the statement would be rejected forthwith as ridiculous. People outside the U.S.S.R., except for a few Communists, cannot accept the statement that insight into a scientific problem has been achieved by a study of the principles laid down by Marx, Engels, and Stalin. Even the finest scientific data would find an unreceptive audience with such an introduction. No politician, no matter how well respected, would be an acceptable mentor for a scientific presentation to an American scientific audience. Lysenko probably lost his Western audiences through his acceptance of a political mentor. The statement that graft hybrids had been achieved was rejected, or if accepted, explained as the result of the growth of scion into the stock.

Sinoto's Experiments with Graft Hybrids

In 1958, at the International Genetics Meeting in Montreal, Dr. Yosita Sinoto of the University of Tokyo presented some extremely interesting evidence that changed the entire picture concerning Lysenko's graft hybrids. Dr. Sinoto is a thoroughly reliable botanist with more than 30 years' experience and no political affiliations with the Communists. He is aware of the problem of mixed growth, technically known as the problem of the chimaera, and, in his judgment as a botanist and geneticist, chimaeras are not involved in his results. He is a hard-working, serious, nonpolitical scientist, well-trained, circumspect, and a man of the highest integrity. He is also a man of great skill. He used two kinds of eggplants, a black one with a pear-shaped fruit and a green one with a rounder fruit. First, he grafted four black scions on green stocks. The results are shown in Figure 14. The leaves of two of the four graft-hybrids turned purple, and the stock bore black fruit. In the other two grafts no hybridization occurred.

From twenty grafts (Figure 15) of a green-fruited scion on a black stock he obtained sixteen viable plants. In seven of these, the green-fruited scion produced black fruit. Thirty-five seedlings from the black fruit produced ten purple and twenty-five green seedlings.

This illustration supplies an adequate confirmation of Lysenko's experiment by an unbiased experimenter of great skill and integrity. The fact that it was performed with eggplant instead of tomato is trivial. If no one were ever able to perform this experiment with tomato, or had never reported such a result previously, the eggplant experiment would have to be explained. The chimaera explanation is the simplest: Some of the blue cells of the stock had grown up into the scion and penetrated the fruit produced on the scion so that the fruit was made up of both green and purple cells, hence, some of the seeds produced green plants while others produced purple plants. If such mixtures of tissues had occurred, all the old ideas would still be intact, and a painful adjustment of thinking would not be required. But Sinoto states that the possibility that a chimaera was made can be rejected.

If grafting can produce a change which can be transmitted through its seed, it is a phenomenon of great interest. It does not destroy Mendelism, but it does suggest that Lysenko once performed the experiment and supports the Michurinist claim that acquired characters can be inherited. Sinoto's

EGGPLANT

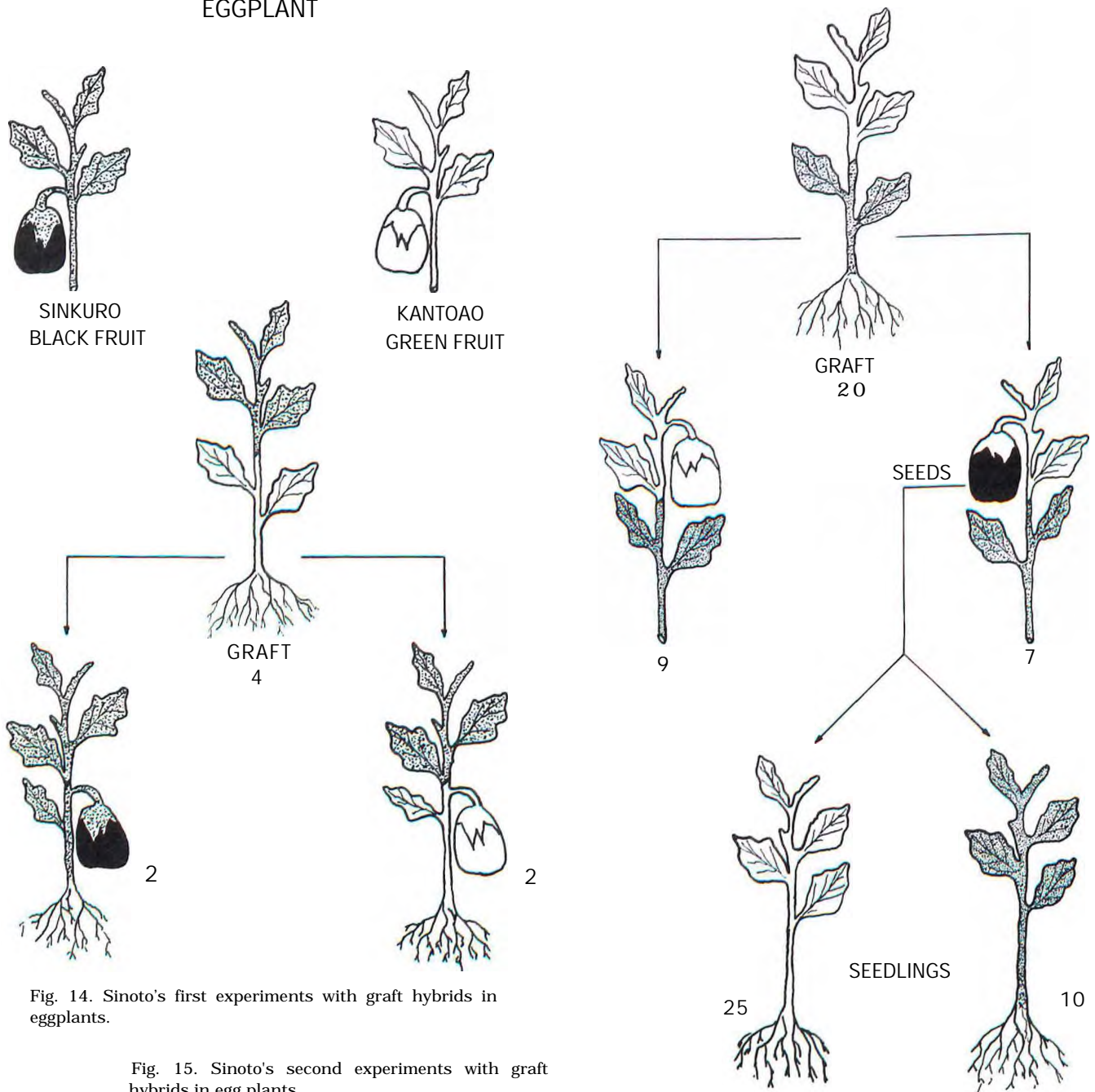


Fig. 14. Sinoto's first experiments with graft hybrids in eggplants.

Fig. 15. Sinoto's second experiments with graft hybrids in egg plants.

experiments must still stand the test of the chimaera theory. If it is demonstrated that the tissue of the scion grew down into the stock or vice versa then Lysenko's views that the stock takes on the hereditary characteristics of the scion by diffusion of substances will not be supported. But we have Sinoto's expert testimony that a chimaera was not produced in his eggplant experiments.

The Significance of Michurinism as a Biological Philosophy

Since any theory is only a tool which should be under the control of the scientist, rather than the converse, one can work at applied biology as fruitfully under Michurinism as under Mendelism. For example, Mendelian doctrine supposes that only the single pollen grain contributes to the heredity of

the hybrid. For this reason, experiments with mixtures of pollen have not been carried out by Mendelists. There are many experiments which Michurinist theory suggests that have not been performed because they are not suggested by Mendelian theory. One value of a theory lies in the possibility that it will suggest new experiments. Glouschenko, one of Lysenko's associates, has shown that pollen mixtures produce results that are different from those obtained by unmixed pollen. Kushner, using the Michurin theory, transfused animals with blood of other varieties to study the effect of transfusion on heredity. He reported some success in effecting temporary changes. Experiments of this kind would not be performed or even thought of by a Mendelist because Mendelian theory suggests that blood transfusion could not possibly change the hereditary condition of an animal.

Pirie, who is distinguished by the clarity of his insight, has pointed out that the real value of Michurinism lies in its exposure of the fallacy of Mendelism. Pirie states:

Empiricism need not be restricted to the subject matter of science, it can usefully be extended to the technique also. Thus experience shows that it is seldom sufficient to oppose a baseless conclusion by the bald assertion that it is baseless, and, therefore, not to be preferred to many of the alternatives. It is more effective to propose a rival though equally baseless conclusion. A wrangle then starts, and in the course of it the correct impression is conveyed that, in the field under discussion, fact and logic are not well founded. Until such a wrangle starts people do not think about fundamentals; they think, and want to go on thinking, that the foundations are sound. In practice, most of us cannot bring ourselves to use the technique of counter-nonsense as a means of getting rid of baseless assumptions or conclusions. In the same way some psychologists believe that childhood frustrations are the cause of much that is useful and productive in a personality and yet may hesitate deliberately to frustrate their children. But we generally lack neither baseless conclusions nor frustrations for long. Thus the most effective agent in forcing general recognition of many points of weakness in the genetical systematizations of Weissman and Morgan was Lysenko's equally unsatisfactory alternative.⁶

FOOTNOTES

- X. Trofim Lysenko, *The Science of Biology Today*. (New York: International Publishers, 1948) pp. 18-40.
2. *Ibid.*, p. 19.
3. T. D. Lysenko, "The Situation in Biological Science," from *Conway Zirkle's Death of a Science in Russia* (Philadelphia: University of Pennsylvania Press, 1949) pp. 107-134.
4. Conway Zirkle, *Death of a Science in Russia* (Philadelphia: University of Pennsylvania Press, 1949) Footnote on p. 109.
5. Hans Winkler, *Untersuchungen über Pforpfbastarde* (Jena: Verlag Von Gustav Fischer, 1912).
6. N. W. Pirie, "Selecting Facts and Avoiding Assumptions," *The Rationalist Annual* (1959) p. 61.

Inadequacy of the Cell Theory in Its Current Form

The Current Cell Theory; Plant Cell Division by Cleavage Plates Versus Animal Cell Division by Central Constriction; Organ Formation by Plant Cells and by Animal Cells; The Cell as a Unit of Structure; The Bud—Cell Division by Extrusion; The Clamp Connection and the Crozier; Cells Inside of Cells; The Plasmodia Within Walls; Evaluation of the Cell Theory; the Cell as a Society of Independent Autonomous Coacervates.

The Current Cell Theory

On any of the current theories of the origin of life, cells must have been recent developments. One may suppose that, previous to the association of the various cellular organelles, there must have been an extremely extended period of precellular evolution. But the cell theory has not yet adjusted to the concept of precellular evolution. Hence, it is important to consider critically the current concept of the cell.

The orthodox expression of the cell theory taught to beginning students in the U.S.A. is clearly stated by Swanson:

The now familiar idea that the cell is the basic unit of life is known as the cell theory or the cell doctrine. Enunciated in 1839 by two German scientists, M. J. Schleiden and Theodor Schwann, the former a botanist and the latter a zoologist, the cell doctrine represented a decisive advance in the development of biological thought which now ranks with Charles Darwin's evolution theory as one of the foundation stones of modern biology. Indeed, we understand life itself only to the extent that we understand the structure and function of cells. As one scientist has so aptly stated: "the cell concept is the concept of life, its origin, its nature and its continuity."

... Most generalizations have exceptions to them which cast doubt on their universal validity. This is true as well for the cell theory, and the viruses in particular present a difficult problem.

Over three hundred different viruses are known. Many of them are the infective agents in such diseases as yellow fever, rabies, poliomyelitis, small pox, mumps, and measles in humans, and peach yellows and tobacco mosaic disease in plants. The plant viruses tend to be elongated structures, the animal ones spherical in shape. If we apply to them our usual definition of a cell, they do not qualify as living organisms. Since they are so minute, we cannot see them except through an electron microscope, but we know that they lack the internal organization normally considered indispensable to a functioning cell. When they exist outside a living cell, they are simply inert molecules, although very elaborate and complex ones that may take a crystalline form. Inside a cell, however, where they are pathological parasites, they are clothed with the characteristics of life: they grow, multiply to produce exact replicas of themselves, and possess a type of inheritance not too far different from our own. They also contain the key molecules of protein and nucleic acid invariably found in every living organism.

Their ambiguous nature has led biologists to describe them in various ways: living chemicals; cellular forms that have degenerated through parasitism; or primitive organisms that have not reached a cellular state. Fortunately, we are not forced to decide whether a virus is or is not a cell, or even whether it is living or nonliving. The biologist generally treats them as if they were individual cells, and recognizes that their extreme simplicity of structure, when compared to a normal cell, makes them ideal objects for certain types of biological research.

Certain protozoa, algae, and fungi also provide exceptions to the concept that the cell is the basic unit of life. They appear to have abandoned the cell as a mechanical and structural unit, although their ancestral forms probably once had cells. The protozoan, *Paramecium*, is seemingly a single cell, but it has a mouth or gullet, contractile vacuoles for the elimination of water and waste, other vacuoles for digestion, and many cilia (fine surface hairs) for mobility. Although the point is debatable, *Paramecium* is probably best thought of as noncellular rather than cellular in nature.

A similar designation can be given to certain algae such as *Valonia*, or *Vaucheria*, or to fungi such as the black bread mold, *Rhizopus*. They are simply a mass of living substance within an outer retaining wall, and it would be difficult to define the basic unit of such living bodies. These organisms, however, are related to cellular forms, so we can speculate that they have simply discarded the usual type of cellular organization for one that is mechanically better suited to their mode of existence.¹

Swanson affirms that the cell is the unit of life and states that this attitude is consistent with the view that viruses may or may not be considered cellular and that they may or may not be considered living. He does not attempt to define life except in terms of the cell. If one defines living material as any material with the capacity to propagate and maintain an orderly nonhomogeneous association of molecules (an autocatalytic coacervate), the definition will include viruses and exclude such things as copper sulphate crystals and clouds.

It is Swanson's treatment of the problem of acellular but more obviously living organisms that reveal his implicit assumption that all life is cellular. He states that the ancestral forms of protozoa, algae and fungi "once had cells" but that they "abandoned the cell as a mechanical and structural unit." This statement is inconsistent with (1) the most modern views of the origin of life and (2) with the great diversity of different kinds of cells. Swanson says that many organisms which are "simply a mass of living substance within an outer retaining wall". . . "have simply discarded the usual type of cellular organization." This statement asserts that life originated in cellular form and can only be conceived of as cellular. It seems more reasonable to support that the enclosure and partitioning of living matter into "cells" did not occur until long after the origin of the kind of life with which we are familiar and that the cell is no more "the unit of life" than the chloroplast, the mitochondrion or the gene. The cell is a highly specialized structure designed to solve the special problem of producing and maintaining a complex morphological structure. Some organisms have developed and survived without producing complex morphological structures. The development of precisely specialized gross morphological tissues and organs is probably a relatively recent event. Some slime molds may weigh nearly thirty pounds without containing a single cell, while a mammal of the same weight is divided into many billions of cells. It seems reasonable to suppose that life probably existed on this planet for hundreds or thousands of millennia and accumulated an enormous mass before the first cell appeared.

Plant Cell Division by Cleavage Plates Versus Animal Cell Division by Central Constriction

The basic assumption of the cell theory is that all cells are homologous; this view is certainly incorrect. The partitioning of the cytoplasm into what are called "cells" occurred many times in the course of evolution. Although there are many different structures which are classified under the single category of "cells," the nuclei which they contain are all very similar. The similarity in the structure of the chromosomes, their centromeres, the spindles and the achromatic apparatuses in the most diverse kinds of organisms indicates that all nuclei are descended from a single original nucleus. The great uniformity of the coacervate comprising the limpid cytoplasm suggests that all cytoplasm is descended from a single original cytoplasm. The various components of the nucleus were probably integrated into nuclei long before the first "cells" were produced. Before cells appeared, the nuclear membrane was essential, just as it is today in the Ascomycetes in which the nuclei are jumbled together in a common cytoplasm. Although the chromosomes, nucleoli, mitochondria and other organelles which are common to plants and animals, are practically indistinguishable, the cells of multicellular plants and animals are conspicuously different (Fig. 16).

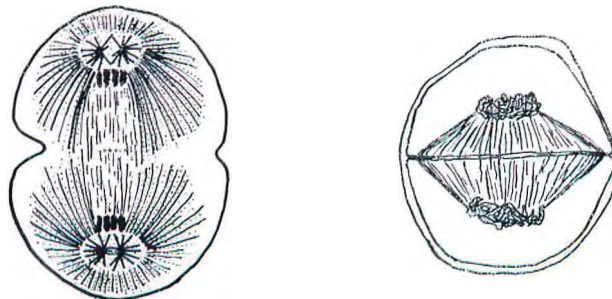


Fig. 16. Cell division in animals and plants. The animal cell divides by constriction of the cell membrane in which asters, centrioles and centrosomes are conspicuous. A heavy cell wall confines the plant cell which divides by the deposition of a cell wall across the spindle. No asters, centrioles or centrosomes are visible in the plant cell.

Plant Cells	Animal Cells
1. A cell wall usually composed largely of carbohydrates but often of other materials.	1. No cell wall.
2. A delicate plasma membrane incapable of withstanding osmotic shocks.	2. A tough plasma membrane capable of withstanding osmotic shock.
3. Cell division by laying down two cell plates through the center of the widely expanded spindle (the phragmoblast).	3. Cell division by invagination of the plasma membrane constricting through the narrow spindle.
4. No clearly defined centriole and centrosome.	4. A clearly defined centriole and centrosome.
5. A spindle within which the chromosomes are usually free to move.	5. Usually the spindle is solid and cannot be penetrated by the chromosomes.

Organ Formation by Plant Cells and by Animal Cells

The most outstanding difference between plant and animal cells is the manner in which they form the organs of which they are composed. Plant cells (i.e., of higher plants) find their places in the plant by the division which precedes the partition of one cell into two. The position of each cell in the multicellular plant is determined by the sequence of division and this place is, in general, maintained without alteration as far as the relative positions of adjacent cells are concerned throughout the life of the plant. The heavy cellulose wall which surrounds each cell limits its freedom of movement.

In animals the situation is quite different. The recent work of Moscona (1960) shows that the organs in embryonic animals are usually produced by the migration of cells into place after division. Moscona disassociated the embryonic cells of fetal mammals and was able to show that contact of the cells (induced by rotating a flask in which they were suspended) led to the reorganization of the cells into multi-cellular arrangements strikingly similar to the structures present before the cells were disassociated. A cell which had occupied a certain position in an organ is apparently polarized and finds the same position, presumably by amoeboid movement, in a new structure in which it is associated with other cells in a position comparable to that which it had previously occupied. Moscona also found that rat and rabbit cells could cooperate to form chimaeras in which parts of organs were reconstructed of cells from two different species associated in relationships which made it easy to recognize the structure of the organ. The absence of the cell wall gives animal cells much greater mobility and makes much more complicated structures possible. It also makes repair of damage much easier. But morphogenesis by migration is not confined to animals and not necessarily prevented by a cell wall. In the slime molds and in some of the more complex bacteria it is a standard way of producing complex structures.

Pirie has pointed out that the attempt to fit all living organisms into the categories of either "plant or animal" has its origin in the fact that multicellular plants and animals were the forms of "life" with which people were familiar before the advent of the microscope, and all life was classified into these two categories (e.g., in Genesis). Familiarity with a greater variety of living things led to the attempt to identify all living things as either plant or animal. The concept of the cell tended to favor this procedure since many of the microscopic organisms were also "cellular" and the cell theory seemed superficially to provide a unifying concept provided the differences in the different kinds of cells were not considered too critically, and provided also that noncellular forms were considered to be the exceptions which proved the rule. It seems preferable to consider the unity underlying the phenomenon of life to stem from (1) a primary origin of the coacervate known as the cytoplasm and (2) a secondary, but much later, integration of different components into the nucleus. The solution to the problem of partitioning bits of cytoplasm each with one or more nuclei is probably an even later complication, which was solved many times, and in many different ways. And some conspicuous organisms survived without ever passing through a cellular phase: the greater "freedom" of the plasmodial form probably offered distinct biological advantage in certain instances.

The Cell as a Unit of Structure

The conventional cell is the cell of multicellular plants and animals in which a single nucleus is partitioned into each cell and in which a new partition is formed whenever the nucleus divides to form two new cells; this "cell" is a "tissue-builder." It gives integrity to a multicellular organism. The

cell forms a structure in the same sense that bricks "make" a brick wall. The diploid nucleus in the cells of higher plants and animals insures the stability of the structure. If one member of the set of chromosomes carries a defective gene, the doubleness of the nucleus makes it highly probable that the same gene will be represented in the other set of chromosomes by a normal gene and, therefore, the tissue or organ produced by the cell will be normal. This tissue-building component of a multicellular organism is not homologous (i.e., not related by line of descent) to the "cell" of a "single-celled," or acellular, plant or animal; the only resemblance is that each time the nucleus divides, the cytoplasm is also partitioned and two new "units" are formed. The boundary of an acellular organism does not serve to make it a unit of structure but to keep its cytoplasm from getting mixed up with other cytoplasm; the wall of the cell of a multicellular organism separates that cell from its neighbor to make it a component of a structure.

The Bud—Cell Division by Extrusion

The yeast "cell" falls into a very special category. Although each yeast cell generally contains a single nucleus, the yeast cell is not a unit of structure comparable to the cell of a higher plant nor is it homologous to a free-living protozoan. The phylogenetical relationship of the yeasts to the Ascomycetes suggests that the yeast cell has only recently become free-living. One of the differentiated structures in the Ascomycetes is its male sex organ (Fig. 17). The sperm or "spermatia" of the

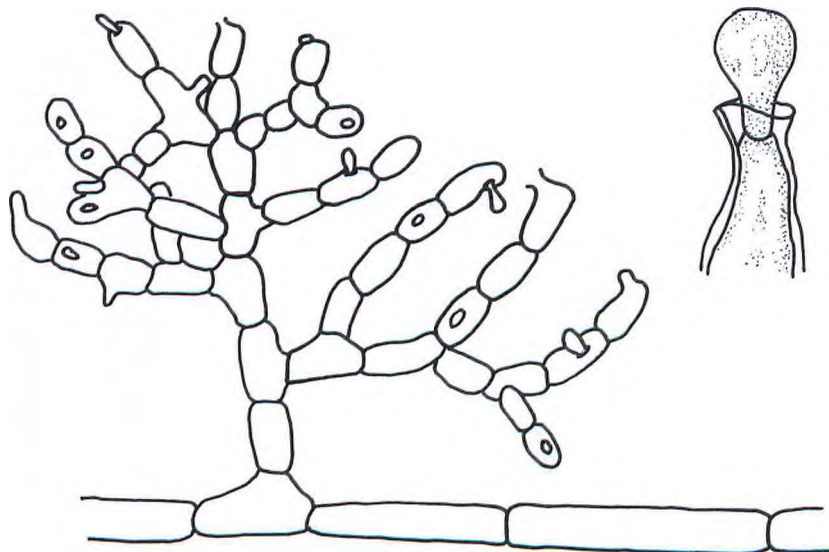


Fig. 17. The budding of spermatia. The spermatia of *Neurospora* "bud" out of the spermatophore through pores. Spermatia are not covered with the heavy outer wall of the spermatophore. The spermatia are the male sex cells. After Dodge.

Ascomycetes resemble yeast buds except that yeast buds are always covered by a cell wall. In forming "spermatia" small parcels of protoplasm each containing a single nucleus are extruded through a pore (from a differentiated structure called the spermatophore) and released as free individual cells. The spermatia do not share the "cell wall" of the spermatophore. This process is not a cell "division" since the nuclei and cytoplasm of which the "cell" is formed have been in existence before the "cell" was produced. In this sense, the mechanism of spermatium-formation parallels the budding of yeast.

The Clamp Connection and the Crozier

The clamp connection was discovered by Mathilde Bensaude, a student of Dangeard. It is a device in mushrooms by which two haploid (unfused) nuclei of different origin, instead of one diploid

(fused) nucleus, are kept together in each successive "cell" by a process so unlike conventional cell division that it is obviously not related. The stability of the mushroom structure is assured by the clamp connection. If one of the unfused nuclei were defective the other could supply its deficiency. The additional advantage of carrying two different kinds of unfused haploid nuclei in each cell is that each nucleus comprises an independent potential sexual nucleus which is immediately available as a sexual partner whenever another different complementary sexual partner appears. The "cell" with two nuclei is a unit of structure which carries two different potential gametic nuclei. If the two nuclei were fused into a diploid nucleus the entire elaborate procedure by which sex cells are produced, would have to take place before a sex cell and a new fusion, could occur. The conditions under which sex-cell formation occurs are very precisely specified and attained only under special circumstances.

Each of the nuclei in the cell of the mushroom is haploid with a single complete set of chromosomes. The two associated nuclei are genetically different in a complementary sense. They carry fertility factors which will permit them to fuse to form a zygote. In the vegetative tissue these fertility factors cause the nuclei to attract each other by a mechanism which keeps them associated and maintains synchronized mitoses in which the two spindles are parallel and orientated side by side. The parallel orientation of spindles in synchronized division is a common device in both the Ascomycetes and the Basidiomycetes and serves to maintain specific relationships between complementary, unfused, associated nuclei of different gene-types. Figure 18 shows the mechanism by which the association is maintained in the vegetative tissue. Figure 18a shows a hypha in which each "cell" contains two complementary nuclei. Figure 18b shows the terminal cell producing a clamp and two parallel spindles one of which passes into the clamp. After the synchronized division, Figure 18c shows one nucleus in the clamp and the other nucleus in the penultimate cell cut off from the ultimate cell by a wall. In Figure 18d the clamp has fused with the penultimate cell and has been cut off from the ultimate cell by a wall, and in Figure 18e the two nuclei have migrated to the center of the penultimate

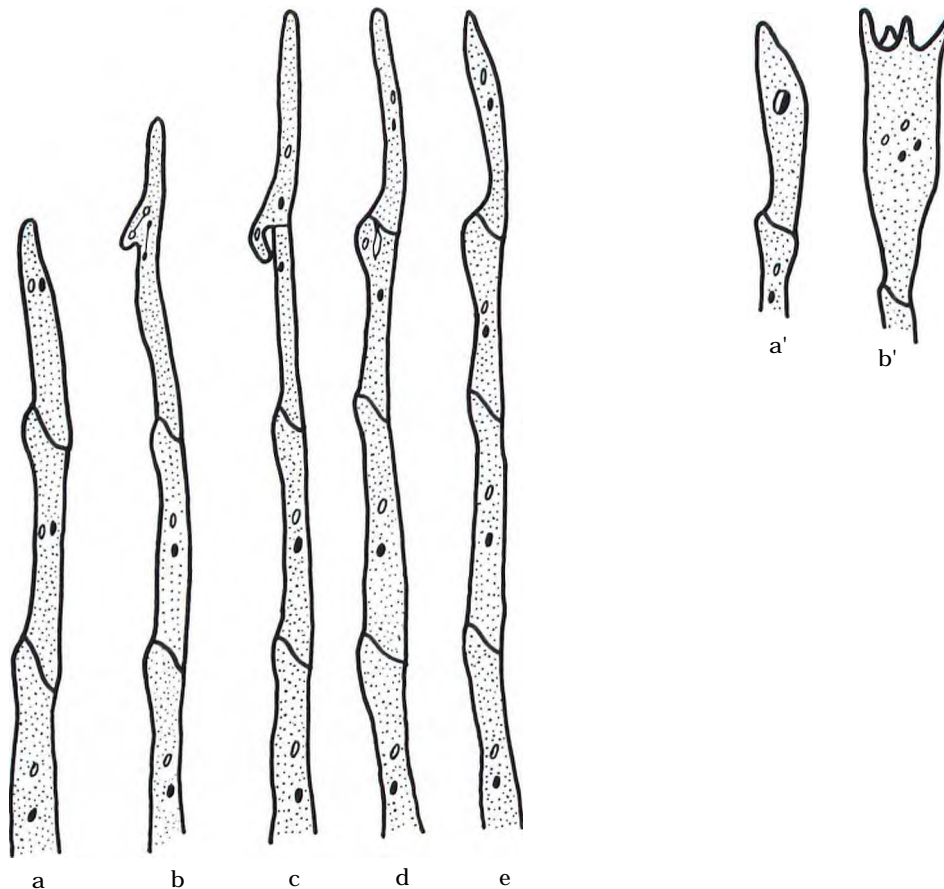


Fig. 18. The formation of clamp connections in the mycelium of Basidiomycetes and the reduction division in the basidium.

cell. Eventually the two nuclei will fuse in the fruiting body as indicated in Figure 18a' and meiosis (indicated b') will produce the tetrad in which the genetical characters are reassorted.

The crozier of the Ascomycetes is a unique process for partitioning nuclei. In the crozier there are walls which separate nuclei into individual compartments. These walls function together with the nuclear divisions to keep the genetically different unfused nuclei together in each "cell."

Dangeard discovered the crozier. It is probably the evolutionary precursor of the clamp connection. The crozier is also a mechanism for maintaining two genetically different complementary nuclei in an association with each other. Its function is to segregate two (and only two) paired and synchronously-dividing nuclei into an ascus in which the reduction division will occur. Figure 19 shows the crozier, or shepherd's crook, beginning to grow out of a "cell" containing two complementary nuclei. The protuberance (19b) turns back to form the shepherd's crook and two parallel, synchronized, associated mitoses occur, orientating two unfused nuclei in the ultimate cell and one in the tip of the crook (19c) and one in the basal cell. The tip of the crozier fuses with the penultimate cell (19d) and the two descendant nuclei are reassorted in the same relation as their parents in both the ultimate and the penultimate cells. The two nuclei in the ultimate cell fuse (19f) while the two in the penultimate continue to divide synchronously, producing more duplicates of the two associated nuclei. The fused nucleus in the ultimate cell undergoes two meiotic divisions (19h and 19i) in which the genetical characters are reassorted. This is followed by a third division and finally by the formation of eight spores.

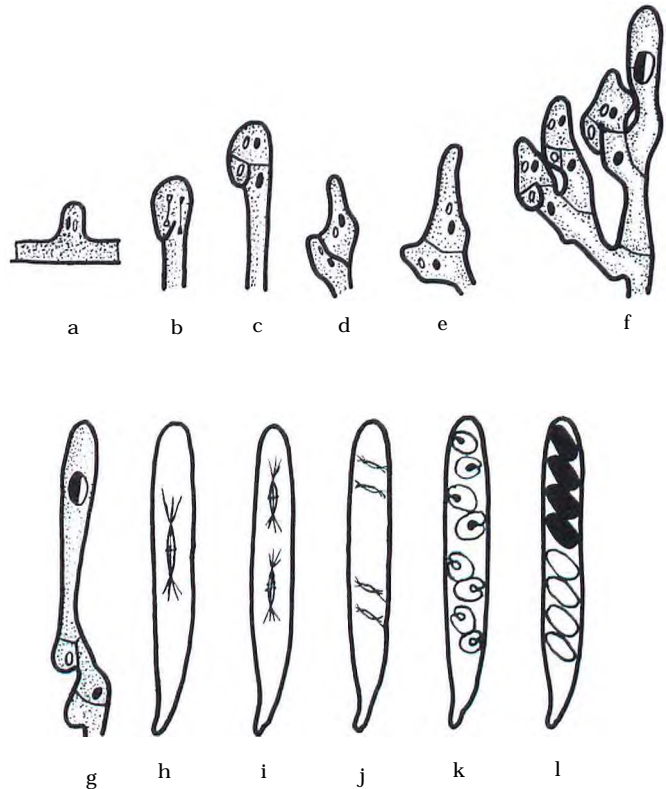


Fig. 19. The conjugate, parallel, synchronous nuclear divisions in the crozier and the ascus which orient and maintain nuclei in specific relation to each other.

Cells Inside of Cells

Harper was the first to describe a unique process which he called "free cell formation." This is a process in which the free cell is cut out of the cytoplasm and a cell wall is formed about a single nucleus to include only part of the cytoplasm in the cell, leaving a residual cytoplasm called the "epiplasm." According to Harper this process is initiated by the nucleus through the formation of cleavage furrows along the lines of an umbrella-shaped aster which arises from the central body (Fig. 20). Dodge showed that this process occurred in *Neurospora*. In Figure 19 the astral rays of the eight nuclei in the ascus are cutting out the spore cytoplasm from the cytoplasm of the ascus. Dodge added the observation that in *N. tetrasperma*, in which two nuclei are initially included in each ascospore by free cell formation, the two central bodies are oriented parallel to each other and then the umbrella-shaped cleavage pattern produced by the aster includes both nuclei in a single spore.

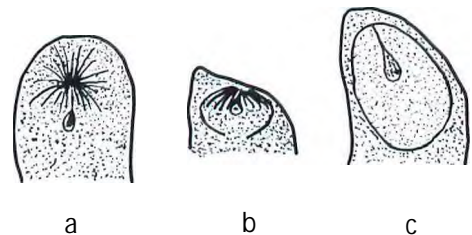


Fig. 20. Free cell formation, (a) A nucleus is shown attached by its spindle to an aster in the ascus of an ascomycete prior to spore formation. (b) Lines of cleavage originating from the astral rays enclose a portion of the cytoplasm. (c) The enclosure is completed and a single nucleus is isolated in the free cell which eventually becomes a spore. This is the only instance known in which cells are formed in cytoplasm leaving a residual epiplasm.

The Plasmodia Within Walls

The Ascomycetes are essentially plasmodia with outer walls in which millions of nuclei are mixed together in a common cytoplasm in which no detectable "order" is maintained in terms of the distribution of nuclei. Most of the partitions which look like "cell-walls" in the Ascomycetes are only partial partitions; they contain a large central pore through which nuclei and cytoplasm pass rapidly from "cell" to "cell." These partitions prevent the outer walls from collapsing but do not separate nuclei from each other. Some differentiation into structures occurs in these relatively cell-less Ascomycetes in spite of the fact that the nuclei are distributed at random in the cytoplasm and not separated into individual cells. Although the mobility of the nuclei in the enclosed tube is not sacrificed, the mass of material is somehow differentiated into sex organs, croziers, asci and perithecia all of which are morphologically different. The differentiation is not of a high order but it is achieved. The low order of differentiation, compared to that of the tissues of the higher plants and animals, suggests that diploid nuclei, isolated in single cells, provide a much more effective solution to the problem of producing stable structures.

Evaluation of the Cell Theory

The great differences among the different kinds of "cells" prove that the cell theory is not a unifying concept but quite the contrary. "Cells" are not necessarily related nor are many of the different kinds of cells even casually related.

The first cells were not produced until long after the origin of living material, at a time when nuclei, mitochondria and a variety of other cellular organelles had been perfected in almost their present form. One may imagine that the first living material spread over the moist earth or at the bottom of tide pools in the form of an undifferentiated slime. The advantage of partitioning this slime into "cells" led to a variety of different solutions. The cell theory has emphasized the one-nucleus : one-cell concept and such emphasis has tended to magnify the importance of the nucleus vis-a-vis the cytoplasm. The one-nucleus : one-cell concept has created the impression that although one could not imagine a cell without a nucleus, one might conceive of a "cell" without cytoplasm, while actually the reverse is more probable. The cell theory was important a hundred years ago in directing the interest of biologists to the structure of different living organisms but its proponents drew the untenable inference that all cells are related to each other in a single line of descent. This generalization has now outlived its usefulness.

Sergius Morgulis, in the following statement, compares the cell theory to the outdated atomic theory:

As long as the cell is considered as the unit of life, the origin of life must remain a paradox. But like the erstwhile atom in chemistry, the cell has lost its prestige as the ultimate unit in biology. Both the atomic and the cellular theories have become obsolete. The cell, like the "indivisible" atom, is now recognized as a highly organized and integrated system built up from extremely small distinct particles. Whether the ultimate particles of life have been found and identified is very doubtful, some of the units themselves being highly organized entities, but the concept of a cell as the unit of life has been thrown out of the window together with the atom.²

The Cell as a Society of Independent Autonomous Coacervates

Each cell is a society of autonomous organelles which have become incorporated into a single system. It comprises a symbiotic association of a diversity of individual structures each of which in some special manner serves to maintain the total society of the components which make up a single cell. One member after another was added to the membership of the society during the many millennia that ensued while life was manifested only as a slimy growth without boundaries. Each of the very ancient components of the society became a permanent component of the society by selective synchronization of its growth rate or by direct attachment to some other component, as a coacervate. Each separate component had its origin, probably externally, as an independent coacervate and began its association with the society as an infectious agent, preying upon the total society, but finally changed from a parasite to a symbiont. In many instances, one may suppose that both the host and the infectious parasite succumbed. The more recently incorporated symbiotic coacervates, such as the mitochondria and the chloroplasts, have not yet become synchronized precisely to the division rate of the total society, nor attached to another coacervate and, hence, may occasionally be lost.

The significance of the cell is that it keeps the total membership of the cell-society together in a single structural unit. Cells were only developed long after a basic society of organelles had been well-integrated. Many different, separate, specific solutions to the problem of incorporating all the different members of the society into a single structural cellular unit were achieved. Although cells seem to be various in origin, it seems reasonable to suppose that the corresponding opposite-number components of cells (for example, all the mitochondria in all cells) are all rather closely related.

FOOTNOTES

1. Carl P. Swanson, *The Cell* (Englewood Cliffs, N.J.: Prentice-Hall, Inc., 1960), pp. 1307.
2. Sergius Morgulis, in his introduction to his translation of Oparin's *The Origin of Life*. (New York: Dover Publications, Inc., 1953).

Concerning the Origin of Life

The "Disproof" of the Spontaneous Generation of Life; The Scientific Attitude toward Negative Evidence; Darwin and the Creator; Oparin's Theory of the Origin of Life; The Coacervate of Bungenberg de Jong; The Autocatalytic Catalysis of Coacervates; Muller on the Origin of Life; Hard and Soft Pattern-Dependent Heredity; Pirie on the Origin of Life.

The "Disproof" of the Spontaneous Generation of Life

Both the early Hebrews and the early Greeks believed in the "spontaneous generation of life" or the origin of life from the mud and slime. In Genesis it states that God created the earth, the waters, and the sky. He did not create all living things, for Genesis states that the earth "brought forth" the plants and the animals. This theory accepts or states the theory of spontaneous generation of life, but it has a corollary: although the earth brought forth the plants and the animals, God created Man and Woman. It was more than a thousand years before the theory of spontaneous origin of life propounded in Genesis was questioned. The simple experiment by which the theory was brought into question may seem almost absurd in light of our present complex biological apparatuses, but it was actually one of the most sensational biological experiments ever performed. Francesco Redi placed one piece of meat in a box covered with a thin piece of cheesecloth, nailed tightly in place so that flies could not settle on the meat. He left another piece of meat outside the box. In a short time the meat outside the box was covered with maggots while no maggots appeared on the meat inside the box. Of course, the meat inside the box did not keep; it spoiled, but maggots did not appear on it. This proved that decaying meat did not "bring forth" maggots, but that maggots were produced in some other way. Redi proposed that flies laid eggs on the meat and the maggots originated from the flies' eggs. This simple experiment brought into question the whole idea of spontaneous generation of life and had a profound influence on current thought. It questioned theories which had been held for thousands of years and much debate concerning the spontaneous generation of life was engendered. About a hundred years later microorganisms were discovered; by looking through microscopes people found organisms much smaller than maggots. The debate concerning the spontaneous origin of life began anew. It was maintained that although organisms as complex as maggots may only be produced by the eggs laid by flies, bacteria and the other smaller organisms which one could see through the microscope must be spontaneously generated. Everyone knew that meat spoiled and that no matter what one did to it the meat was bound to spoil. However, some experimenters showed that if broth or soups were carefully boiled and thoroughly sealed they did not spoil, that is, microorganisms did not generate spontaneously within them. Others objected to these experiments saying that air had been excluded and that air was essential for spontaneous generation. The general attitude was that spontaneous generation was a philosophical necessity and absolutely essential, and that no matter what the evidence was, some idea of spontaneous generation of life must eventually prevail. Persistent and continued experimentation, however, planned to test whether or not organisms could be generated spontaneously in broths and soups, gave negative results. It was found that microorganisms could be carried through the air, on dust particles, that they were relatively less abundant in the country than in the city, and still less abundant on mountain tops than at the bottom of the mountain. It was also discovered that microorganisms lived in both a resistant and a sensitive phase and that the resistant organisms were very difficult to destroy by heating. The whole problem was finally solved by Pasteur with one of the most economical and elegant biological experiments ever performed. He showed that if one boiled broth in a glass bulb which had a long, narrow, twisted opening, then the broth would keep indefinitely. In this experiment, he allowed the broth to have contact with air after the boiling, but the long, narrow tube by which the bulb communicated with the outside air would not permit the re-entry of dust. Furthermore, he boiled the broth three times on three successive days so that the resistant forms had a chance to begin growth and turn into sensitive forms, which were killed on the second and third boilings. This brought a

complete end to the idea that bacteria were generated spontaneously and all work in this field stopped. Investigation discontinued, not because people had lost faith in the idea that spontaneous generation occurred or because they did not need to believe this as a "philosophical necessity," but because there seemed to be no reasonable way to approach the problem at that time. Pasteur had proved that it was reasonable to assume that most organisms have a continuous history. It was proposed as a fundamental rule that all cells come from preexisting cells, that is, that spontaneous generation does not occur, at least, as a common event, and that all existing cells have their origin in other similar cells.

After considering this proposition carefully, some experimenters proposed that life came to this planet from outer space and that cells in some dried or frozen condition traversed outer space and finally reached earth. It did not seem too improbable that spores or other resistant living forms or forms with a "potential" for life might be floating throughout the universe in the interstellar space where the absence of O₂ or water in a liquid state could keep them eternally viable much as frozen bacteria are preserved in cold storage today. The effect of radiation on these forms was discounted except to point out that the presence of light could disseminate them to the most remote reaches of the universe. This solution was never very satisfactory or satisfying and was not generally accepted, but no one really knew what to do about it. The problem still was where did the first "cell" come from.

The Scientific Attitude toward Negative Evidence

In commenting on this situation, George Wald argues that Pasteur's demonstration was not a triumph of reason over mysticism, but more nearly the opposite because the only alternative to spontaneous generation was a single, primary act of supernatural creation. The belief in spontaneous generation is actually a "philosophical necessity" according to Wald. Because of the philosophical poverty of our times this necessity is no longer appreciated and the unwillingness of modern biologists to accept the alternative belief in special creation leaves them with nothing. Wald believes that a scientist has no choice but to accept the hypothesis of spontaneous generation.

It is clear that the simple circumstance of negative experiment cannot become a decisive factor in the rejection of a concept. Some other more cogent reason is required.

Darwin and the Creator

Darwin did not attempt to explain or even to consider the origin of life. Actually, Darwin was more convinced of Divine Intervention in the creation of life than the early Hebrews; his argument was against the view that God had created each separate species by a special act. Darwin says:

Authors of the highest eminence seem to be fully satisfied with the view that each species has been independently created. To my mind it accords better with what we know of the laws impressed on matter by the Creator, that the production and extinction of the past and present inhabitants of the world should have been due to secondary causes, like those determining the birth and death of the individual Thus, from the war of nature, from famine and death, the most exalted object which we are capable of conceiving, namely, the production of the higher animals, directly follows. There is grandeur in this view of life, with its several powers, having been originally breathed by the Creator into a few forms or into one; and that, whilst this planet has gone cycling on according to the fixed law of gravity, from so simple a beginning endless forms most beautiful and most wonderful have been, and are being evolved.*

This quotation proves that Darwin believed that God created life originally but that the subsequent variations were imposed by the struggle for survival.

Oparin's Theory of the Origin of Life

The problem of the origin of life was reopened by the Russian biochemist, A. I. Oparin, in a manner that seems to promise fruitful consequences. Oparin began his study when the prospect of experimental investigations seemed quite hopeless, and he brought the subject of his study to a point where it is now possible to consider with some optimism the synthesis of living matter in the laboratory. Because the fashion in Russian biology is different from that in the U.S.A., it has been assumed by those

who follow the American fashion that the Russian product is inferior, and vice versa. This is particularly evident, for example, in the discussions of the origin of life by American biologists. Their discussions usually concentrate on the idea that the gene is the original living material, a point repeatedly made by Muller. Oparin, on the contrary, argues that the original living material is not the gene but a cytoplasmic coacervate.

In his book, *The Origin of Life* (1924), Oparin proposed that the first living matter probably did not arise until an enormous mass of organic matter had accumulated covering the surface of the earth. He pointed out that organic matter could accumulate in the absence of life, but that it could not be expected to accumulate today since organic matter of this type would be used as food by the living organisms. He proposed that previous to the origin of life on earth the gases in the air reacted with water under the influence of sunlight to make oceans full of proteins and sugars and other complex organic materials, and that from these materials the first living thing developed. Oparin proposed that at first various simple structures originated, previous to the origin of what we would now call the "cell." These structures achieved stability by the arrangements of their component molecules. He assumed that these "stable" complex structures competed with each other for the materials of which they were formed. Oparin conceived of a struggle for existence between pre-living organized noncellular materials, materials which we might or might not call "living." This material was organized in a more complex manner than other nonliving things. These "organisms" competed with each other and consumed one another. The stable association of different kinds of molecules in a single "organism" was due to coacervation—a technical term invented by Bungenberg de Jong for a reaction which is produced by forces at a level considerably below chemical bonds. A coacervate is an organized complex of different kinds of molecules held together in a specific pattern by mutual attractions. Oparin assumed competition for survival to occur between coacervates. He assumed that living material was a society resulting from the association of a variety of coacervates into one organized structure. In the preliminary stages, different coacervates were tested for stability and finally one after another were incorporated into the structure which formed the first living matter.

Oparin developed a theory which made it possible to conceive of the origin of life by supplying (1) a background of rich nutrients, (2) a selection of competing components and (3) a means of association which produced the complicated original living material.

Oparin's general philosophy provided another basic idea different from that previously held. It was simply this: that life is the inevitable outcome of the association of molecules in combination with each other and that in any circumstance in which complex molecules are formed in the absence of life they will develop into stable combinations which will inevitably produce living material. Instead of looking upon our planet as the only planet in the entire universe on which life exists in the form with which we are familiar, Oparin has proposed that there are almost a hundred million planets like our own on which life not too much unlike that with which we are acquainted today may exist. Oparin has thus given us a completely new concept of the cosmos and has proposed that life is not a unique accidental event but is the inevitable outcome of complex molecular associations. This is a theory of the origin of life which is "useful" today in understanding man's place in nature and in planning future experiments.

The Coacervate of Bungenberg de Jong

The coacervate of Bungenberg de Jong occupies a central position in Oparin's theory. Bungenberg de Jong studied the phenomenon in which solutions of hydrophilic colloids separated spontaneously into two layers, one rich in colloids which he called the "coacervate" and one poor in colloids which he called the "equilibrium liquid." Some coacervates separated from the equilibrium fluid as small droplets from two to several hundred microns in diameter. Bungenberg de Jong proposed that a colloid in an aqueous system was (a) dispersed by hydration which tended to stabilize it as a solution, but that the individual molecules were also (b) attracted to each other by electrostatic forces which tended to resist the forces of hydration and form large aggregates. Thus every coacervate was under the influence of (a) electrostatic forces which tended to aggregate the coacervate and (b) forces of hydration which tended to disperse it into its free component parts.

Oparin discusses the similarity of coacervates and biological structures:

The following two characteristic properties of complex coacervates are especially important in relation to the argument which follows: (1) their tendency to form structures; (2) their ability to adsorb selectively substances from the surrounding equilibrium liquid. . . .

According to Bungenberg de Jong, the colloidal particles in complex coacervates are not, as a rule, oriented in a definite way, because in such coacervates there is no cohesion between the particles. But

if, by some means, the positive or negative charge on the micelles of the coacervate is increased or their hydration is decreased, then the micelles approach one another and become oriented in a definite mutual relationship. The so-called "oriented coacervates" which are thus obtained show many signs of having a structure. For example, if the particles of which it is composed are rod-shaped, the drops of the coacervate will be ellipsoidal. In oriented coacervates one may also detect the formation of "micellar crystals," fibrils and fibrillar structures. Bungenberg de Jong and his colleagues observed the formation and disappearance of these structures in coacervates of various proteins, lecithin, nucleic acid, polymeric carbohydrates, etc.

. . . At some point or another in the primeval ocean, there must necessarily have come into existence collections of molecules of organic polymers and their separation in particular places from the surrounding medium to form drops of complex coacervates.

This must have been largely facilitated by the relatively very high concentrations of organic substances in the primitive "terrestrial soup" to which we have already drawn attention. The formation of complex coacervates could, however, have occurred even when the concentration of organic polymers was far lower. Under experimental conditions it takes place in solutions containing only a few parts per million of these substances.

An artificially produced coacervate, or a drop which arose naturally by separating out from organic solution in the waters of the ocean, is in itself a static system. . . . The more stable a coacervate drop, regarded from a purely colloidal point of view, the less likely it will be to disappear as an individual formation after any given lapse of time by amalgamating with other drops or by dissipating itself into the surrounding solution. Unlike this, the coacervate structure peculiar to living protoplasm can only exist so long as it carries out an unending succession of multitudinous biochemical processes at a great speed, which together make up its metabolism. Thus it is only necessary for these processes to be suspended or radically changed for the protoplasmic system itself to be destroyed. Its continued existence, the maintenance of its form, is associated not with immutability or rest but with continual motion. Thus protoplasm is not a static but a "stationary" or flowing system.²

Oparin's comment on the "necessity" of a continuous metabolism for the preservation of the structure of protoplasm is a common conception of those who study higher animals. But in many forms the structure of the protoplasm can be maintained indefinitely in the dried or frozen state. This fact simplifies the problem of the origin of the primeval protoplasm, since it suggests that long gaps could have intervened between the origins of the different coacervates. A continuous and steady advance with time was not essential to "success."

The Autocatalytic Catalysis of Coacervates

Under the title "Some Physico-chemical Aspects of Life, Mutation and Evolution," Jerome Alexander and Calvin B. Bridges discussed possible chemical mechanisms involved in the duplication of biological entities. Quite independently of Bungenberg de Jong, Alexander and Bridges developed a similar idea of structures they called "molecular groups." The important contribution of Alexander and Bridges involved their proposal for a mechanism for autocatalysis of the coacervate or "molecular group."

To epitomize the biological evidence, the genes are particles, of molecular order, which locally duplicate themselves from what is admittedly non-living matter, and which control and direct the material changes of development and life. Can we interpret such behavior in the light of our present chemical and physical knowledge? It seems to us that this can be done through the idea of catalytic synthesis.

Before considering the modern view of catalysis, let us first review some consequences of the structure of matter which make catalysis possible and specific. When electrons and protons combine to form atoms, when atoms combine to form molecules and when molecules combine to form larger groups, there are always left over some outwardly directed, unsatisfied fields of force. The residual forces of molecules exert powerful attractions or repulsions on particles which come within the range of attraction.

If we consider a single molecule, or a very small molecular group, A, it is obvious that the residual electrostatic or electromagnetic surface forces present to the milieu a mosaic which is highly specific in various directions. In [Fig. 21] the specific nature of the surface of A is shown very diagrammatically by the convention of specific jaggedness in the outline. In consequence of its mosaic pattern, a particle may exhibit several different kinds of specific actions separately or simultaneously, on different portions of its periphery.

Let us now imagine a simple molecule, B, approaching A, and the process of fixing itself at the surface. This will occur only if the surface charges presented by the approaching molecule bear a lock-and-key relation to those of the particle, and if the velocity of approach lies within critical limits.

As soon as the oppositely charged areas come within their critical distance, fixation occurs, as is diagrammed A + B. Instantaneously thereafter occurs a mutual neutralization of forces and a complete reshuffling of all the internal and surface fields. The compound molecule, after the fixation, will present to the milieu a different configuration from what it presented before fixation. This is diagrammed as AB. The former B portion might now be able to make other attachments previously not possible to it. The

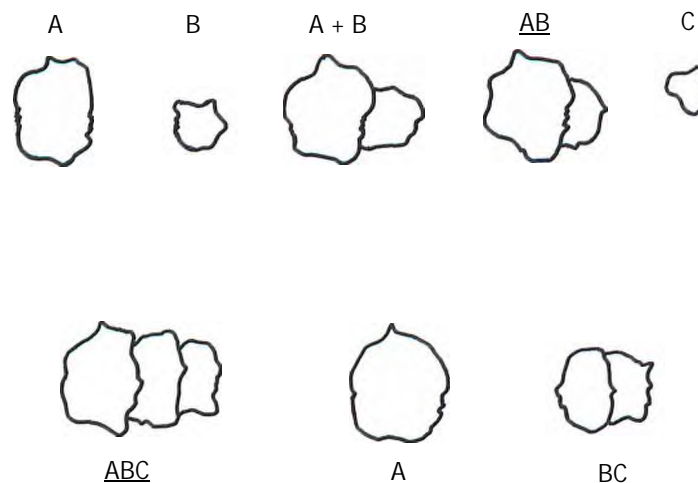


Fig. 21. Diagrammatic representation of Alexander and Bridges' concept of catalytic growth of particles through the action of "surface fixations."

attachment of a second molecule, C, would once more cause a reshuffling of all the fields involved, as is diagrammed ABC. Now, if the resulting bond between the two added molecules were stronger than the bond between the former A and B portions, then there might be released to the milieu a new type of duplex molecule, BC, while the fixation surface of A would be freed for renewed action.

Suppose now that we have a catalyst particle composed of several simple molecular subunits which we can diagram roughly as A in [Fig. 22.] Suppose that at some one of its faces the catalyst fixes or adsorbs the several subunits of which it is composed; that, because of the order of their fixation or because of the reshuffling of electronic fields which follows each addition, these component subunits form a new group identical with the fixation or catalyst group, and suppose, lastly, that the duplicate particles now separate or are separated. Each would be an exact duplicate of the other in catalytic and in self-duplicating behavior. Our original particle could properly be called an autocatalytic catalyst.

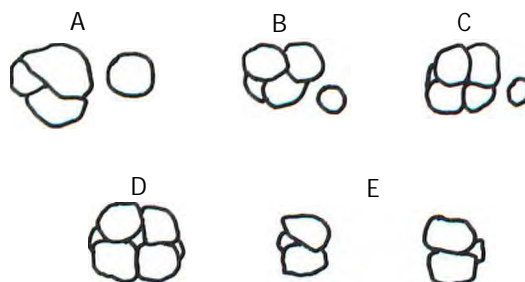


Fig. 22. Diagrammatic representation of Alexander and Bridges' concept of a possible mechanism for the reproduction of a "self-reproducing" structure.

As an example of a simple and well-known chemical process, analogous in a rudimentary way to the autocatalytic synthesis postulated above, one may mention the formation of crystals of the alums. If to pure cold water is added the salt potassium sulphate and the salt aluminum sulphate, a solution strongly supersaturated for the potential double salt, alum, may be obtained. But, in the absence of a fragment of a previously formed crystal of alum the supersaturated solution remains practically indefinitely without giving rise to alum crystals. However, if a tiny fragment of alum crystal is dropped in, or was present in the materials used, at its surface occurs an adsorption of the two separate salts together with a definite number of water units, the whole addition condensing into a very specific space lattice with repetitions of the unitary alum complex. Mechanical, or even thermal, agitation may break the bonds between the newly formed alum complexes and the parental crystal so that a host of descendants may grow or reproduce in the nutrient solution.

We do not contend that an alum crystal constitutes simple life, although there may be some who would do so. In vital units the building stones of the finer structure are not potassium, aluminum and

sulphanion, but are carbon, nitrogen, phosphorus, etc., which are united in a unit complex which is far more voluminous and involved than alum is. Besides this difference in constituents, or more probably because of it, the units properly called vital are more flexible in their bonding and more diversified in the activities carried on at the catalytic surfaces. . . .

To return to our oversimplified analogy in the alum crystal: It is remarkable that alum crystals retain their specific structure through a host of substitutions of materials, or "mutations." Thus, rubidium, caesium and even ammonium can be substituted for the potassium; iron, manganese, etc., can be utilized instead of the aluminum; selenion (SeO_4), etc., instead of the sulphanion. The most essential characteristic of an alum crystal seems to be the particular strain set up in the local ether when alum crystals originated. It is the structure, the particular space-lattice present, that matters, and the points in that lattice can be taken by any materials whose outwardly directed fields of force are flexible enough to adapt themselves to the particular "set" that is in the local ether.

Considering briefly the bearing of these ideas on the origin of life— a very speculative endeavor—it would seem that no biont as complex in its order of aggregation as a cell, or even a bacterium, could have been an initial form of life. The structure of a cell is a box-within-box series of units, of successively simpler orders of aggregation, and it seems reasonable to suppose that the simplest of these units was the first to appear in evolution. Life began, then, in the molecular order of complexity with an autocatalytic molecule of definite structure and less definite constituents.

It is interesting to read Alexander and Bridges' paper in conjunction with Oparin's and Bungenberg de Jong's and to observe that except for the fact that Alexander and Bridges insist on relating the phenomenon of coacervation to the "gene" the concept of oriented structures produced by electrostatic or other similar forces, different from chemical bonds, shows all three workers to be in essential agreement concerning the nature of the origin of life. The concept of the primacy of the gene was to be expected from Alexander and Bridges in 1929, because Bridges was a strongly indoctrinated Mendelist who firmly believed that the gene was the "simplest unit of vital activity."

Muller on the Origin of Life

In the opinion of many geneticists, the gene is the unique "living" particle that is characterized by (1) the ability to reproduce itself, (2) the ability to undergo variation or mutation, (3) the ability to reproduce the variation as faithfully as it produced the original form, and (4) the ability of both the original form and the variant to produce specific substances that control cellular metabolism. The most recent distillation of biological thought on this subject is summarized by Beadle's slogan "one gene—one enzyme."

After Mendelian genetics began to advance with startling rapidity, many Mendelists were convinced that the gene was an autonomous agent, specifically different from any other cellular component and it was inferred that both the origin of life and evolution were simply a history of the origin, mutation and redistribution of genes. But many Western embryologists who studied the origin of the whole animal from a single apparently uniform cell disagreed with the view and argued that the gene was a relatively trivial part of the hereditary apparatus, accounting only for differences between the races of a species, or the species of a genus. They proposed that all the really fundamental characters were controlled by the "cytoplasm." This opposition forced the Mendelists to overemphasize the importance of the gene and contend that the gene was the "fundamental living particle." At present, this swing of the pendulum prevails in the U.S.A. Professor H. J. Muller is the most articulate proponent of this view, in arguing for his hypothesis that the gene arose first, Muller states;

In place, then, of the time-honored view according to which protoplasm and the metabolism of proteins evolved first, and then developed a more specialized genetic material within it, a view whose basis is traceable to Haeckel and which has recently been espoused again in Russia by Oparin, it has seemed more reasonable to infer that the genetic or chromosome material arose first, and that it was able practically from the start to conduct its own replication by utilization of readymade constituents in the non-living medium around it. Later, in the course of carrying out its distinctive operation of differential multiplication of mutant types, this genetic material must have gradually assumed forms that enabled it to refashion scattered materials from the medium around it into a highly organized system, protoplasm, a system that has survived because it served to enhance the potentialities for survival and further multiplication of the genetic material that had created it.⁴

In this statement, Muller says that "the genetic material must have gradually" (?) produced protoplasm. He says further that the protoplasm survived, but since he does not believe protoplasm to be autonomous, he must mean that the genes continued to make and still continue to make cytoplasm.

Muller states that the gene can reproduce itself, but the normal gene does not and cannot reproduce itself; the gene is reduplicated by a system of which it is only a part. Genes also mutate. This

phenomenon has led to the view that genes are structures that differ from other cellular components by their specific ability to reproduce variations of themselves as if the mutant gene were a "new" gene that produced something new and different. This is fundamentally incorrect. No chemical possesses the capacity for self-reproduction; it must depend upon the environment for its components. The defective nature of an organism that carries a mutant gene is caused by the absence, diminution, or deviation of the contribution ordinarily made by the normal gene. The defect becomes apparent because the deficient organism produces sufficient material to enable it to reproduce without the contribution previously made by the normal gene, but in a characteristically different, defective manner. The altered condition of the defective mutant is due to the defect in the chromosome at the location technically known as the "mutant" gene. When a defect or deletion occurs in a small segment of a chromosome the rest of the organism can continue, albeit in a changed condition. During evolution changes may occur more frequently in the chromosomes than in other organelles, because chromosomes (which differ from the other organelles in their high degree of linear heterogeneity) can be altered with fewer ill effects than any other organelle.

Direct examination of cells suggests that many organelles other than the chromosomes are as autonomous as are chromosomes. The yeast cell has its capacity for continuous growth because the whole cell is capable of producing all of the components of all the organelles when placed in an adequate milieu. The organelles are self-duplicating in the sense that they do not arise *de novo*. The cell can function only if all of its component parts are present in proper structural correlation and in adequate amounts. A permanent organelle would be rate-limiting, if the other organelles would not obtain an adequate supply of the molecules necessary for maintenance and increase, when the respective (rate-limiting) organelle cannot make its normal contribution.

Hard and Soft Pattern-Dependent Heredity

Darlington classifies theories of inheritance either as proposing that heredity is "soft" or "hard." Darlington infers that (1) all heredity is genic and (2) all genes are "hard." He concludes, therefore, that all heredity is "hard." Darlington respects Erasmus Darwin (1731-1802) as the preeminent thinker and innovator in this field and states that Erasmus had concluded that both kinds of heredity must be operative. But after Erasmus all students of the subject accepted either one or the other alternative; no one after Erasmus chose to propose that both hard and soft heredity existed side-by-side. I suggest that the living state requires that both systems exist and cooperate.

Goldschmidt and Jollos by a considerable amount of experimental work supported the concept that some kind of "soft" heredity existed. But to argue, as Lysenko did, that all heredity is "soft" ignores the many demonstrations of gene-controlled heredity.

Martin (See Chapter 9) has argued that "soft" heredity must exist and must precede the development of "hard" heredity.

Michaelis (See Chapter 5) has made a convincing demonstration of "hard" heredity, independent of genes, hence, residing in the "cytoplasm."

The successful demonstration of the role played by nucleic acids in cell physiology has led molecular biologists to the conviction that heredity is completely under the control of genes and that genic heredity is determined exclusively by the transmission from parent to offspring of the hereditary pattern of a specific kind of nucleic acid molecule: They have concluded that all variations in heredity result from variations in the structure of this molecule. This molecule is extremely stable and its replication is not directly affected by minor changes in the physical and chemical environment, but only through changes in the structure of the "parental" molecule, however these may be effected. Darlington would say that nucleic acid heredity is "pattern-dependent" because the pattern of the "parent" molecule is precisely duplicated in the offspring.

But molecular "biology" is a paradox since a very simple disorganization of the pattern of a few of the structures present in a living organism may produce a non-living state, which no amount of subsequent reorganization, either spontaneously or by an experimental operation, can restore to the living state. Hence, molecules alone cannot maintain life. Structures of certain specific kinds, rather than specific kinds of molecules, are the fundamental basis for life. The difference between biological structures and non-biological structures in the borderline state cannot be specified, but the kinds of structures involved in current, living organisms are rapidly being disclosed by a combination of electron-microscopy and biochemical investigations. These investigations have given much added force to Bungenburg de Jong's emphasis on the phenomenon of coacervation as a basic biological phenomenon. Alexander and Bridges suggested how the pattern of an organelle can determine the continuity of the

original pattern in a daughter organelle. That is, the orientation of the molecules already present in the living coacervate can guide and orient the molecules which are added to the coacervate and this is the mechanism by which the molecules in living coacervates arrive at their proper positions in the structures. Thus the molecules already present in the living coacervates determine the positions into which newly added molecules will be directed. This means that the pattern of the living coacervate is autonomous and self-directed with the characteristic of an hereditary particle. Although Alexander and Bridges apply their concept of self-duplication only to genes, Oparin points out that the apparently limpid cytoplasm is a coacervate and proposes that it is the primeval, biological material. The living state is a social phenomenon in which a society of diverse molecules and coacervates of molecules are able to maintain and propagate by collective action a particular society of molecules and their aggregated states. Although one observer may place emphasis on the molecule and another on the structure, both are equally involved in the maintenance of the living society.

The living state is very conservative since most of the organelles have had a long history and some specific coacervates may have been maintained with only minor changes through millions of daily reproductions over billions of years. Reasoning from Danielli's hypothesis of the nature of the biological membrane it becomes apparent that, when the living state collectively produces the molecules comprising a membrane, the molecules apparently fall into place simply because there is a primer pattern in the form of the membrane already present in the society. Hence, the biological membrane provides an example of pattern-dependent heredity at the coacervate (rather than the molecular) level. A change in a gene may result in a change in the kind of molecule presented to a coacervate to change the membrane by presenting a different competitive molecule from an outside source. But an environmental change of this kind would be quickly reversible because of the basic stability of the naturally selected coacervate.

The hereditary apparatus determines the characteristics of offspring by the dependence of offspring on the existence in the parent of a particular specific pattern. One parental, pattern-controlling, hard heredity is nuclear (and molecular, based on nucleic acid structures); the other is "cytoplasmic" (but presumably includes such structures as chromosomes) and is based on coacervation.

According to this reasoning there are two kinds of hard, pattern-dependent, heredity (1) the heredity of the DNA molecule and (2) the heredity of the ancient organelles such as (a) the various membranes (the cell walls, the plasma membrane, the vacuolar membranes, the mitochondrial membranes, the endoplasmic reticulum and the variety of other boundaries), (b) the small particulate bodies (ribosomes, plastids, elementary respiratory particles, nucleoli), (c) the larger structures (chromosomes with their histone backbones, plastids, spindles) and, finally, (d) the ancient fluid coacervates such as the limpid cytoplasm and the nucleoplasm.

The Receptor-Hypothesis. In addition to these two kinds of "hard" heredity, I have proposed the receptor-hypothesis, which maintains that there exists in the nucleus, as an essential component of each gene, one outstanding, exceedingly "soft," pattern-dependent component of the hereditary apparatus, namely the receptor of the gene. Life in its present state would be impossible without the receptor by which the living state adapts from day-to-day and even from moment-to-moment to the tremendously variable milieu in which it has its being. The receptor-hypothesis proposes that nearly all the environmental variability encountered in (a) adaptation, (b) ontogeny, and (c) the control of gene-action arises from the response of different receptors to the effect of the environment. Each receptor is a coil of protein which is an essential component of its respective gene.

Experiments have shown that recessive genes may be modified by the environment to become dominant genes and that dominant genes by disuse may "wear out."

It has been inferred from numerous experiments, that receptor-heredity is "soft" and that the receptors of genes may lose or change their conformations rather readily under the influence of molecules which are present while the receptor-protein is being built into the locus.

If the site of "soft" heredity is the receptor of the gene and if the folding of the receptor-protein is controlled and directed while the protein is becoming a component of the particulate gene then the two principal factors controlling the characteristics of the offspring are (1) the pattern of the folded receptor already present at the locus and (2) the presence or absence of some specific substance during the insertion of "new" protein molecules into the receptor.

Pirie on the Origin of Life

Both Muller and Oparin have considered the original form of life to be more or less similar to that existing at present, for example, to have been some kind of nucleic acid, protein-oriented point. Pirie has developed a much more penetrating concept and has discussed the origin of life in terms that include neither nucleic acids nor proteins, genes, or cytoplasm. He proposes that life originated on earth

by the "repeated coordination of eobionts or sub-vital units," and hence, supports the view that there were several, separate origins of the different sub-vital units which became associated by symbiosis. Pirie says:

. . . the statement that a system is or is not alive is a statement about the speaker's attitude of mind rather than about the system and no question is scientifically relevant unless the questioner has an experiment in mind by which the answer could be approached. When we are concerned with extreme states, such as the higher plants and animals on one hand and rocks and chemicals on the other, there is little uncertainty. It is when the borderline is being considered, as with viruses or some metabolically active fragments from cells, that definition could be useful and is impossible. . . it seems invidious to pick any one substance as the *sine qua non* of life. We are not even justified in assuming that there was any single type of substance in this unique position. It is just as likely that primitive forms of life, or eobionts, made use of many different mechanisms, and that the mechanisms we see now are the end result of an immense process of evolution and selection. Proteins may be the most efficient rather than the only vehicle for living. On this view a detailed discussion of the contemporary metabolic behaviour of amino-acids, nucleic acids or proteins may have no more to do with the origins of life than a study of the mechanism of a cigarette lighter has with the origins of fire making. Extending this type of scepticism, there is also no reason for the general assumption that life has, at all epochs, been predominantly the affair of the carbon compounds. Small, atypical regions, in which elements that no longer play a large part quantitatively were concentrated, may have been the sites of biopoiesis.

This outlook is illustrated crudely in [Fig. 23.] There are two cones set apex to apex and the diameter of a cone (the abscissa) at any level of time (the ordinate) represents the number of different ways in which systems with living or lifelike properties worked. The lower cone represents an immense chemical diversity narrowing down as a result of biochemical selection to give a few forms of life operating on a more restricted group of efficient chemical mechanisms. From that point on there has been little or no increase in biochemical complexity but there has been the immense increase in morphological complexity with which we are familiar and of which fossils give evidence. The great difficulty of discussions on the origins of life is that they are attempts to describe events long before the beginning of the fossil record; metaphorically, they are attempts to see through the apices of the double cones.

Two courses are open. One is an intensification of geochemical studies, and if they are to be useful it is important that they should not be conceived narrowly but keep all the biopoietic possibilities in mind.

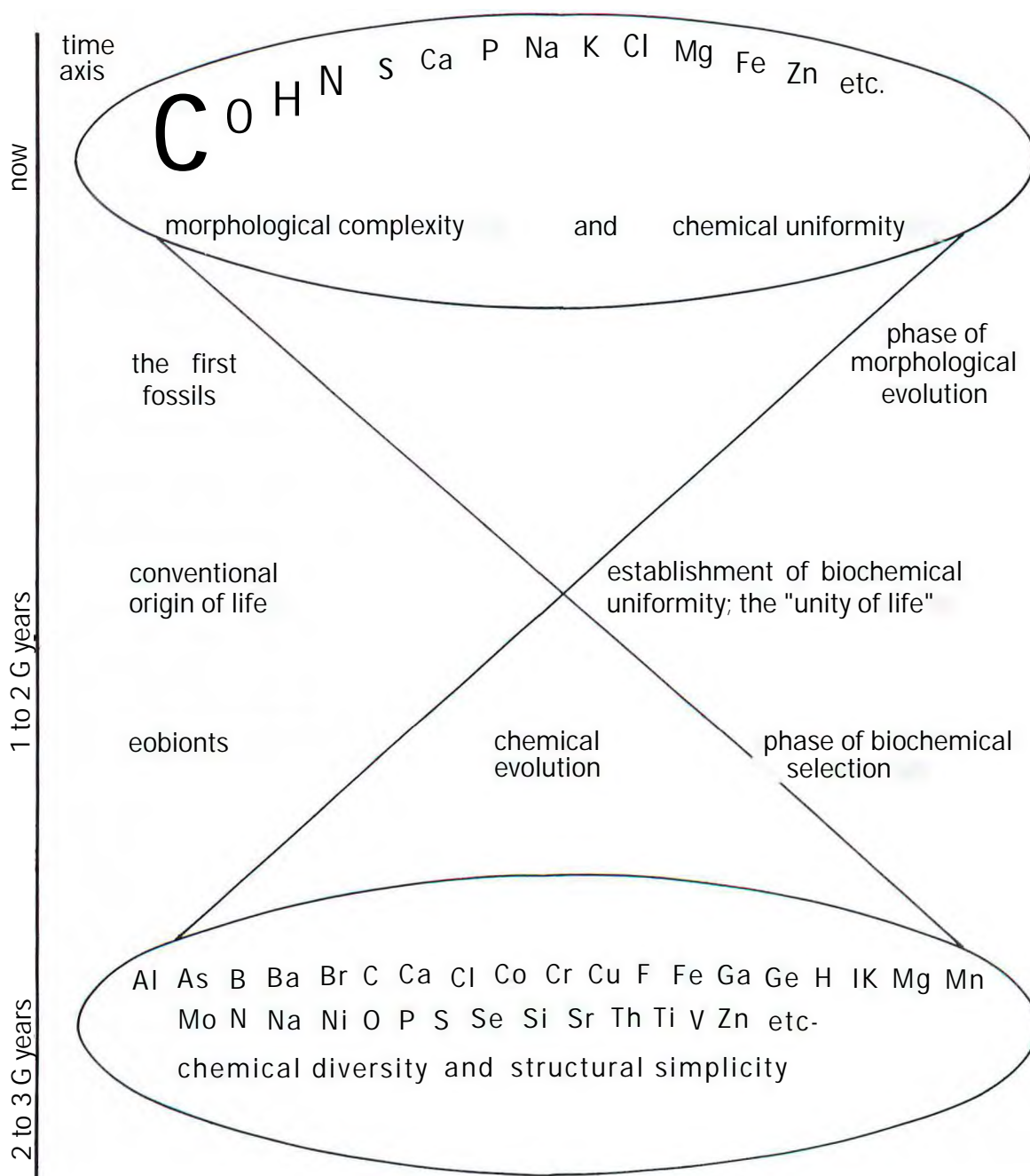
The other is to follow the course of evolution backwards to see if the apparent direction, in the period about which we have evidence, can be used to give hints about the period before that. M. Florkin attempted this for aspects of the metabolism of complex molecules, and I did so for some of the elements. Florkin showed how often a substance that seems perfectly adapted for one role appears in more primitive organisms filling an entirely different one. Thus oxytocin exerts uterine control in mammals but controls water metabolism in amphibians. Furthermore, as evolution proceeds there is good evidence for biochemical simplification. Haldane, who unfortunately was not at the symposium, has already argued that the only exception to this generalization is protein synthesis, which seems to get more elaborate in the higher organisms. If this is indeed so, and if we follow the logic of the generalization, it suggests that proteins, far from being the original essential vehicles of life, are a relatively recent innovation. The efficiency given by proteins may have made them dominant. Thus it is the vertebrates that use them for nearly all purposes, structural as well as catalytic. As we descend the evolutionary scale their structural and protective functions are increasingly taken over by polysaccharides and matrices loaded with mineral crystals.

The use of the elements suggests a similar trend. It is primitive organisms and not the most highly developed that have the most catholic approach to biochemistry and use vanadium, selenium, the halogens, aluminium, silicon and so on, most readily. That is why I give all these elements an equal status with the contemporary bio-elements on the base of the lower cone of [Fig. 23],⁵

. . . I have already argued . . . that, even with existing organisms and systems a rigid division into the living and the non-living is not possible. Every criterion that has been suggested will both exclude something that, for aesthetic reasons, we wish to call living and include something that we do not. Something more satisfactory could be achieved by saying that a living organism had to show some arbitrary number out of a group of qualities but in practice this would be almost as clumsy as a catalogue of the things we intend to call living and it would operate particularly badly among the simpler systems where the issue becomes of most interest. It seems better to recognise that life is not a definable quality but a statement of our attitude of mind towards a system. This makes life a fallible guide through geochemistry.

Even if it is not possible to say that a system with certain activities is alive it may yet be possible to say that certain chemical substances or processes are peculiar to life and essential for it. A cursory study of present day organisms shows many uniformities in their use of proteins, fats, carbohydrates, phosphoric esters, etc. At one time particular attention was attached to the proteins, now there is a tendency to use the phosphoric esters as the fundamental criterion of life. It is of course perfectly legitimate to say that you do not propose to call any system alive unless it contains protein. That establishes a simple linguistic rule and it is essentially what Engels did in his celebrated dictum. But it is not a very useful point to make because not all systems containing protein or phosphoric esters are alive and to say that, whatever else a system may be doing, it cannot be called alive if it does not contain the chosen substance, seems to be as arbitrary as the erection of a colour bar among people.

All present-day forms of life that have been examined contain protein. The number examined is only a small proportion of the whole but protein-based mechanisms seem to be so efficient that it is likely that most or even all the other forms of life also use proteins now. If this turns out to be so it will have no more relevance for a discussion about the origin of life than the now almost universal use of paper has for the origin of writing or the use of matches for the original making of fire. The first metal frying pan



At each level of time the width of the cone represents the number of ways in which living or lifelike systems worked.

The size of the atomic symbol is an indication of the contribution that element may have made to the process at the time.

Fig. 23. Pirie's diagram representing three steps in Diopoesis: (I) The early stage of chemical diversity and structural simplicity during which inorganic catalysts prevailed. (II) The chemical evolution which established the first "unit of life." (III) The morphological evolution which led to the current morphologically complex living state based on a relatively uniform biochemical metabolism.

was probably made of gold because that metal was available and useable though later ousted. The point is worth labouring because very many people have written as if the problem of the origin of life was the same as the problem of the spontaneous synthesis of proteins and some, having realized that the latter involves difficulties, have concluded that God or some similar agency must be involved.

Proteins, so far as we know, are mainly useful to an organism because they are enzymes that catalyze metabolic actions very efficiently. But there are innumerable non-protein catalysts of similar actions. Oxidations can be catalyzed by many metals and by thiourea; some of the rare earth elements are esterases and so on. An organism using such systems might be sluggish but it would be conceivable. If *Corycium* is indeed the fossil of an organism, it was enigmatic in more ways than the paleontologists have thought of and probably organized its metabolism with the help of molecules that would not fit neatly into our systems of classification. Proteins, built economically out of about 25 [different] amino acids, are probably a late development selected from a more chaotic group of primitive chemical experiments. Evolution operates to give us morphological structures that are relatively simple and efficient without being by any means the only possible structures; it is only reasonable to conclude that it also operated on chemical structure to make the efficient enzymes with which we are familiar.⁶

Pirie has gone back to consider even earlier beginnings of life than either Muller or Oparin, and he emphasizes that one of the most confusing aspects of the problem is that the definition of life is necessarily arbitrary, and we may choose to define an alum crystal as living or refuse to settle for anything that does not have a functional nervous system.

Oparin proposes that life originated with the origin of cytoplasm, while Muller suggests that the genes arose first. Pirie has suggested that long before the origin of the present protein-nucleic acid-oriented metabolism, there were living organisms which existed through other much different, probably less efficient, but more diverse metabolisms.

Although it is abundantly clear that the nucleus and the cytoplasm are at present completely interdependent and that the chromosomes and their genes are essential components of contemporary living things, it does not follow that genes are the primary components of living material. Electrical devices are essential components of the organism which we call Chicago, and there is little doubt that, without electrical devices, Chicago would perish and yield its place to some competing metropolis not similarly handicapped. It is equally clear that such devices are not primary components of Chicago and that Chicago existed as an organism for a long time without them, although they now play a vital part in the city's life. Pirie has argued that even proteins may represent a recent aspect of life, although they now appear to be inseparable from it.

During the early stages of the origin of life all heredity was probably "soft." Later some phases of "hard" heredity developed and at present both types of heredity cooperate to maintain the living state.

FOOTNOTES

1. Charles Darwin, *The Origin of Species* (New York: D. Appleton and Company, 1873), pp. 428-29.
2. A. I. Oparin, *The Origin of Life on the Earth*, trans. Ann Synge (Edinburgh: Oliver and Boyd, X957), pp. 3X4-322.
3. J. Alexander and C. B. Bridges, "Some Physico-chemical Aspects of Life, Mutation and Evolution," *Science*, 70 . 508-510 (1959).
4. H. J. Muller, "Evolution and Genetics," *Accademia Nazionale Dei Lincei*, 15-37 (I960)
Estratto dal Quaderna N. 47, *Evoluzione E Genetica Colloquio Internazionale*, Rome (April 8-1X, X959).
5. N. W. Pirie, "The Origins of Life," *Nature* 180:886-888 (November 2, X957).
6. N. W. Pirie, *Chemical Diversity and the Origin of Life*, Moscow Symposium (X957).

CHAPTER 9

The Various and Disparate Theories of Biological Evolution

The Unsolved Problem; The Mutation-Selection Theory: Mutation by "Accident"; "Acquired" Characters: Permanent and Temporary Modifications: Acquired Characters are not Inherited; The Lingering Modifications of Jollos: Acquired Characters are Inherited; The Phenocopies of Jollos and Goldschmidt; Sturtevant's Theory of Delayed Gene Action; Delbrück's Explanation of Environmentally-Induced, Stable (Inheritable) Variation; Lamarck and the Lamarckian Theory; Darwin's Theory of Pangenesis or the Inheritance of Acquired Characters; Weismann's Rejection of Lamarck and Darwin; Bateson's Theory of Evolution by Loss; DeVries and the Mutation Theory; Morgan's Views on the Mutation-Selection Theory; Morgan's Comments on the Relation of Experimentally Produced Mutations to "Wild Type" Genes; Karpechenko and the First New Species; Martin's Criticism of the Mutation-Selection Theory; Fritz Went on Competition Versus the Biological Niche; The Isolating Effects of Food Preferences; Adaptation by Lingering Modifications; The Effect of the Environment Upon the Domestication of Animals; Grigg's Defense of Orthogenetic Evolution; Russell on Orthogenesis; Sturtevant's Rejection of Orthogenesis; Goldschmidt's Rejection of the Gene-Mutation Theory of Evolution; The Mysterious Liquidation of Michael Guyer; Twentieth-Century Weismannism à la Delbrück and Luria; Lindegren's Experiments on Directed Mutations in Yeasts; Two-Step Directed Mutations; The Choice of the Simplest Explanation.

The Unsolved Problem

The theory of evolution is the most widely accepted biological generalization that has ever been proposed. Darlington, in a small book entitled *Darwin's Place in History*, has given a vivid account of the difficulties encountered by Darwin in presenting the theory to the world, and especially to the British public. Darwin's theory in its unchanged original form (albeit Darlington made it clear that there is a considerable ambiguity purposely built into the theory) has the additional distinction of being the only biological theory that has ever become established as a political principle. Marx and Engels incorporated the theory into the Communist credo, and many of the conflicts that have torn the fabric of Russian biology arise from the fact that Darwin's theory is one of the Articles of Faith. The current dominance of the mutation-selection theory in the Western world, and the weak voices of those who oppose it, have led many nonbiologists to accept the dominant view that the problem of evolution has been solved. It is the purpose of this chapter to demonstrate that this view is unduly optimistic.

The Mutation-Selection Theory: Mutation by "Accident"

The mutation-selection theory stated briefly holds (a) that only genes control the heredity characters that are transmitted from parent to offspring, (b) that genes are capable of mutation, (c) that these mutations are never "directed" by the organism nor by the environment but only by the "accident" of the event which causes the mutation, (d) that these accidentally-caused mutations change the characteristics of the offspring, and (e) that the changed offspring are either favored by natural selection and become important in the subsequent population or die and are eliminated. Hence, small "accidental" changes in genes gradually change one species into another and bring about the replacement of an older species by a newer different one, better adapted to survive in a new and possibly quite different environment. This currently dominant concept of evolution has been bitterly attacked by several

biological minorities. Each specialist looks on the problem from his own peculiar vantage points and the unanimity of their different objections to the theory has brought with it no unity on which a replacement for the mutation-selection theory would be possible. Hence, as was pointed out in the earlier chapters, an unsatisfactory theory may continue to occupy a dominant position because it fills a vacuum which must be filled by some concept.

"Acquired" Characters

The principal differences among the disputants arise from different views on the effects of environment on heredity. There is a considerable disagreement concerning the inheritance of "acquired" characters. But both the adherents of mutation-selection and their opponents speak of the inheritance of acquired characters without defining the terms. It is obvious that the characters which differentiate the different kinds of cells in the body of a mammal must have been acquired in the course of the differentiation of the fertilized egg into the body cells, either by a change in the cytoplasm or by a change in the nucleus, or both, and, also, that these characters, which have obviously been acquired, become inherited characters, at least during the process of differentiation. The acquired characters that differentiate the different cells of the body comprising the liver, heart, lung, etc., the cells of which are descended from the single cell produced by the fusion of two sex cells must have been acquired by some environmental effect upon the initial cell of the tissue, probably because the position of that cell in relation to other body cells determined whether or not it would be differentiated. Hence, one might infer that the position must involve some difference in the external influences that impinge upon the cell and that directed the differentiation. It is clear, especially from Sonneborn's recent experiments, as well as from Boveri's much earlier ones, that the change may be due to a change in the nucleus or a change in the cytoplasm, and that a change in either, once induced, can be perpetuated indefinitely by vegetative division. Even in the absence of specific experiments, such as the above, the simple description of the differentiation of cells and tissues during the development of a fertilized egg into an adult would suffice to establish the fact that in a population arising from a single cell, environmentally-acquired characters are directed and inherited, and that the item producing the effect may be either the nucleus or the cytoplasm.

But differentiation in development from fertilized egg to maturity involves the transmission of a change through the members of a series of vegetative cells, while the transmission of acquired characters is usually discussed in terms of the sex cells, i.e., transmission from parent to offspring, rather than from cell to cell. The fact that characters acquired during development are inherited is taken for granted, and apparently ignored both by the proponents of mutation-selection and by their opponents. The Mendelists say that if the skin becomes tanned, the ability to produce dark skin cannot, by the act of tanning, become an inherited character in the next generation. This problem is assumed to be unrelated to the fact that the environmentally-acquired characters which differentiate the nerves from skin cells are inherited, as they obviously are.

Permanent and Temporary Modifications: Acquired Characters Are Not Inherited

According to the conventional Morganist-Mendelist theory, there are two kinds of hereditary change: (1) temporary or somatic modification and (2) permanent or genetic modification. The permanent modifications are controlled by genes and transmitted to the offspring according to Mendel's laws. Temporary modifications are not transmitted to the progeny. An example is the deposition of fat in a well-nourished animal. If an animal consumes more than his normal requirement for food, he becomes fat, but the hereditary differences characteristic of the offspring of a fat and a thin animal should not, according to Mendelian theory, result from the fatness or thinness of the parent. It is conceivable that the offspring may be modified, that is, extreme fatness or extreme thinness of the mother might affect the child in utero, but it would be assumed that, at conception, the embryo in a fat mother and the embryo in a thin mother would possess the same potentials—provided the eggs were identical genetically and had been fertilized by identical sperm. This general idea seems to be fairly well supported by a large accumulation of evidence. Another type of somatic or temporary modification is the darkening of the skin through exposure to the sun. This modification is temporary for each human concerned, but skin tan and adiposity differ because in the fat animal, each separate cell accumulates fat and then these same cells lose the fat as it is consumed by the metabolic activity of the body. But when the skin is tanned and pigment is deposited in a cell, the pigment is not lost until the cells themselves are lost by the sloughing off of the outer layer of skin. Thus, in tanning, the

effect on each cell is a relatively permanent one, while in becoming fat the effect on each cell is reversible. It is generally assumed that neither of these processes has any effect on the germ cells and this is the crux of the situation.

The Lingering Modifications of Jollos: Acquired Characters are Inherited

A third kind of hereditary change (different from temporary or somatic modification and permanent or genetic modification) was discovered by Jollos; he called it "Dauermodifikation." This is a modification which persists among the asexual offspring of an affected organism for a long time after the inducing agent has been removed and which disappears finally, but only after many generations. These lingering modifications, which persist on vegetative propagation, usually disappear quickly upon sexual reproduction. Jollos began his work in Germany in 1914 and was not able to obtain a sympathetic hearing in his own country. He escaped to the U.S.A. after Hitler took power, and the only sympathetic ear he found in this country was that of Goldschmidt, but Goldschmidt was an exile too, who, in spite of his brilliance, was equally if not more vehemently rejected by the Mendelists. In Germany, Jollos had had the prestige of being a professor, which was considerable in the days before Hitler. He found to his sorrow that an American professor was a step below a dentist, and this disillusionment broke his spirit even more than the failure of geneticists to recognize the value of his investigations. Jollos pointed out that the after-effects of a marked change in the environment can last an exceptionally long time in bacteria and protozoa. He found that exposure to high temperatures induced resistance to temperature and that exposure to arsenic induced a resistance to arsenic that persisted for many cell divisions in bacteria or paramecia. The resistance was lost rapidly, however, following sexual reproduction. As long as paramecia reproduced asexually they retained the resistance to arsenic that had been induced by exposure to arsenic, but immediately after sexual reproduction the resistance disappeared. In bacteria and paramecia the single cell is both a germ cell (that is, a sexual cell) and a vegetative cell, and the germ track is not isolated as it is in higher animals.

The German word "Dauermodifikation" can be translated into "lingering modifications" or "persistent modifications" and both terms are used to describe the changes that Jollos discovered. Mendelists do not accept the significance of these changes in evolution; they apparently do not consider them important in the origin of the species. But asexually propagated effects are important in the origin of the organs, that is, in the development of the complex differentiated structures that are produced in a multi-cellular animal or plant. The multi-cellular organism begins from a single fertilized cell that finally produces a great variety of cells, each one of which is supposed to contain the identical set of chromosomes and presumably the identical set of genes. If these genes are identical, the differences in cells from one tissue to another must have occurred in the plasmon. The previous discussion (Chapter 5) has shown that there is considerable evidence for the autonomy of the plasmon. Jollos' discovery that certain changes in the characteristics of single cells that had been exposed to different environmental conditions were transmissible to the descendants of the affected cell relates to the problem of the development of an organism from a fertilized cell (the origin of the organs), for the modifications characteristic of the cells of an organ persist for many cell-generations.

The Phenocopies of Jollos and Goldschmidt

Jollos and Goldschmidt investigated the occurrence of lingering modifications in a higher organism, the fruit fly, and their possible transmission to the offspring in successive generations. Jollos found that when fruit flies were exposed to a high temperature in the larval stage, alterations of the wing muscles occurred which caused the wings to be folded together in an abnormal way. These changes were not due to gene-mutations because they were not inherited as gene-mutations, but they resembled a gene-mutation called *Aeroplane*. Goldschmidt coined the word phenocopy to describe a change which was not a gene-change but which had the same appearance as a gene-change. The effect of abnormal temperature on the larvae of *Drosophila* had been observed by many geneticists but had always been considered to be a temporary modification. In Jollos' cultures most of these modifications were limited to a single generation, but in some cases the descendants of the abnormal fly also showed the aberrations. The changes were transmitted only by the mother. The abnormal fathers did not transmit the character to their offspring. The change persisted for only a few generations. Since the change was transmitted only through the mother, it appears that the changes that occur when a fertilized egg develops into the whole animal, that is, the origin of the organs, may be lingering modifications like

those that Jollos discovered in paramecia and in *Drosophila*. Jollos' results also suggest that lingering modifications may occasionally be transmitted to the offspring for several generations through the female line, that is, through the plasme. It seems strange that the Mendelists should have rejected Jollos' work on lingering modifications, because it provides an explanation of the origin of the variety of organs derived from a single fertilized egg. It is even stranger that the Michurinists do not exploit his theory, since it is directly pertinent to their ideas concerning the effect of the environment.

Sturtevant's Theory of Delayed Gene Action

The shells of fresh water snails may exhibit either left-handed or right-handed coiling, i.e., two kinds of mirror-images are found. All hybrids between these two kinds of snails produce progeny in which the shells coil precisely as they do in the mother. All progeny of left-handed mothers are left-handed and all progeny of right-handed mothers are right-handed. Because snails are hermaphrodites, it is possible for the hybrids to be self-fertilized. The appearance of left-handed shells among the offspring of self-fertilized right-handed hybrids revealed that the gene for right-handedness is dominant (or normal) while the gene for left-handedness is recessive.

Sturtevant says: "Other examples are known in which there is a delay in the expression of a phenotype, the result being that individuals may show a phenotype dependent on genes no longer present" (The italics are mine.).¹ Sturtevant's views were extended by him to cover those cases of maternal inheritance in which maternal characteristics persist after backcrossing for more than ten generations to the male, but it hardly seems that the effect of "female" genes could persist over so long a period.

Delbrück's Explanation of Environmentally-Induced, Stable (Inheritable) Variations

Delbrück has recently formulated another theory (consistent with the one gene-one enzyme concept) to explain the persistence of the changes induced by the environment, such as the lingering modifications of Jollos. Delbrück proposed that if different genes control the synthesis of the substances A and B, it might be possible that only one of the compounds could be produced at a time. Once the production of substance A is initiated, for example, conditions are established under which substance B cannot be produced, and substance A would continue to be produced until some condition removed it. The removal of substance A would make possible the production of substance B, and once production of substance B was initiated, it would continue to be produced, excluding the production of substance A. Waddington has devised a similar theory to explain differentiation. Both of these theories deny the autonomy of the plasme and identify the genome alone as the autonomous hereditary apparatus. But Delbrück's theory concerns only the balances between an existing series of potentials, i.e., mechanisms already established under gene control involving a series of alternative pathways; it in no wise explains the origin of the new and hitherto unknown potentials.

Both Delbrück and Bateson look upon the changes that occurred during evolution or during adaptation as involving no new changes in the organism. Although the mechanism imagined by Delbrück² may very well exist, it is a negative rather than a positive answer to the basic question of progressive evolution and is strongly reminiscent of Bateson's concept of evolution by loss. The possibility that another mechanism does exist that can achieve the addition of totally new capacities to the organism is not excluded.

Lamarck and the Lamarckian Theory

After this necessarily brief account of the principal differences among contemporary biologists concerning the inheritance of environmentally-induced changes in living organisms, it may be useful to begin a roughly chronological consideration of the theories which preceded, and then followed, the mutation-selection theory of evolution currently espoused by the Morganist-Mendelists.

Jean Baptiste Pierre de Lamarck worked in France during the late eighteenth and early nineteenth centuries. He was a figure in the French Revolution and a biologist of wide interests. In many respects he may be considered to be the most conspicuous originator of the idea that environmentally-acquired characteristics may become inherited characteristics. Indeed, the type of evolutionary thought which accepts this view is known as Lamarckism. According to Lamarck, variations arise in organisms in response to an urgent need and striving on the part of individuals and through use and disuse of organs. Lamarck regarded these variations as heritable. Sirks has translated two of Lamarck's (1809) basic rules:

"1) In every animal which has not reached the bounds of its development, one or another organ is gradually developed by frequent and continued use and an ability is given to this organ proportional to the duration of its use. On the other hand, a continual neglect of an organ results in an almost imperceptible weakening and gradual decline until final disappearance occurs.

"2) Everything that nature gains or loses in individuals under the influence of environment (to which the race was exposed over a long period of time and thus through the continued use of an organ, or by a continued non-use of a part of the body) will be preserved in individuals which originate by means of reproduction provided that these changes occur jointly in both sexes, or at least in those individuals which have given rise to the new ones."³

Darwin's Theory of Pangenesis or the Inheritance of Acquired Characters

According to the theory of evolution propounded by Darwin, natural selection operates to eliminate those least fit to survive. The phrase "survival of the fittest" was coined by Spencer, who was a more rigorous proponent of selection than Darwin himself. Darwin proposed (1) that new species did originate and that they were related to each other by a single line of descent (2) that these new species were selected by competition: one species driving out another, the individuals of the new species eliminating their less fit competitors and thus gaining supremacy. The acceptance of Darwin's views concerning the occurrence of evolution does not necessarily lead to an acceptance of the mechanism of evolution proposed by him. Geneticists are satisfied with the fact that evolution occurred and with Darwin's theory of natural selection, but they reject his theory of pangenesis to explain the inheritance of acquired characters.

Darwin's pangenesis-hypothesis assumed that some of the temporary changes in an animal or a plant eventually became permanent hereditary characters, for example, if the skin cells became dark through tanning, something was transmitted from the skin cells to the sex cells which increased the capacity of the sperm or the eggs for making the offspring dark.

Darwin proposed that all organs or cells of the body produced "gemmules" or "pangenes" that circulated in the blood and were transmitted to the sex organs where they participated in the formation of the sex cells. He suggested that when the body underwent environmental modification the "pangenes" were also modified and communicated the modification to the sex cells, thus transmitting the modification to the succeeding generation. Even today the Communist party line insists on strict adherence to Darwin's original views as espoused by Marx, Engels and Lenin.

Weismann's Rejection of Lamarck and Darwin

August Weismann (1834-1914) achieved fame by rejecting the theories of Lamarck and Darwin concerning the inheritance of acquired characters. He developed the concept of the isolation and the purity of the germ-plasm. He proposed that the germ-plasm is separate from the somato-plasm and that a change in the latter could not affect the former. His experimental evidence was obtained by cutting off the tails of mice for a series of generations and observing that the tails of the progeny were all of normal length.

It seems remarkable that this experiment could have influenced the thinking as deeply as it did for so long a time. Weismann designed the experiment to test Darwin's theory of the effect of changes in the body on changes in the sex cells. Weismann suggested that an amputated tail could no longer send back its messages to the sex cells and impress the sex cells with the memory which would enable them to reproduce new tails in the next generation. The fallacy in this experiment is that the tail could not be cut off before it was formed and had, presumably, already sent its message to the sex organ.

Although Weismann's theory of the isolation of the germ-plasm might apply to higher animals, it cannot apply to plants because the sex cells of plants may arise from any tissue, and the sex organs are not completely insulated, nor isolated, from the body tissues. Mendelists emphasize the autonomy of the genome without considering the possibility that the plasmone may be changed by the environment, and Mendelists often define the genotype as "the essence of life," thus excluding the plasmone. Mendelists state that it is not possible for an organism to acquire any capacity except that controlled by a gene, and that such acquisitions can only occur through the mechanism of gene-mutations. The concept is a definitive denial of the autonomy of the cytoplasm and any of its components, except, of course, the plastids. It is interesting that so much stress should be laid on the theory of the germ-plasm in animals when it is known that the theory does not hold in any plant nor even in all lower animals. The limitation of the concept of the continuity of the germ-plasm theory has not been understood by many prominent Mendelists whose backgrounds were exclusively in Zoology.

Bateson's Theory of Evolution by Loss

The earliest proponent of Mendelism in Britain was William Bateson. Although he was an ardent Mendelist, he was never really convinced that the genes were located on the chromosomes. He held the theory that a dominant gene was the presence of a factor while a recessive gene was the absence or loss of the corresponding factor. This view was later altered when it was discovered that there were more than two manifestations of a gene, i.e., many genes are characterized by several different recessive manifestations. In 1914, fifty-five years after the appearance of *The Origin of the Species*, Bateson was inaugurated as president of the British Association. In his inaugural address he formulated his theory of evolution by loss.

The first full perception of the significance of variation we owe to Darwin. . .[but] the principle of natural selection cannot have been the chief factor in delimiting the species of animals and plants, such as we now with fuller knowledge see them actually to be. We are even more sceptical as to the validity of that appeal to changes in the conditions of life as direct causes of modification, upon which latterly at all events Darwin laid much emphasis, . . . We go to Darwin for his incomparable collection of facts. . . . but to us he speaks no more with philosophical authority. . . .

The practical and experimental study of variation and heredity has not merely opened a new field, it has given a new point of view and new standards of criticism. . . . [Bateson is saying that Mendelism has changed the concept of evolution.]

Now, of the origin of new forms by loss there seems to me to be fairly clear evidence, but of the contemporary acquisition of any new factor I see no satisfactory proof, though I admit there are rare examples which may be so interpreted. We are left with a picture of variation utterly different from that which we saw at first. Variation now stands out as a definite physiological event. We have done with the notion that Darwin came latterly to favour, that large differences can arise by accumulation of small differences.

. . . At first it may seem rank absurdity to suppose that the primordial form or forms of protoplasm could have contained complexity enough to produce the diverse types of life. But is it easier to imagine that these powers could have been conveyed by extrinsic additions? Of what nature could these additions be? Additions of material cannot surely be in question. We are told that salts of iron in the soil may turn a pink hydrangea blue. The iron cannot be passed on to the next generation. How can the iron multiply itself? The power to assimilate the iron is all that can be transmitted. A disease-producing organism like the pebrine of silkworms can in a very few cases be passed on through the germ-cells. Such an organism can multiply and can produce its characteristic effects in the next generation. But it does not become part of the invaded host, and we cannot conceive it taking part in the geometrically ordered processes of segregation. . . .

That primordial life may have been of small dimensions need not disturb us. Quantity is of no account in these considerations. Shakespeare once existed as a speck of protoplasm not so big as a small pin's head. To this nothing was added that would not equally well have served to build up a baboon or a rat.

In spite of seeming perversity, therefore, we have to admit that there is no evolutionary change which in the present state of our knowledge we can positively declare to be not due to loss.⁴

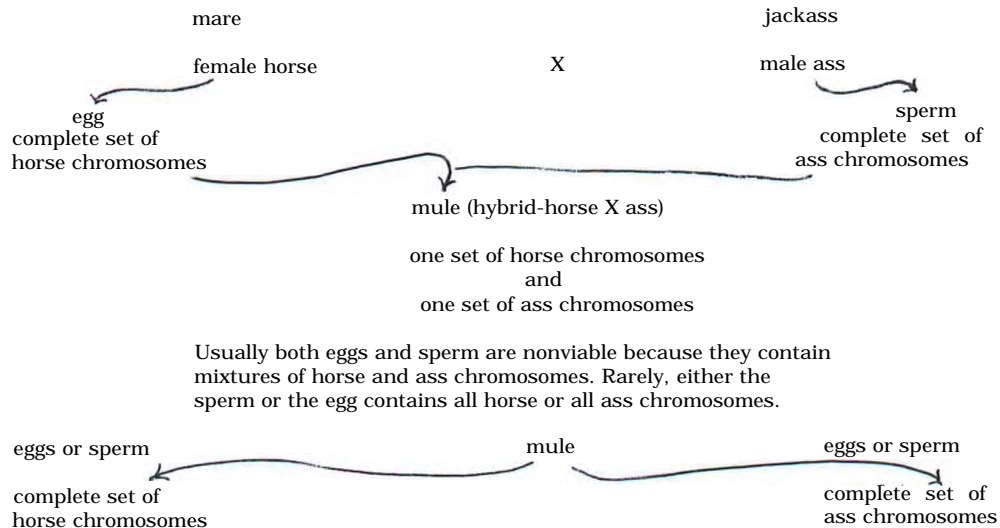
On first reading one might suppose that Bateson was proposing to reduce the concept of the evolution by mutation to an absurdity and that his whole lecture was a masterpiece of irony. But he was deadly serious. He actually believed that the first primordial life carried the complete potential of all life and that all advances had been made by a series of losses. It is interesting that he was skeptical of the effects of natural selection, for he made the statement, "The principle of natural selection cannot have been the chief factor." Bateson rejects the idea that life could have become more complicated by the addition of external autonomous components to a complex system, but it is this view which appears to many to offer the only reasonable explanation to the complexity of contemporary living things. Bateson's lecture is interesting in relation to Goldschmidt's view that the genome has not increased significantly in volume over long evolutionary periods.

DeVries and the Mutation Theory

DeVries is generally credited with the formulation of the mutation theory of evolution. DeVries worked with the evening primroses, making crosses between different species of the evening primrose on the assumption that each parent species was a pure species. These so-called species, however, were not actually pure species, but each was a hybrid between two different species, comparable to the mule which is a hybrid produced by crossing a mare and an ass. Occasionally, DeVries recovered a new kind of hybrid by crossing two of the different hybrid parents, as one might expect occasionally to recover a horse or an ass (or a mule) by hybridizing mules. The supposedly new species which DeVries discovered "bred true," i.e., when inbred they produced individuals only like themselves. It

was this particular fact that convinced deVries that he had really solved the problem of the Origin of the Species. On the basis of the supposedly new species that deVries recovered by crossing two supposedly pure species, he formulated the mutation-theory. It is an interesting paradox that deVries formulated his mutation-theory without actually working with changes in individual genes.

The following diagram shows the mule parallel of deVries' experiments and considers the theoretical possibilities of horse X ass hybrids.



Mules are generally sterile either when mated to other mules or to either horses or asses because the chromosomes in the hybrid are assorted at random and generally the sex cells of the hybrid contain mixtures of horse and ass chromosomes so that it is highly improbable on a statistical basis that either a "pure horse" or a "pure mule" sex-cell will emerge. But a mule-by-mule hybrid could produce, on rare occasions, either a horse or an ass or another mule. If the chromosomes in the sperm or the egg were assorted in such a manner that a single mule sperm contained only horse chromosomes (or only ass chromosomes), such a sperm should act essentially the same as a horse (or ass) sperm. Hence, horse by mule matings could produce either horses or mules; ass by mule matings could produce either asses or mules. If one were unacquainted with the original species, the horses or asses produced by the hybrid would be looked upon as rare "mutations" especially when one discovered they "bred true."

Morgan's Views on the Mutation-Selection Theory

In *The Theory of the Gene*, Morgan used Johannsen's experiments on the heredity of pure bred lines of beans to support the mutation-selection theory of evolution. Beans are self-pollinated, hence highly inbred, and there is much less genetical variation in beans than in cross-bred organisms. The seeds from a single plant, i.e., from a single inbred line, vary considerably in size, but Johannsen found that if he planted large and small seeds from the same plant, the large seeds and the small seeds both produced plants which yielded seeds of the same average size; the average seed size was the same whether the plants had grown from the large or small seeds, provided they came from the same plant. Thus, although the sizes of the different seeds depended on the environmental conditions of nutrition and position in the pod, Johannsen inferred that the genes were stable and that the environment had relatively little effect on the capacity of the parent to transmit its genetical potential to the offspring; he inferred that although environmental conditions may change the phenotype, that is, the size of the seed, such conditions do not change the genotype nor the genetical potential of the plant. Michurinists have not deigned to answer Johannsen probably because they have not examined the basic philosophy of Mendelism with critical care. To quote Johannsen directly:

The isolation of pure lines from plant-populations has been the instrument for gaining the conviction that selection is not able to shift the nature of genotypes. The well-known displacement of the "type" of a population by selection—this displacement proceeding from generation to generation in the direction

indicated by the selection—is due to the existence a priori of genotypical differences in such populations.

. . . [This remark of Johannsen's refers to selection experiments in plants and animals by which either the largest or the smallest progeny are inbred and the selection succeeds in producing, respectively, larger or smaller strains. This kind of selection, Johannsen says, is a priori due to gene selection. It does not occur in beans.]

Within pure lines—if no mutation or other disturbances have been at work—or within a population in which there is no genotypical difference as to the character in question, selection will have no hereditary influence.⁵

In discussing Johannsen's experiments, Morgan says:

Johannsen detected nine races of beans in those he examined. He interpreted his results to mean that the differences in size of the beans from a given plant are due to its environment in the widest sense.

It was possible to demonstrate this with material in which the members of each pair of genes were identical when selection began. Selection is shown to have no effect in changing the genes themselves. . . . If selection changes the character of the individual, it must, under these conditions, do so by changing the gene itself.⁶

Morgan's Comments on the Relation of Experimentally Produced Mutations to "Wild Type" Genes

The mutation-selection theory of evolution is based on the assumption that the changes in evolution are based on the selection of gene-controlled characters of the kind that distinguished Johannsen's pure lines of beans from each other. Mutations studied in the laboratory have never produced a new species, but, in spite of this, the concept has been used to explain the origin of new species. Morgan, who was concerned about this discrepancy, says:

Since only the differences that are due to genes are inherited, it seems to follow that evolution must have taken place through changes in the genes. It does not follow, however, that these evolutionary changes are identical with those that we see arising as mutations. It is possible that the genes of wild types have had a different origin. In fact, this view is often implied and sometimes vigorously asserted. [Morgan means that since the normal (wild-type) genes are almost always dominant over the mutant genes, it is difficult to understand how the recessive mutants could become established well enough to effect evolution. Dominant mutations are lethal in the homozygous condition, and Morgan realized that the inviability of dominant mutations raised a question concerning their significance in evolution. It seems clear that Morgan felt that Bateson's theory of evolution by loss was unacceptable. Although he did accept the view that most of the mutations encountered in *Drosophila* were losses, he felt that those that he believed were important in evolution must be somehow different if they were to account for evolution. Morgan's mind was too honest and too restless not to be disturbed by the inconsistency. In continuing his discussion Morgan says:] It is important, therefore, to find out whether there is any evidence in support of such a view. DeVries' earlier formulation of his famous mutation theory might at first sight seem to suggest the creation of new genes.⁷

But deVries' experiments, it was discovered later, had failed to achieve this end. Morgan began his experiments in *Drosophila* because he had expected, on the basis of deVries' experiments, to discover mutations in *Drosophila* that would transform one species into another. But he did not succeed, nor has anyone else ever succeeded, in transforming one species into another by gene-mutation. It is even more pertinent to the theory to realize that no one has ever discovered a gene-mutation that produced anything except an organism less capable of survival under natural conditions than the normal organism.

In a subsequent lecture, Morgan discussed experiments in which hybrids between naturally occurring species of *Drosophila* had revealed that the differences between these species were inherited in the same manner as gene-controlled characteristics. He followed this discussion with a comment so uncharacteristic of his natural disposition that one might suspect that criticism of the mutation-selection theory had disturbed his generally unflinching good nature. The quotation follows:

Without elaborating, I wish to point out briefly that there is to-day abundant evidence showing that the differences, distinguishing the characteristics of one wild-type or variety from others, follow the same laws of heredity as do the so-called aberrant types studied by geneticists.

Even this evidence may not satisfy the members of the old school because, they may still say, all these characters that follow Mendel's laws, even those found in wild species, are still not the kind that have contributed to evolution. They may claim that these characters are in a class by themselves, and not amenable to Mendelian laws. If they take this attitude, we can only reply that here we part company, since ex cathedra statements are not arguments, and an appeal to mysticism is outside of science.⁸

Karpechenko and the First New Species

Genetics has produced a new species, however. It was called Raphano-brassica because it was a hybrid between the radish (*Raphanus*) and the cabbage (*Brassica*). The hybrid was produced by Karpechenko, a Mendelist, who died during the war in Leningrad under unspecified circumstances. The hybrid "bred true" like the "mutational" hybrids first described by deVries, but had the additional unexpected character of being unable to crossbreed with either of the two parental species. It would not repay us to explore the complicated technical details by which this new species was made, but they are clearly understood and formed the basis for many significant advances in the improvements of plants.

Martin's Criticism of the Mutation-Selection Theory

Cecil Martin, of McGill University at Montreal, has pointed out that publication of Darwin's *Origin of the Species* touched off a debate revolving around the question of whether evolution is, or is not, a fact; that none of the disputants distinguished the question, have species evolved? from the question, how do species evolve?, scarcely noting that these two questions are distinct and separate. Martin says:

The mutation-selection theory which, with some minor variations, is the doctrine championed by all geneticists, has attained an almost universal acceptance

What actually has been experimentally demonstrated is that disturbances of a certain type occur not infrequently in germ cells; that most of these render the individuals to whose formation the affected germ cell goes, incapable of living; that many do not completely destroy the individual's power to live, but gravely lower its vigour and fertility; that a few affect the individual's vigour and fertility so slightly that it can survive in the shelter of domestication, that, so far as we know, no race carrying one of the disturbances is able to survive in a wild state for more than a few generations. These disturbances can be produced by applying some very injurious agents to germ cells. When the resulting individual is able to survive for a while, it usually manifests some change in its hereditary constitution, usually of a grossly disruptive kind. We call these disturbances gene mutations. That, and no more, is experimentally verifiable. All the rest of the mutation-selection theory is an over-stretching, an inflation of these facts.

There are, of course, many other experimentally established facts in genetical science, but they do not affect the truth of the mutation-selection theory one way or another.

There is another reason for believing that whatever role selection may play in natural evolution, mutations do not supply the raw material on which it operates. Mutations affect viability. All known ones affect it adversely and whether any affect it favourably is highly doubtful. Anyhow, all affect viability, and viability is an independent character. The changes which mutations effect in viability are not dependent on, or parallel to, the value—advantageous or disadvantageous—of the changes if any which they produce in visible hereditary characteristics. Often the two are directly contrary to each other. Now, viability is a character of such supreme importance that in any process of natural selection its variations would take a high priority over variations of any other characteristic; so much higher that it would bring selection for a high perfection of minute individual parts to a complete standstill.⁹

Some biologists may, and I believe do, feel uneasy over some of the geneticists' dogmas but they hesitate to voice their misgiving. . . . For geneticists in general have not been backward in asserting or implying the exclusive right of their science to arbitrate on such matters. So biologists in general find it is safer to keep any doubts they may have to themselves. . . .

It is the contention of this book that nevertheless the mutation-selection theory is unsustainable and that the usual genetical approach to the problem of the mechanism of evolution is too narrow and too speculative. . . . And it involves a great many hidden and unrealized subsidiary speculations most of which are unsupported by any evidence and many of which are highly conjectural and extravagant.

"It is the great strength of Darwinian selection theory," writes Professor Medawar (1951), "that it appeals to the working of no mechanisms that are not severally well understood and demonstrable. 'Selection' does occur—that is, the members of a population do indeed make unequal contributions to the ancestry of future generations; new variants do arise by the process of mutations; the process of segregation does reassert the combination of hereditary factors."

Each of Professor Medawar's assertions is indisputably true, yet the import of his statement, as a whole, may be utterly false. For it implies that the three facts mentioned are not only certain in themselves but provide a sure and complete foundation for the mutation-selection theory, and this tacit implication is very far from being certain. While it is certain that "the members of a population make unequal contributions to the ancestry of future generations," it is not at all certain that these inequalities depend so heavily on the organisms' own characteristics and so lightly on the accidents of time, place and circumstance that they are often equivalent to a directed selection. While it is true "new variants do arise by the process of mutation," it is definitely not true that healthy and fully viable variants, such as occur in endless millions in natural wild populations and such as could participate in a process of natural evolution, are known to arise by mutation. While it is true that "the process of segregation does reassert the combinations of hereditary factors," it is not true that segregation stops there. Having shuffled the pack and dealt an excellent hand, segregation immediately reshuffles the pack and distributes the cards again.

It is just as speculative to press known facts beyond their proper range and force from them an explanation of events as it is to invent facts. It is indeed a more subtle and dangerous form of speculation. It speculates under the guise of avoiding speculation.

. . . Perhaps it was unfortunate that the question had been engrossed by genetics for many years. For I hope that without giving offence I may say that a young and very successful science like genetics somehow imparts to its devotees some measure of those tendencies which are characteristic of youth, particularly of successful youth, everywhere, namely the tendencies to overestimate the relative size and significance of its own activities and to be not backward in expressing assurances.¹⁰

Fritz Went on Competition Versus the Biological Niche

Martin's emphasis of the low viability of mutations leads him to the view that whatever gene mutation does, it does not produce a stock capable of surviving under natural conditions. Martin also points out that an enormous population does not lead to the selection of superior individuals but merely to degrading of the entire population. A heavy seeding of plants in a field does not lead to the production of one superior plant; it only makes all the plants stunted. The enormous population flourishing in India has not led to excessive vigor of any individual member but to a general decrease in vigor of all members of the population. Thus, one should not look to selection from a dense population of higher plants or animals for a solution to the problem of evolution but rather to a general loss of vigor of the entire population under such circumstances.

It is interesting that Fritz Went, formerly of the California Institute of Technology and later director of the Missouri Botanical Gardens, has arrived at a similar view. Dr. Went is not a geneticist but a plant physiologist with a long and distinguished record of achievement. He has explored every continent and is familiar with the growth of plants in the rain forest, the desert and the arctic. He makes a particular point of the fact that competition between plants does not seem to be a significant item. Each plant seems to find a peculiar niche in the environment, and it fits this niche rather than enter into competition with other organisms. He particularly points out that in spite of the density of growth in the rain forest, where plants grow with a profusion completely unknown elsewhere, there is little evidence of competition between plants but rather of a precise fitting of each plant into its environment. He concludes that natural selection and competition cannot have had the overwhelming importance in evolution ascribed to them by geneticists. An interesting parallel to this phenomenon is the experiment performed by Jens Clausen of Stanford University. Clausen discovered two species of flowers which were abundant in nature and which could be hybridized in the laboratory. The hybrid grew perfectly well in the laboratory but was nowhere in evidence in nature. Clausen discovered that the hybrid had peculiar requirements concerning the acidity of the soil, and since there was no soil meeting precisely this requirement in the environment of the parents, the hybrid seed did not grow in nature. This fits the view that seeds are produced in enormous profusion and planted everywhere, not with the result of producing an enormous population in which the members compete with each other for survival, but rather with the end result that seeds are planted in every conceivable ecological niche and every kind of environment, and that those which land in the environment for which they are fitted may grow and produce a plant, while those which fall elsewhere do not compete; they simply fail to germinate.

The Isolating Effects of Food Preferences

Martin proposes that biological races in animals may have originated by the isolation produced by feeding habits rather than by mutation and that this kind of isolation may be the first step in the development of a new species. He points out that feeding habits are difficult to change once they become established, and may produce an isolation even more effective than geographical isolation.

The severe winter of 1881 destroyed the marine grass at Abbotsbury on which the swans used to feed, and for three years the birds had to be given grain. They took to it reluctantly and many died. Meanwhile, the marine grass recovered and grew again, but the swans by now had developed a preference for the grain and were unwilling to return to the grass (Cornish, 1895). Here a new habit imposed on the birds for three years was finally adopted and preferred. The red deer was originally a forest animal. But with depletion of the Scottish forests they were driven out and compelled to live on the open moors. Now after many generations on the moors, they evince an unwillingness to return to the forested lands (Matthews, 1952). The human head louse and body louse are so unlike in appearance and habits that for long they were regarded as distinct species. Then, in 1917, Sikora reported that by compelling the head louse to live on the human body, she had gradually converted it, in the course of four generations, into the body louse. In 1919, she withdrew her paper, stating it had been based on a misunderstanding. But meanwhile her assertion had been confirmed (Howlett, 1917-18; Bacot, 1917; Keilin and Nuttall,

1918-19). Howlett stated that by the third generation 75% of the individuals would be identified as body lice and they had now lost all tendency to migrate to the scalp and laid their eggs on clothing. Once more a new habit, at first imposed, was ultimately adopted.

. . . Gause (1934) . . . enunciated an important principle, namely that "two closely related species with identical ecology cannot live together in the same place." Commenting on this principle, Fisher and Lockley (1954) point out that it means that, "Unless two races derived from the same parent-species which meet in the same area are already, at least partly, differentiated as regards their feeding habits, one will eliminate the other. If this is true—and there is every reason from the evidence to believe that it is—then the origin of a species will depend on its possession of a special pattern of food preferences." In other words, the first step in evolution is the breaking up of a species into two or more biological races through the development of different habit preferences. Somehow the addictions of biological races must, in time, become truly hereditary. But how?

To recapitulate, all living organisms form habits. They develop preferences in all their activities and these preferences are transmitted, in a measure, from generation to generation. In this way biological races are formed. The distinguishing characteristics of these biological races are not simple modifications, that is, individual characteristics, individual responses to environmental factors, for they do not appear fully in the first generation placed in the environment concerned. . . . They obviously fall into a category intermediate between modifications and hereditary characteristics to which the name of lingering modifications has been given.¹¹

Thus in dealing with the question of the origin of biological races, which is the first step in the origin of species, Martin contends that the important thing in animals is the psychology of habit-forming characteristics. That is, when animals feed, they tend to form a habit which is imposed upon the species and these feeding habits tend to isolate them in such a manner that two different species, or even two different races, can meet in the same area without competing. In applying this concept to the problem of evolution of animals he suggests that the psychology of habit formation is an effective means of producing a new biological race.

Adaptation by Lingering Modification

After considering the effects of habit on the formation of biological races, Martin turns to the effect of lingering modifications on adaptation. He suggests that most adaptations are due to lingering modifications which (unlike gene-mutation) do not reduce viability.

One particular instance of protective colouration which at first sight looks as if it were due to natural selection, the whiteness of animals living in areas of perpetual snow, proves on examination to be more probably a product of lingering modifications. . . . If stoats from a region where they do not usually turn white are experimentally exposed in autumn to cold, about 50% of them turn white. Furthermore, a stoat exposed thus one autumn to cold till it turns white will whiten the next autumn even though the temperature is high (Matthews, 1952). The same author states that an American weasel exposed during summer to long periods of artificial daylight turns white in autumn even though the temperature remains above 50 degrees F. Hares from Scotland introduced into Southern Ireland, where snow is rare continued to whiten each winter for some years and then gradually lost the habit' (Barrett-Hamilton' 1899).

. . . Turesson (1925a, 1925b) found that the strains of many plants occurring naturally on the island of Oland, differed in certain characteristics from the strains of the same species on the mainland. . . . When mainland strains of the same species were cultured on the island they developed the exact same characteristics in the course of a few generations. In this case, however, the characteristics were not hereditary, they disappeared in the course of a few generations when the strains were once more returned to the mainland. Obviously they were lingering modifications.

. . . The modificatory and hereditary strains are exactly alike. Turesson could not distinguish between them except that when both were cultured for several generations in a slightly different environment, the modificatory race slowly lost, while the hereditary race retained the characteristics they possessed on the island. So it is the modificatory race that enjoys an advantage over the hereditary one, namely that of being better able to meet a change of environment.

Alone among modern biologists, Turesson (1931) grasps and tries to meet this point. He suggests that strains in which such characteristics are hereditary may enjoy the advantage of developing them at an earlier age and to a more marked degree than races in which the characteristics are modificatory do. He cites no direct evidence for this, but thinks it is supported by the fact that towards the centre of a race's distribution its peculiar characteristics are usually hereditary, while at the periphery they are more often modificatory. . . . The point at issue is, not whether such lingering modifications are, in time, converted into truly hereditary characters, but whether this conversion could possibly take place by means of mutations and selection. It seems quite certain that in time the conversion is accomplished.

Turesson's point, that at the centre of a race's range the characteristics are usually hereditary, whereas at the periphery they are usually modificatory, points to this, for at the centre of the race's range the characteristics are probably phylogenetically older.¹²

Thus, in addition to considering the importance of habit formation in producing biological races, Martin suggests that lingering modifications, like those described by Jollos, could be responsible for the changes in animals which have been supposed to be due to mutation-selection. He also supposes that lingering modifications eventually become hereditary characteristics. Genes originating at the center of the range, according to Martin and Turesson, control stable hereditary factors while at the periphery of the range these same characters are lingering modifications not yet gene-controlled. They suggest that a lingering modification may become a gene-controlled character, but no mechanism by which this can be effected has been proposed or demonstrated.

The Effect of the Environment Upon the Domestication of Animals

Martin considered the problems involved in the domestication of animals and noted that Darwin was familiar with the peculiarities of the domestication of animals. To quote directly from Martin:

Of our domestic duck, Darwin (1868) wrote:

"An accurate and well-known observer in England has described in detail his oft repeated and successful experiments in domesticating the wild duck. . . . His young birds always changed and deteriorated in the course of two or three generations; notwithstanding that great care was taken to prevent any crossing with tame ducks. After the third generation his birds lost the elegant carriage of the wild species, and began to acquire the gait of the common duck. They increased in size with each generation and their legs became less fine. . . . His birds continued to pair together and never became polygamous. . . . I have given these details because no other case, as far as I know, has been so carefully recorded by a competent observer of the progress of change in wild birds reared for several generations in domestic conditions."

As regards the turkey, Darwin (1868) quoted Bachman "who had seen turkeys raised from the eggs of the wild species, lose their metallic tints and become spotted with white in the third generation." McIlhenney (1915) wrote:

"My experiments establish first, the turkey can be domesticated and that each succeeding generation bred in domestication loses something of the wild disposition of its ancestors; second, that the wild turkey bred in domestication, changes its form and the colour of its plumage and its legs, each succeeding generation, degenerating more and more from those brilliant colours which are so constant in the wild turkey of the forest; so that it is simply a question of time, and indeed a very short time—when they will lose all their native wildness and become clothed in all the varied colours of the common domestic turkey, in fact, be like our domestic turkey—yes, be our domestic turkey."

. . . Unfortunately, reliable records of the procedures followed in domesticating wild animals are scarce. Ritchie (1920) states that in Scotland a half-domesticated type of pig was common over a long period. These animals lived in herds, closely resembled wild pigs, were covered with bristles and foraged for themselves in the woods. But their habits had changed to the extent that they fed by day instead of by night and twilight and the boars remained with the sows. Such pigs were to be found in Orkney and Shetland up to the second half of the nineteenth century. The "Irish" pig of the eighteenth century was similar. The characteristic features of our modern highly domesticated breeds did not begin to appear until the animals were brought into high domestic conditions. From all accounts it seems quite evident that down to relatively recent times domestic cattle and sheep were of the same half-domesticated type. Indeed the resources available to farmers until comparatively recent times did not permit of a high standard of domestication. No forage plant except grass was known and the means for saving and preserving large quantities of hay did not exist. During summer when grass was plentiful the cattle put on flesh and those required for human consumption were slaughtered in autumn and their carcasses salted. They were poor lanky beasts at best. The remainder, the breeding stock, had to fend for themselves in winter on what poor forage was available, supplemented perhaps sometimes in times of snowfall with a little hay.

The introduction of the turnip into England revolutionized farming. It gave farmers a rich supply of winter feed. The industrial revolution and rise of technology developed machinery and means of transport which enabled farmers to maintain animals the whole year round on full diets and in comfort and shelter. All breeds, even the poorest, responded to the new and better environment. In all, the special characteristics of modern superior domestic breeds, greater size, early maturity, increased and irregular fertility, developed to some degree.

All our domestic breeds, even the most superior, lose their superiority in a few generations when poorly housed and fed. Domestic animals have been turned out in many countries and have given rise to feral herds. Feral goats are almost or entirely indistinguishable from native wild goats. The feral horse everywhere becomes a shaggy, medium-sized animal like the wild pony. Domestic pigs become feral, according to Darwin, in the West Indies, South America, the Falkland Islands and other places, and in all of these the feral animals, in a few generations, became lanky, long-faced, coarse skinned and bristly and the boars had large tusks. The young, moreover, were again striped.

Some domestic pigs were given to the Maoris by De Surville in 1769, and some more by Capt. Cook in 1773. The descendants of these are now very wild, cunning and speedy and the boars have very large tusks (Donne, 1924). It is not possible to attribute this development of certain traits in domestic breeds

to mutations and natural selection. The change in both directions is too rapid to be accounted for by any known mutation rate, and both changes are invariably associated with diet and general care. In every well-fed, well-housed stock these traits arise in some degree; in every poorly-fed, ill-housed stock they regress. The changes come on en masse, though with different speed in different individuals, and not individually as would be the case if they were due to mutations. . . .

It seems therefore that Darwin greatly overestimated the part that human selection has played in the genesis of superior domestic breeds. He first overestimated the degree of selective breeding practiced by farmers. He was misled by some ancient writers who realized the value of selection and advocated its use into thinking that selection was generally practiced. But until quite recent times the overwhelming majority of farmers had neither the means nor opportunity to select. They were hard put to keep the few poor beasts they had alive through the winter and were in no position to discard any animals or any chance of replenishing their stock. Consequently farmers in general became quite careless and bred from any animal that would breed.

Even today when opportunities for careful selection abound and agricultural communities enjoy a far higher standard of education, governments find it necessary to enact very strict laws against using inferior animals for breeding purposes. To be sure, in ancient times much care and selection was practised in breeding the animals used as playthings or for sport by the rich, but selective breeding of farm stock in general is a modern innovation. Then, secondly, Darwin overlooked the fact that far-reaching and revolutionary improvements in the care and feeding of farm live stock had been introduced in the era immediately preceding the application of careful selective breeding to farm animals. He attributed all of the improvement which the selected strains acquired to the selection practised upon them and none to the immeasurably better conditions in which the strains were maintained for several generations. No doubt, selection played an important part in the building up of these strains but it was probably a much smaller part than Darwin estimated. Anyhow, three facts seem quite certain: 1) No superior strain has ever emerged in a poorly fed and poorly housed stock. 2) All stocks receiving superior food and care for several successive generations improve greatly though of course different strains respond at different rates to such conditions. 3) The most superior breeds ever attained degenerate in the course of a few generations if they are poorly fed and poorly housed, and this despite intense selection. . . . Wild mallards have been domesticated many times, and on every occasion the birds in domestication slowly and progressively became polygamous, developed irregularities in their breeding habits, lost their brilliant colours; their wings became shorter, their bodies heavier and their legs larger. In comparison with wild birds, domestic ones have smaller wing bones and stronger leg bones. The same results attended the domestication of the wild turkey. Jungle fowl were domesticated so long ago that we have no record of the precise stages of the process, but we know that modern domesticated fowl have almost lost the power to fly and that relative to those of the wild jungle fowl, their wing bones are reduced and their leg bones enlarged. The cocks are polygamous and the hens' reproductive activities enormously increased.

Every time that wild pigs have been fully domesticated, their progeny have gradually and progressively lost the coarse skin of their wild ancestors; their young lose the striping of young wild pigs and the tusks of the boars are enormously reduced. These changes cannot be mutational; they occur universally in all individuals, in every stock, though with different ease and rapidity in different individuals. If they are mutational in origin, the aid of human selection would have been necessary to eliminate all the non-mutants and bring it to pass that the whole of existing domestic breeds possess these characteristics. But there is no evidence that any selection, conscious or unconscious, was exercised on them. In some quarters there is a vague idea that an unconscious selection takes place in a newly domesticated race by the wilder and stronger individuals escaping. . . .

A final and conclusive proof that the physiological and structural changes which gradually and progressively arise en masse in newly domesticated animals are not mutational, is furnished by the fact that they are reversible. No doubt they persist, or progress, as long as the stock remains in a domestic environment. Many of them are so deeply set that even if the stock is turned out of domestication they persist for a time that exceeds the duration of any scientific experiment carried out so far. These two facts have beguiled us into thinking that such characteristics as, for example, the reduced tusk's of domestic boars are hereditary. Yet from the evidence it seems clear that they are not. Everywhere and every time that domestic pigs have become feral the reduced tusks, in a few generations, revert to the enormous tusks of wild pigs. It even seems that the reduced wing bones of our domestic poultry are not hereditary. Whenever domestic poultry are turned out into an environment in which the birds are obliged or induced to use whatever powers of flight remain to them, their wings regain at least a part of their original power.¹³

Darwin supposed that selection was the principle factor in improving domesticated animals, but Martin points out that the phenomena of domestication occur (1) too rapidly and (2) that they occur en masse, making it seem inconceivable that the changes effected in domestication could result from the selection of genes. Darwin was unfamiliar with the idea of gene-controlled selection and the changes that he discussed were not considered in view of the gene theory. Martin argues that most of the changes in domesticated animals are produced by the environment and that these changes revert to the wild-type very quickly when the environment of domestication has disappeared.

It is interesting that one does not have to rely upon evidence from Lysenko's school for the argument that modifications produced by nutrition become hereditary. Martin, who does not mention Lysenko or the Russian controversy, has presented information that is specifically in line with the argument that

nutrition and the environment are critical items in the domestication of animals. Martin does not present a theory that makes it possible to describe how evolution has occurred but he makes it clear that the mutation-selection theory is unsatisfactory. This is the situation that precedes a new advance. The opposition from those holding the older views should be anticipated since the security and comfort of the older views are displaced by insecurity; but the older views will not and cannot be rejected until some adequate, new theory is constructed.

The standard attitude of the proponents of the older views will be to say that they have not been "convinced." Or they say that this has all been considered before, without specifying where or by whom. Generally no responses will be made in print. Just how to get a full scale debate going in a matter of this kind is one of the truly unsolved problems of biology and, probably, of other sciences as well.

Griggs' Defense of Orthogenetic Evolution

The Mendelists rejected both Darwin's theory of pangenesis and Lamarckism as bases for theories of evolution, and they ignored Jollos' work completely. There is a quite different theory concerning the mechanism of evolution called orthogenesis which proposes (1) that evolution is directed rather than random, following definite trends, and (2) that the tendency to fall into such definite lines of evolution is characteristic of the nature of protoplasm itself.

Griggs, an American anti-Mendelist, has criticized the mutation-selection theory of evolution and has summarized the different steps in orthogenetic evolution. The concept of orthogenesis has largely disappeared from the textbooks, but the fact that many serious biologists still regard it as the only possible explanation of the geological record is of primary interest:

Is evolution haphazard, produced by mutations which occur in a miraculous manner, essentially supernatural in that they are caused by circumstances entirely outside of the ordinary run of nature? In this view, the only means by which the orderly relationships which we observe throughout nature could be produced is by natural selection. The adherents of such a theory account for the steady progress of the Equidae from a primitive five-toed ancestry down to the single-hoofed horses of today by the natural selection of random mutations alone. This theory would seem to me to put its adherents under a serious disadvantage at the start by imposing on them the necessity of proving that at every step in the evolution of the horse each slight decrease in the size of the lateral toes was an advantage great enough to favor in the struggle for existence those individuals which possessed it over those which did not.

Not all the geneticists, even though they have no use for orthogenesis, adopt this extreme view. Newman states a very much stronger and I believe more generally held position when he writes, "It should be said that definitely directed evolution is now believed to be one of the laws of organic evolution but we have no clear ideas as yet as to what are its underlying causes. Therefore orthogenesis is not a cause-mechanical theory of evolution at all." Having thus delivered themselves, the geneticists smugly withdrew to their milk bottles to nurse their *Drosophila* and the paleontologists may throw as many of their figured stones at them as they please without in the least disturbing their self-satisfied self-sufficiency.

... For I believe It can be demonstrated not only that evolution proceeded orthogenetically but that the orthogenetic lines in many groups of organisms, both animals and plants, have pursued similar trends. In other words that evolution runs a definite course and that the course has followed the same paths in entirely unrelated phyla.

[Orthogeneticists rely on the geological (paleontological) record primarily and Griggs develops a long argument which the interested reader might study pointing out that evolution follows a similar pattern in a large number of different living forms.]

This narrowing of the path of evolution seems to me to refute the claim of the geneticists that mutations are purely at random. You might as well argue about the random aberrations of a canal boat swinging on its tow rope as compared with the course of a ship on the open sea, as to conclude that the random mutations of *Drosophila* tell us much about the evolution of insects.

I am not trying to minimize the importance of the mutations of *Drosophila*. They have been the key to wonderful advances in our understanding of inheritance. But their relation to the evolution of insects has yet to be made known.

Those inclined to believe that changes significant for evolution occur at random would do well to ponder the implication of a paper by one of the greatest of geneticists, N. I. Vavilov, entitled Homologous Variation. Assembling all the species and varieties of cultivated plants and their relatives in his experimental gardens, Vavilov observed that related types repeat over and over again the same series of characters, i.e., that homologous mutations had occurred in related types.

Finally, it should be pointed out that these orthogenetic trends are largely unadaptive. In a few cases, such as the differentiation of the teeth, advantages to the organism may be made out. But generally, nothing of the sort can be imagined. For the most part, the adaptive sequences in evolution are superposed on the great orthogenetic trends but are entirely independent of them.

Our concern with the lack of adaptiveness in the main trends of evolution is its relation to the claims of the geneticists. In their belief, the orderliness of nature has been brought about entirely by the elimination of unfit mutations through natural selection.

Thus their case is entirely dependent on a demonstration that all trends observed in the evolution of all groups are adaptive, i.e., so useful to the organism that natural selection can take hold of them. It appears to me, as it has to others, that it is fairly easy to show that many of these trends are not so related.¹⁴

The "phenomenon" of orthogenesis seems indisputable. But since no explanation, in the form of a theory, is available it cannot be discussed critically. Even a very unattractive theory would give a basis for discussion. Actually, Sturtevant (see below) has proposed a theory to explain the unadaptive characteristics of some orthogenetic changes but his theory does not refute the grand pattern. It may be that Goldschmidt's views on the highly individualistic nature of the chromosome complex of animals in a single phylum may mean that very early in phylogeny, a given phylum (originating from one primitive nucleus) was endowed with both potentials and limitations that no amount of selection could transcend.

Russell on Orthogenesis

Dr. E. S. Russell proposed that orthogenesis proves the directiveness and purposiveness of life activities.

. . . in addition to the Darwinian and the Lamarckian factors, a mode of evolutionary change which is directive and unified, occurs at an early stage in ontogeny, and is cumulative from generation to generation. It brings about structural modifications of considerable magnitude, and not merely alterations in the degree of development of superficial characters. Such . . . changes are in the main internally determined, the "initiative" to change coming from within. In the case of major adaptive specialisations they are incited by, and follow up, direct functional response to changed needs. . . . They cannot have arisen through macro-mutation, which is a nondirective process.

Directive ontogenetic variation obviously does not fit into the genetical scheme; there is no hereditary "mechanism" that will account for it. For this reason its reality and efficacy are likely to be disregarded or denied by the geneticists who . . . take account only of the "external aspect" of evolution, admitting only those factors "for which there is a substantial basis in genetics'". . . .

. . . There arises here a question of fundamental importance, on the answer to which depends our whole attitude to the problems and theories of evolution. Can we conceive life and evolution adequately in terms of "mechanism," taking account only of physical causes, or is this conception incomplete and limited? It is very widely, though not universally, held as an article of scientific faith that the living organism must be treated as if it were a physical system, differing only in its orderliness and complexity from the simpler systems of the inorganic world. On this assumption all but physical causes are eliminated from consideration. The same attitude is adopted with respect to evolution. . . .

The great objection to the materialistic conception of life and evolution is that it takes a very limited and restricted view of its object. Logically applied, it must disregard all that is distinctive of life, the directiveness and creativeness of organic activities and the essential role played by psychological functions, such as drive and perception, in animals at least, functions which cannot possibly be exhibited by a purely material system. It is of course a conception to which the human mind is peculiarly prone; the mind feels at home in mechanisms, and in the manipulation of matter, as the amazing technological achievements of the past hundred years so clearly demonstrate. No wonder that the same mechanistic method is applied to the organic as has shown itself so powerful in the study and mastery of inorganic nature. No wonder that the study of evolution is directed towards the discovery of its "mechanism" to the neglect of all other modes of approach.

But for the abstract and superficial materialistic view of living organism there must be substituted a conception which takes into account the unique character of organic activities, their directiveness towards biological ends. That the activities of living organisms, morphogenetic, behavioural and physiological, are purposive in a biological sense, and show persistence with varied effort towards achieving the ends of development, self maintenance and reproduction, is the most obvious and characteristic thing about them. . . . It runs directly contrary to the mechanistic view, which can find no place for directiveness and goes to great lengths to explain it away, as a product of chance variation and natural selection. . . . Between this mechanistic view and the acceptance of directiveness as a fundamental characteristic of life a complete cleavage exists. To those who have shaken free from the mechanistic obsession; the attempted explanation of directiveness and adaptation in terms of chance will appear irrational indeed.

Directiveness is no product of an undirected process of evolution; on the contrary, without directive and creative variation there can have been no large-scale evolution at all. . . evolution appears in the main as a directive and creative process, largely determined from within, issuing in the amazing variety and multiplicity of forms of which I have given some account. . . . Only in quite minor evolutionary change, as in the formation of races and species, can we properly speak of a "mechanism" of evolution.¹⁵

Russell has chosen to regard the living state as possessing some power for controlling evolution which transcends "materialism" or "mechanism." It does not appear to me that it is necessary to go

this far. I would prefer to accept as a fact the view that such competent observers as Griggs and Russell have evidence for a directive trend in evolution or ontogeny and to search for a materialistic or mechanistic explanation.

Sturtevant's Rejection of Orthogenesis

Sturtevant has interpreted the unadaptive aspects of some orthogenetic changes in terms consistent with Mendelian theory and has outlined the position of the Mendelists in his characteristically terse manner. The following is abstracted from a paper that he published in *Science* in 1924:

. . . The occurrence of "directive" evolution in characters that can not be supposed to be of selective value is often held to be incompatible with the view that evolution results from the action of natural selection on random variations. It is variously argued that the occurrence of orthogenetic series proves that variations do not occur in a random manner, that natural selection can not be the directive agent of evolution, or that the Lamarckian principle of the inheritance of acquired characters must be true. . . .

As was pointed out by Morgan (1923), mutations in single genes usually produce changes in several characters. . . . [and] that these physiological variations are the ones most likely to be acted on by natural selection, and that such selection would be expected to bring about changes in the associated somatic characters that are themselves of little or no selective value. . . .

. . . If we suppose that the antlers of the Irish elk were dependent for their size largely upon testicular secretions, then selection may have increased the testicular secretions for reproductive or other reasons, and thus have resulted in a purely incidental [unadaptive] increase in size of antlers.

In the example given it is assumed that the character not subject to selection is directly dependent for its degree of development upon another character whose variations have selective value. . . . It is not to be supposed that multiple effects of genes will always show such a correlation—but if such correlated effects do occur where one of the characters concerned is subject to natural selection, orthogenesis is to be expected.¹⁶

The problem of orthogenesis has not yet been properly disposed of. It is interesting that the Michurinists do not even mention it. The derelictions of both the Mendelists and the Michurinists with regard to Jollos and to orthogenesis indicate a general tendency to disregard many critical factors involved in evolutionary theory.

Goldschmidt's Rejection of the Gene-Mutation Theory of Evolution

Goldschmidt was skeptical of the mutation-selection theory of evolution. He felt that evolution had not been achieved by micro-evolutions (small or minute changes) due to gene-mutations but by "macroevolutions involving large and spectacular hereditary changes." He looked for changes of the type that would change an antenna into a foot or similar drastic modifications, in hopes of finding a key to the change of one species into another. He proposed (1) that the transposition of heterochromatin into various parts of the chromosomes and (2) that chromosomal rearrangements and repatterning might produce the large and drastic transformations of the organism required for evolution. But his theory did not meet with general approval. In his book *Theoretical Genetics* Goldschmidt says:

. . . It is one of the surprising features of cytogenetics that the chromosomal cycle and the karyotype [the form, structure, size and distribution of the chromosomes] have not changed much in the phylogenetic tree [The "tree" that Goldschmidt means involves lines of descent that extend over hundreds if not thousands of millions of years.]. . . If we assume that the chromosome has been "invented" to make possible the exact duplication of the genic material (Roux, 1883), the lack of visible evolutionary changes in this mechanism indicates that whatever evolutionary changes took place within the chromosome, they were changes that did not affect the visible features of the chromosome over hundreds of millions of years].

. . . A number of larger or smaller taxonomic groups have karyotypes so characteristic that the group could be diagnosed from a metaphase plate. All birds and reptiles [which are descended from a common ancestor] have a circle of large chromosomes with a number of small ones in the center. . . . The majority of Lepidoptera [moths and butterflies] have a group of about 60 dotlike chromosomes arranged in a very characteristic way.

It is possible that all these facts on the evolution of the karyotype have no meaning at all, and are just chance happenings. When the sauropsids originated. . . the karyotype was there by chance and, not having any significance, persisted even to the almost mammalian Monotremata. [The mammals originated from lizard-like reptilians.] But why did it change when the marsupials originated? In the same way the different configurations in the drosophilids may be the product of the chance alone that the first ancestor

of each species carried an otherwise meaningless translocation, and so on. . . . The alternative is that these features have a definite genetic meaning. What could this be?

. . . If genes produce their primary products in loco and the first reactions between them take place on the chromosomal surface, and if, further, the reaction products diffuse along the surface of the chromosome to enter into new reactions . . . the conclusion could be drawn that the establishment of new linkage groups allows new primary reactions along the chromosome. If such were the case, we should expect to find definite laws for the change of the karyotype from species to genus to family, and so on. . . .

If we renounce the classic gene and accept the theory of the hierarchical pattern of the genic material, the changes in the karyotype would mean the introduction or removal of some of the categories of concerted action, especially the higher ones. But up to the point of discussion reached so far, not much is gained by this interpretation, because it would also lead to the postulate of some order in the observed facts of phyto-geny of the karyotype. However, the situation is different when we proceed from the karyotype to. . . the chromosome itself. . . [some regions are] genetically identical. . . still other regions do not synapse at all and seem structurally completely different. . . . The patterns of these chromosomes between (uncrossable) species are so different that they cannot be compared directly . . . one definite fact is visible, namely, that the intimate structural pattern of the chromosomes changes, diversifies with taxonomic distance. There is no reason to deny that this is a general feature, though only the giant salivary chromosomes of Diptera permit observing it.

. . . Bridges introduced the idea that a duplicated gene, first in tandem duplication, later located anywhere else by translocation, may in time transform into a completely new gene. . . .

I have always felt that this idea is very crude and, in addition, contrary to all we know about the action of the gene. . . . In all cases known, the assumed duplicate has generally the same action. . . .

[This is the only reference I have ever found in the literature to a theory of Bridges which I have always believed to be his most important scientific contribution. I was disappointed to discover that Goldschmidt had such little regard for it.]

. . . How can the new gene get out of its connection with consecutive steps of a synthetic reaction to catalyze a completely new chain of reactions, as we must expect when a new gene for completely new evolutionary steps originates? Such an event seems to me to be much more miraculous than a repatterning within supermolecules for which we have known chemical models and, in addition, actually see the result in the known chromosomal patterns.

. . . I am aware of only one proposal that was intended to overcome these difficulties within the classical theory of the gene. Weir (1953) notes that there is a lack of correlation between chromatin content of the nucleus and complexity of the species. . . . Hence the question arises, How can an organism acquire new functions without an increase in gene number?

All these difficulties disappear when we accept the theory of the genic material which dispenses with the corpuscular gene and replaces it by the hierarchy of organizational (molecular) patterns in the chromosome. If small changes of pattern underlie the origin of the typical mutations, any degree of repatterning of the chromosomal material . . . is possible. . . . In a crude way, this is what is actually visible when the salivary chromosomes of *Drosophila* species of different taxonomic diversity are compared. . . . Evolution, in this case, would not require the origin of new genes, but only shifts in the hierarchy of patterns and sub- or super-patterns. . . . In this picture the chromosomes of protozoa do not have fewer genes but a simpler, less diversified and less hierarchical pattern of the genic material. . . . Evolution of the genic material, then, is internal diversification, not addition of new atomistic units.

Considerations like these have led me to postulate . . . that . . . repatterning . . . of chromosomal sections may occur occasionally in a single event, which I called "systemic mutation." Such repatternings . . . may lead, if viable, to a large over-all effect changing major features of development and producing in one step . . . a major evolutionary deviation . . . nobody has ever succeeded in producing a new species . . . by selection of micromutations . . . evolution, except on the lowest intraspecific level, proceeds by saltations rather than by slow accumulation of small differences.¹⁷

The Mysterious Liquidation of Michael Guyer

One of the most amazing and surprising phenomena of Western biology is the liquidation of Guyer—for a man may be liquidated as thoroughly by ignoring him and burying his work as by sending him to Siberia or putting him before a firing squad. Michael Guyer was active in the early twenties and in 1921 published a sensational paper that is not quoted or even obliquely hinted at in any modern textbook of genetics. His experiments were neither repeated nor refuted. It is even more curious that Dr. A. H. Sturtevant designed and Dr. S. H. Emerson performed an experiment on *Neurospora* which was a precise parallel, as nearly as it could be on *Neurospora*, with the experiment performed 20 years earlier by Guyer on rabbits, without mentioning him. It is clear that they had either completely forgotten Guyer or had never heard of him. Emerson's experiment yielded negative results but Guyer's experiment clearly yielded positive results. There seems no reason to dispute the report made by Guyer; the report is so unambiguous that it is hardly credible that it could have been falsified. And if it has been the man deserves the privilege of open refutation because he made a claim to proof of the phenomenon of the inheritance of an acquired character by an experimental procedure much more sophisticated than

the ridiculous, oft-quoted experiments of Weismann, and Guyer reported a positive result, whereas Weismann had reported the opposite. The following is an extraction from Guyer's report:

The crystalline lens of . . . newly killed rabbits were pulped thoroughly. . . with normal saline . . . and injected intraperitoneally into each of several fowls. . . the blood-serum of one or more of the fowls was used for injection into pregnant rabbits. . . . Several rabbits died from the treatment and many young were killed in utero. Of sixty-one surviving young from mothers thus treated, four had one or both eyes conspicuously defective and five others had eyes which were clearly abnormal. . . .

The commonest abnormality seen in both the original subjects and in their descendants was partial or complete opacity of the lens, usually accompanied by reduction in size. Other defects were cleft iris, persistent hyaloid artery, bluish or silvery color instead of the characteristic red of the albino eye, microphthalmia and even almost complete disappearance of the eyeball. . . . The eyes of the mothers apparently remained unaffected. . . .

. . . in not one of the forty-eight controls obtained from mothers which had been treated with unsensitized fowl-serum or with fowl-serum sensitized to rabbit tissue other than lens, was there evidence of eye-defects, and I may add, that among the hundred or more young obtained later from mothers which were being experimented upon with various types of sera or protein extracts, for other purposes, not a single case of eye-defect has appeared.

. . . we have succeeded in passing it [the defect] to the eighth generation without any other than the original treatment. The imperfection . . . tends to become worse in succeeding generations and also to occur in a proportionately greater number of young . . . it has in general, the characteristics of a Mendelian recessive . . . not infrequently of an irregular, unilateral type, sometimes only the right, at others only the left eye showing the defect. In the later generations, probably in some measure as the result of selective breeding, there is an increasing number of young which have both eyes affected.

. . . we mated defective-eyed males to normal females from strains of rabbits unrelated to our defective-eyed stock. The first generations produced in this way were invariably normal-eyed, but when females of this generation were mated to defective-eyed males again, we secured defective-eyed young after the manner of an extracted Mendelian recessive. It is obvious that in such cases the abnormality could only have been conveyed through the germ-cells of the male, and that it is, therefore, an example of true inheritance. . . .

the most significant fact is that specific antibodies can induce specific modifications in the germ-cell.

after many attempts we have succeeded in securing a defective-eyed young rabbit from a mother of normal stock by injecting her repeatedly with pulped rabbit lens before and during pregnancy. Since the young rabbit in question has both eyes badly affected there can be no question that a rabbit can build antibodies against rabbit-tissue which are as effective as those engendered in a foreign species such as the fowl. . . .

The blood-serum of any organism with blood thus affords a means of conveying the effects of changes in a parental organ to the germ-cell which contains the antecedent of such an organ. . . . Such a hypothesis would seem to be plausible at least in accounting for degenerative changes such as the deterioration of eyes in such forms as the mole, or in fact, in the formation of vestigial organs in general.

there is no reason to infer that changes induced in the blood-serum may not also be instrumental in leading to progressive as well as regressive evolution. . . .

May we not surmise . . . that . . . Lamarck was not wholly in error when he stressed the importance of use and disuse of a part, or of modifications due to environmental change. . . .¹⁸

I cannot read Guyer's report without accepting as a fact the induction of a recessive gene mutation due to the destruction of the crystalline lens. These are such definite experiments, so clearly described, the phenomenon seems undisputable. But experiments of this type, which refute a dominant theory without substituting a new theory cannot gain acceptance, often cannot even be published.

Twentieth Century Weismannism a la Delbrück and Luria

In the twentieth century the dogma of the inviolability of the germ track (in animals, if not in plants) has been reinforced or replaced by the doctrine that the genome is never altered by design: A new gene only arises by accident. The most recent and substantial support for this fundament of Mendelism and the mutation-selection theory comes from two brilliant anti-Nazi and Anti-Fascist émigrés, one from Germany and the other from Italy, Delbrück and Luria. The question of whether specific mutations in hereditary particles can be induced by exposure to a specific substrate was considered by many to have been definitively answered in the negative by the brilliant "fluctuation-distribution" experiments of Luria and Delbrück. They showed that (1) if a few hundred bacterial cells sensitive to bacteriophage were planted in a few ml of broth in a test tube, and (2) all the cells which grew from the original inoculum were subsequently spread over an agar plate impregnated with bacteriophage, then, (3) colonies, capable of growing on the plate in the presence of the bacteriophage and, hence, resistant to the bacteriophage, emerged. The resistant colonies were henceforth permanently

resistant to the virus as were their offspring and, hence, a heritable change had appeared. If about twenty duplicate test tubes are each inoculated simultaneously and separately with about 200 cells of the same susceptible culture of bacterium, some plates yield many thousands of resistant colonies while others yield only a very few. Delbrück and Luria found, essentially, that two duplicate tubes, each of which had grown from approximately 200 cells to several million in the complete absence of virus, might yield exceedingly different numbers of virus-resistant cells. They reasoned that events had occurred very early in one tube in the absence of virus (and very late in another tube) that led to the expression of virus resistance and that were detected by exposure to virus (after exposure to virus). Since no virus had been present in the tubes in which the cultures had grown from 200 to a million, they inferred that the virus had nothing to do with the specificity of the resistance which was induced. But this view cannot be accepted unconditionally because no controlled experiment can be devised by which it is possible to identify a cell as virus-resistant without exposure to the virus itself. And the cells had to undergo extensive multiplication in the presence of virus before the sensitive died and the resistant multiplied. This experiment is the historical parallel of Weismann's experiment on amputating the tails of mice, but it suffers from the same fallacy. Resistance to virus cannot be tested in the absence of virus. It is principally from this one experiment that the view became generally accepted that viruses or other specific substances, such as poisons, are incapable of inducing the specific resistance that appears in the organism as a result of mutational change. The view that mutations are purely random events and that, following mutation, the mutants are selected by the environment, such as the poison or the virus with which the organism finds itself in contact, became generally accepted. It was believed that neither the poison nor the virus had produced any specific effect controlling or "directing" the kind of mutation which occurred.

Lindgren's Experiments on Directed Mutations in Yeasts

Since 1948, the view that all mutations are accidents occurring independently of the "selective" agent has been challenged by the writer. He demonstrated that the capacity of a yeast cell to achieve the ability to use a particular nutrient, which it could not previously use, may be due to the occurrence of a mutation that is specifically effected only by exposure to the presence of the nutrient, not by accidental mutation followed by selective growth of the mutant. The writer has proposed that the gene must contain a heritable, mutable protein-component, the receptor (in addition to the DNA structural element), which can be imprinted by the nutrient, and the imprint produces a heritable character which is subsequently transmitted from generation to generation in the absence of the specific imprinting substance. In a series of papers this argument has been supported by a variety of experiments: A yeast culture incapable of using a specific sugar was allowed to multiply for many divisions. Cells from this one original plate were then printed onto many other agar surfaces with a velveteen printing pad. These new plates all contained a nutrient which the original cells could not use. The essential aspect of this method is that the "print" of the original population gives an identical duplication of the population distribution that grew freely on the original plate. After several days, isolated colonies capable of using the nutrient began to appear on the "reprinted" plates. Critical inspection of the plates showed that some of the new mutants did not arise at identical sites on the different plates. It was inferred that mutations had been induced by the nutrient.

Two-Step Directed Mutations

There are some yeast cultures, however, that cannot be "directed" to mutate quite so easily. When the same procedure as that described above is performed, no mutants appear on the printed plates. But if the cells are X-rayed before being printed on the nutrient agar on which they cannot grow, they achieve the capacity to use the nutrient. Hence, two steps are involved, the first is the radiation, the second is the exposure to the nutrient. Both are essential. In the first step, a "sensitizing" event occurs that renders the cell capable of reacting to the mutagenic effect of nutrient; in the second step, a specific change in the gene is induced that is specified by the structure of the nutrient molecule.

This demonstration of a two-step directed mutation makes it reasonable to suggest a reinterpretation of Delbrück and Luria's classical experiment.

It seems reasonable now to infer that Delbrück and Luria may have been dealing with a two-step process, the first being one that occurred "spontaneously" in the absence of virus, comparable to the sensitizing effect of X-rays. The frequency of this change was rare, and it might occur either early or late in the growth period. When it occurred early, many resistant cells were found; when it occurred late, only a few were found. The fact that it is designated a "spontaneous" event does not mean that it was not induced by a specific agent but only that the event did not occur with sufficient frequency to insure that it would occur at a specific time during the eighteen-hour growth period. The second event was specified by exposure to virus. In "sensitized" cells exposure to the virus led to resistance to the specific virus, induced by the virus, while in nonsensitized cells, resistance to the virus did not develop. It was reasonable at the time for Delbrück and Luria to infer that only a single event had occurred, especially in the absence of positive evidence that a specific agent could induce a specific mutation, and in consideration of the principle that the simpler hypothesis is to be preferred. But now that data are available that show that a specific agent may specify the mutation induced, it is no longer reasonable to exclude that possibility in their experiment, especially since Delbrück and Luria's experiments provided no controls.

Experiment has demonstrated that microorganisms have the capacity to mutate with rather high frequency to an almost limitless variety of forms that are resistant to an enormous variety of antibiotics and poisons. It is simpler to suppose that this capacity arises from some process (akin to antibody-formation) that involves the folding of protein to "fit" the poison rather than to a random recombination of nucleotides that eventuates in a sequence of amino acids that by chance (rather than by design) effects the resistance. If there were a rather limited number (a few hundred) relatively nonspecific proteins which, when present, could "bind" many different kinds of poisons, then simple refolding of their respective receptors in the presence of the poison could suffice to release the messenger RNA specifying the protein, and the resistance would result. The capacity to detoxify the multitude of potential poisons that impinge upon the living state is so essential to survival that one might expect that during the long history of evolution a variety of mechanisms had been developed that are "stored" in the genome rather than developed anew at each exposure. The plasticity and adaptability of the living material which exists today is so great and so specific that it seems reasonable to suppose that it is not due to a random process.

In a similar vein the adaptation of an organism to the "absence" of a nutriline presupposes that the capacity to synthesize the nutriline may be held in abeyance and may be regenerated at a low frequency (but much higher than would be expected by chance) by the accumulation of a specific metabolite characteristic of a particular type of starvation.

It needs to be pointed out that in Delbrück and Luria's experiment, resistance of the bacteria to bacteriophage infection which has been the subject of much work comprises a negative and not a positive character. It seems necessary in developing a capacity to synthesize a specific nutriline to suppose the necessity for calling forth a protein that had not previously been present. But the converse is true in resistance to bacteriophage; resistance involves only the loss of a site of entry for the parasite. The bacteriophage is a virus adapted to and totally dependent upon the host.

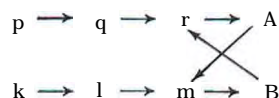
The Choice of the Simplest Explanation

Evolution is clearly a problem on which a great diversity of highly disparate views exist. Why then is a greatly oversimplified concept, one that has been rejected by many highly-qualified and philosophically-oriented scientists, the most widely-accepted explanation of the phenomenon? The answer is probably that the process is so complex and so involved, and has been effected by so many and such different mechanisms, that almost any explanation may have some significance. But instruction and indoctrination demand that complex explanations be simplified and the simplest explanation eventually becomes the most popular because it is most easily taught. At the same time, various thoughtful and speculatively-inclined scientists studying the complex problem come to accent different (often contradictory) aspects which appeal to them. Thus the unanimity of those who prefer simplicity and the disagreements among those who sense the complexity of the problem make it inevitable that the simplest explanation, so unsatisfactory to so many, should be the overwhelming choice of the majority.

FOOTNOTES

1. A. H. Sturtevant and G. W. Beadle, *An Introduction to Genetics* (Philadelphia and London: W. B. Saunders Company, 1939), p. 331
2. If the substance A is produced by a series of synthetic steps going from p to q to r and finally to A, while the substance B is produced by another series of steps going from k to l to m and finally to B, and if the presence of A prevents the transformation of l to m, then in the presence of A, B cannot be produced. But if A is withdrawn or removed, then the inhibition of the production of B is also removed and the synthetic steps k, l, m to B will occur and will prevent the production of more A, since the presence of B itself inhibits transformation of q into r. The operation of such a system would make it impossible to produce both A and B simultaneously, but the withdrawal of either one of the end products would make possible the synthesis of the alternative product.

Delbrück's theory explaining mutually exclusive production of one or the other of two different substances is explained by the diagram below:



3. M. J. Sirks, *General Genetics* (The Hague: Martinus Nijhoff, 1956), pp. 447-448.
4. William Bateson, Presidential address to the Australia Meeting of the British Association, *Nature* 93: 635 - 641 (1914).
5. W. Johannsen, "The Genotype Conception of Heredity," *The American Naturalist* XLV: 129-159 (1911).
6. T. H. Morgan, *The Theory of the Gene* (New Haven: Yale University Press, 1926), pp. 295-296.
7. *Ibid.*, p. 67.
8. T. H. Morgan, "The Rise of Genetics," Presidential address to the Sixth International Congress of Genetics at Cornell University, Ithaca, New York, *Science* 76: 261-267 (1932).
9. Cecil P. Martin, *Psychology, Evolution and Sex* (Springfield, Illinois: Charles C. Thomas, 1956), pp. 77-82.
10. *Ibid.*, pp. vi-x.
11. *Ibid.*, pp. 17-23.
12. *Ibid.*, pp. 71-76.
13. *Ibid.*, pp. 42-52.
14. Robert F. Griggs, "Evolution," *Journal of the Washington Academy of Science*, 29: 118-137 (1939).
15. E. S. Russell, *The Diversity of Animals* (Leiden. E. J. Brill, 1962) pp. 133-139.
16. A. H. Sturtevant, "An Interpretation of Orthogenesis," *Science* 59: 579-580 (1924).
17. R. B. Goldschmidt, *Theoretical Genetics* (Berkeley and Los Angeles: University of California Press, 1955), pp. 482-488.
18. Michael F. Guyer, "Immune Sera and Certain Biological Problems," *The American Naturalist* 60: 97-115 (1921).

Speculations Concerning the Living State

The Living State; The "First" Cell; Evolution by "Accident"; Directed Evolution; The Lamarckian Proteins; Three Phases in the Origin of Life; Might the Nervous System Exercise Control Over Evolutionary Change?; For Higher Objectives in Biology.

The Living State

The living state is a social state which exists by the collective collaboration of a great variety of different types of "patterns" all of which are maintained together in time because the existent patterns act as templates upon which each new pattern is built. Michurinists think of the living state in terms of the coacervate of the cytoplasm and Mendelists think of life in terms of the deoxyribonucleic acid of the gene. Consideration of these almost antithetical concepts of life suggests that life is a phenomenon in which the activities of both the cytoplasm and the nucleus are inextricably integrated.

A coacervate is a stable structure held together by intermolecular forces of considerably less strength than chemical bonds. It may contain several different kinds of molecules some of which may be very large. The molecules in a coacervate are organized into a large complex with a definite pattern. The complex grows by the addition of individual molecules or ions from the environment which repeat the basic pattern of the structure. Growth of a coacervate may occur in the absence of enzymes. Growth of a coacervate, as conceived by Bungenberg de Jong, requires the presence only of the components of the coacervate; the polarity and the inherent charges of these components are alone sufficient to lead to the construction and growth of the coacervate. But if the coacervate is to become autocatalytic, as envisioned by Alexander and Bridges, one would expect that the structure itself would be needed as a "primer" to supply the pattern for its growth. Such a coacervate is a self-duplicating hereditary structure since the kind of arrangement (heredity) of the original parental coacervate would determine the kind of arrangement produced in the offspring coacervate. The coacervates (some of three components) studied experimentally by Bungenberg de Jong produced their complex structures following mixing without requiring either enzyme or a preexisting pattern, but it may be reasonable to suppose that some complex coacervates containing many more components might duplicate a complex preexisting pattern by orienting the charged and polarized molecules upon it and by dividing when the duplicated pattern becomes large. If the environment were capable of supplying all the necessary components, a pattern which could initiate the construction of a duplicate of itself would satisfy one basic criterion for living material. Dobzhansky has said: "Self-reproduction is the most basic attitude of life; the appearance in the world of the first bit of self-reproducing material was the origin of life."¹ But Dobzhansky is thinking of the gene as the only truly living structure in the cell and of nucleic acids as the only "self-reproducing" substances.

Oparin's contention that life had its origin in the production of coacervates, capable of continued replication of a regular pattern, which were made up of a variety of different kinds of molecules in a regular arrangement, seems very reasonable. The absence of the requirement of enzymes for synthesis makes the cytoplasmic coacervate the first choice for the original living jelly. The variety of organic molecules available in the primeval ocean could make the construction of a great variety of different kinds of coacervates possible. The survival of the different coacervates would be determined by their respective stabilities. The fluid cytoplasm present in living material today may be the result of this early selection. Practically nothing is known of the fine structure of the cytoplasm in terms of its components or their interrelations, but the general uniformity of the appearance and the properties of cytoplasm have led biologists to the view that the clear, liquid cytoplasms of all living organisms are fundamentally similar. The tests which reveal differences between cytoplasms (the differences between reciprocal hybrids) may be due to the solid self-reproducing particles carried in the liquid cytoplasm rather than to differences in the fluid cytoplasms of the two parents.

But many Mendelists (notably Muller), in opposition to the concepts discussed in the preceding paragraphs, are committed to the view that the cytoplasm has been produced by the nucleus. The

discovery of the structure of the double-stranded nucleic acids, each of which when split provides two patterns upon which two new double strands can be assembled, has encouraged many to believe, like Muller, that this device is the single, sole, fundamental basis for all biological reproduction. This understandable enthusiasm over a great and fruitful advance in biology does not justify the current down-grading of the potential viability of the cytoplasm. And even if the nucleic acid mechanism is found to be the basis for the perpetuation of most of the patterns maintained in the living state at the present time, such wide-spread predominance might merely be the expression of the selection of a mechanism of superior efficiency.

The enthusiasm over nucleic acid biochemistry in many Western countries has tended to minimize the total dependence of nucleic acids on the cytoplasm. Many parasitic nucleic acids, both of the deoxyribose and the ribonucleic acid types (viruses), are known but no virus has an existence as a saprophyte, no matter how lush the soup or the sewer may be. The fact that these parasitic nucleic acids depend for their existence exclusively on residence in a "living" cytoplasm in which they appear to exercise a "directing" and "controlling" activity argues that they entered the picture rather late, probably after the establishment of a living state which could be directed and controlled. Their inability to exist as saprophytes indicates their inability to assemble the basic materials necessary for their construction without the assistance of "living cytoplasm." These considerations suggest that the living state, as we know it today, has been developed by the integration of an enormous variety of different kinds of coacervates into a single social structure which has come under the control of a more recently developed nucleus.

The "First" Cell

Darwin thought of evolution in terms of the transformation of old species into new ones and did not consider the related idea of the spontaneous generation of life; actually, he seemed to want to avoid discussing that problem. His difficulties in obtaining acceptance of his theory were so considerable that he may be excused for confining his attention to a limited aspect of the grand problem. The advantage of studying the origin of the species by Darwin's methods lay in the availability of the variety of living species, reinforced by geological records. But Darwin performed no experiments, and later experiments gave such uniformly negative results that the study could hardly be called "experimental."

Long after evolution had gained general acceptance, biologists continued to discuss evolution as if the problem of the origin of species from the "first cell" were the central theme. The problem of the origin of the "first cell" was glossed over or simply failed to intrude upon the consciousness. It is Oparin's great contribution to biological philosophy that he made all biologists conscious of the fact that the "first cell" did not emerge suddenly full-blown from the sea, but was itself the product of an immensely slow and unbelievably complicated, evolutionary process. It is not important whether he was the original pioneer; Pirie implies that many British mechanistic biologists had discussed the problem earlier. But it was Oparin who brought the problem to the general consciousness. He argued that the relatively recent origin of species represented, by comparison, only a trivial and relatively insignificant aspect of the grand problem. Actually, after the "first cell," the future of evolution in terms of potential, scope, limitations and results had already been circumscribed and defined by the peculiar interdependence of the component parts of the cooperative society which were associated in the "first cell."

Until the recent development of electron microscopy and biochemistry, so little was known of the functions and characteristics of the components of the society which comprise the living state, that speculations on this subject might have been considered to be useless or even self-defeating. It is my opinion that precisely-worded guesses on precellular evolution will now be fruitful, because, if wrong, they can be refuted unequivocally and, if only partly correct, will open the field for further inquiry.

I propose to reject in toto the concept of the primacy of the gene (or nucleic acids) and to argue that almost any single identifiable structure of the cell including especially the limpid cytoplasm is characterized by (teleologically—"controls its own") specific pattern-dependent heredity unless it can be specifically demonstrated to be a purely epigenetic structure. I shall argue that every membrane, granule, chloroplast, mitochondrion, elementary particle, ribosome, spindle fiber, centriole, flagellum, chromosome, centromere, telomere, nucleolus and even such temporary particles as starch granules, only appear in the cell if a previously existent pattern is present to act as a template for their construction according to the plan characteristic for that particular biotype. To refute this argument experimentally it would be necessary (a) to construct the item in vitro without a "primer" and (b) to demonstrate that the artificial item is biologically equivalent to the natural one. I do not propose these requirements to demand that a putative respondent set about to carry out the necessary experiments, but only to point out the philosophical difficulties involved in a refutation and to demonstrate

that nothing less than such an experimental approach is required to prove the validity of the contrary argument that the nucleic acids, or the genes, are the primary and the only totally autonomous, pattern-dependent, hereditary components of the living state. Since neither view can be either proved or refuted by any currently conceivable experimental approach, it is essential to the vitality of the science that both be kept equally in the fore-conscious and that we do not permit ourselves to be directed either by those Western extremists such as Muller, Dobzhansky, Beadle and Meselson who equate nucleic acids with life, or by those Russian Lysenkoists who claim that the nucleus is a purely epigenetic structure continually resynthesized by the cytoplasm.

As the study of cell biology has advanced from the early primitive microscopes used by Hooke and Leeuwenhoek to the present day electron microscope, the insight into the complexity of biological structure has increased, and in the short space of the last fifty years, when a person could speak with some assurance of the "single cell" as if it were a structure with possibly 100 different kinds of parts, one must at the present time think of this same structure as an association involving possibly hundreds of thousands of different kinds of parts. During the earlier period it was not too difficult to think of the cell as a relatively simple structure, the components of which might have become associated without too much difficulty, but the current evidence of the extreme complexity of the simplest biological apparatus requires a readjustment of point of view that has not yet been generally achieved. There is no such thing as a simple cell. In a book of this kind in which general concepts rather than specific bits of information about the complex mechanism should be considered it is not necessary to discuss or name the multitude of small microscopical and submicroscopical organelles, the structures of which are now subjects of extensive study by electron microscopy and biochemical techniques. Suffice it to say that the numbers of these easily recognizable and distinguishable organelles run into the hundreds, and all of them seem to be in some way or other essential to the existence of the total single cell. It seems more and more apparent that each of these is produced not so much by the control of a central agency, such as the gene, but by the existence within the structure of a pattern that attracts component substances in such a manner that a "new" structure is produced resembling the "old" one. The "organization" of the particle is the determinative factor. It is this concept to which I have assigned the term "pattern-dependent heredity." And when a precisely coordinated population of such organelles is confined within a single cell membrane this complex biological society is spoken of as a single cell. The complexity of organization at the lowest level of metabolic, biochemical physiology is so inconceivably great and the integration so determinate and balanced and still so flexibly durable that it is natural for the human mind to seek simple explanations, but I feel certain that current views are still too greatly oversimplified and that the complexity of the mechanism which makes the complex, inter-related structure of the single cell capable of maintaining itself has not yet been realized. When one considers higher levels of integration in which many different kinds of cells are integrated into an animal the system takes on a completely new level of complexity which is at this time out of range of scientific investigation. Great advances have been made recently in the relationship of nucleic acids to the problem of protein synthesis, and a large number of different organelles have been implicated in this process. A major advance has been achieved in understanding the nature of the life processes, but it would be premature and quite wrong to consider that this insight has given us more than a superficial view of the complexity of the total system or of the means by which the integration and durability of the system is maintained. Some mechanism much more responsive in a directive manner to environmental changes is required to account for the adaptability of the living state.

Evolution by "Accident"

It is now more than a hundred years since Darwin's publication of the *Origin of the Species*. Although Darwin himself was a cautious agnostic, rather than an out-and-out atheist, it is probably the *Origin of the Species* more than any other book which confirmed those members of the well-informed general public in their preferences toward a purely mechanistic attitude concerning the origin of life and the view that living matter was the result of a series of "accidents." It seems almost certain, as is so often the case, that widespread acquaintance with Darwin's ideas and their popularization was due more to the vehemence and violence of the clerical opposition that he encountered than to the missionary zeal of Huxley and the other proponents of Darwin's theory. Darwin had been preceded by other scientists who were atheistic mechanists. One recalls how shocked Napoleon was when the astronomer Laplace said he had no need for the hypothesis of the existence of God, and Napoleon was an excellent example of the thoroughly well-informed layman. But the characteristic atheism of the revolutionary French intellectuals was unusual even in the upper levels of intellectual society at that time. This

situation is in striking contrast to the current one, for the entire communist world is committed to a policy of total and complete atheism as an official dogma founded to a considerable extent upon Darwin's theories. One might be safe in assuming that, roughly, a third of the intelligentsia, in what we call the free world, is atheistic, about a third agnostic and a third committed to religious beliefs, but such numbers can only be guessed at. It is extremely difficult for the modern intellectual atheist to adjust himself to the ease with which biologists and other scientists, preceding the revolutionary intellectual French of the late eighteenth century, accommodated themselves to the concept of the control of the universe by an all-wise, all-loving God. The unusually erudite and unbelievably wide-ranging Linnaeus had no difficulty in accepting the concept of special creation of the different species with which he was so extraordinarily well-acquainted. Nearly all biological theories were submitted to the tests of purpose and economy. God was supposed to be concerned about every individual and to breathe life into every individual. Churchmen were recognized as authorities on biology and they explained that the soul was brought into existence by the first entry of the air into the lungs; this event was considered to be an act of God. Nature, that is God, was supposed to be both purposeful and economical and any apparent waste was always explained away. The Quaker who discovered wind pollination of Indian corn said that surely God would not waste all of these sperm for no purpose and that they must be conserved and used at a later time in some other manner. Purpose and economy were obvious to these biologists in every event, and they were due to God's all-powerful intelligence and His comprehensive and all-encompassing planning.

When the pendulum began to swing the other way, the themes of purpose and economy were rejected by many of the most prominent biologists and all vital activity, or all evolutionary development, was seen as a series of extraordinarily wasteful and nonpurposeful accidents. Darwin was content to assign to the organism some control over its adaptation to the environment and some control over the direction taken by its descendants, but most free world biologists have rejected and ridiculed Darwin's views on this subject, although in the Communist world, Darwin's "old-fashioned" views have precedence and Communist dogma asserts that the organism does have some control over its capacity to adapt to environment and is able to project this adaptive capacity into the next generation. Precisely what the practicing Russian biologist believes may be as difficult to discover as are cases of flagrant atheism among biologists of the free world. But the general rejection of purpose and economy in nature may be an emotional reaction to the long period during which this concept had total acceptance. The idea that all life is the result of a series of accidents which occur with more or less predictable frequency has reached its zenith in the current hypothesis that nucleic acids are synonymous and identical with Life itself. It is interesting that this theory, which finds such wide acceptance in the free world by biochemists and biophysicists and the small number of biologists who have some understanding of chemistry and physics, is in sharp disagreement with the official Communist dogma. The more one searches for the definitive and clearcut experiments which establish the validity of either one or the other point of view, the more frustrating the search appears to be. The hypothesis of the accidental nature of life has been raised to the level of a postulate by its adherents. It has the advantage in their minds of making the solution of practically all the problems of life easily accessible in terms of an understanding of nucleic acid chemistry and to one who is competent in the study of the nucleic acids this is truly a comforting circumstance. Biologists who are not informed in this field are automatically down-graded, and many of the opinions which they express are automatically rejected. No room is left for the judgment or intuition of biologists outside the field of biochemical or molecular biology. But when one examines the circumstances closely, one sees that it is only the judgment or intuition of the molecular biologists which has led them to reject the idea that an organism may have the capacity to exercise a limited control over its own heredity. The scientific theme proposing that everything which leads to change in an organism is a direct reflection of a change in the structure of the nucleic acid of the organism appears to be the culmination of the rejection of "purpose in nature," and in this context the reaction has the appearance of an emotional rather than a rational reaction.

Directed Evolution

If the concept that the organism is totally under the control of a nucleic acid mechanism which adapts it to the environment and controls its heredity, is an emotional and an intuitive reaction, rather than a rational one, it seems reasonable to consider the possibility that an alternative hypothesis might be more fruitful. In fact, it seems that it could hardly be otherwise, because the current "accidental" hypothesis leaves one with no opportunity to develop experimental approaches to the possibility that either the organism itself or its environment may shape its heredity. If the preceding argument is a

reasonable one, then one might ask: "Are there any practicing biologists who have expressed intuitive judgments concerning the 'accidental' hypothesis which has lately become almost completely identified with the nucleic acid hypothesis? In the absence of experimental evidence are there any reasons for opposing this point of view?" One cannot place too much reliance upon the opposition of the Russian Communist scientists nor, indeed, on their noncommunist Russian associates because one realizes what difficulties an opponent of a political scientific dogma may encounter in his own country. Hence, one may begin by discounting the opposition to the accidental hypothesis by the Russian biologists. In the current climate of scientific opinion, one is likely to reject religious interpretations of biological phenomena, since there has been a general loss in confidence of the capacity of an all-loving God to control evolution. The respect for the judgment and the intuition of the religious advocate of purpose and teleological biological mechanisms has considerably diminished in recent years. There may be some justification for this attitude since religious opinion is generally highly emotional and does not stand up well against critical arguments. But there are many biologists who feel that adaptation and evolution are too effective and too rapid to be explained by accidental changes in the chemical nature of nucleic acids. Much evolutionary adaptation is too coordinated and too interdependent to be explained by single small changes. Also, since all experimental nucleic acid rearrangements have led only to defective individuals, the events that are required have never been observed experimentally. Biochemists may argue that there are some changes which are not defects but the answer is that they are merely the reversals of defects previously produced and such reversals are easily comprehensive in terms of nucleic acid chemistry. Laboratory mutations leading to defects are multitudinous, but no mutations have ever been observed in the laboratory which comprise new capacities not hitherto observed in the biological category.

The Lamarckian Proteins

Molecular biologists have generally tended to support Weismann and to reject the views of Lamarck and Darwin concerning the effects of the environment on heredity, but it has become increasingly apparent that the inheritance of acquired characters must be considered seriously. It has recently been discovered that enzyme-action depends on the flexibility and the capacity for proteins to be "deformed" by contact with other molecules. In 1940, Linus Pauling proposed that the antibodies which protect the body against infection were produced by coiling of flexible proteins (globulins) around the proteins of the bacteria. The study of "adaptive" enzymes, induced in yeast by exposure to certain sugars, has suggested that the gene contains a flexible protein and that the pattern of coiling of this protein is a hereditary characteristic which can be changed to produce a transmissible mutation. It follows that a change in the coiling of a protein which was produced by an environmental effect in one generation could be transmitted to the succeeding generation. Now, if the coiling of the proteins assembled into the organelle directed the coiling of the "new" protein molecules subsequently added to the organelle, mutation and heredity on a purely environmental basis could be a reality, completely independent of gene control.

If a hereditary, protein-containing organelle were completely disassembled at each generation, it would not transmit the effects of environmental change to subsequent generations. Most persistent, environmentally-induced, hereditary (nongenetic) modifications (see the "Danermodifikationert" of Jollos, Chapter 9), disappear after sexual reproduction, but persist during vegetative reproduction. This fact suggests that the organelles which transmit acquired, hereditary characters only temporarily, are disassembled during sexual reproduction but not during vegetative reproduction. It also implies that some modified organelles are transmitted in an altered condition to the next sexual generation and that the environment in these instances does control the heredity.

Three Phases in the Origin of Life

Pirie suggested that the origin of life might have involved an early phase of long duration in which inorganic catalysts were of primary importance while organic substances played only a minor role. This first phase (which preceded the organization of different components into a coordinated and cooperative living state) was essentially polyphyletic in the sense that each of the bionts (or prebionts) arose independently and reproduced without incorporation into an integrated living system. Pirie's view has been supported by evidence indicating that the original prebiotic milieu was probably poor in amino-acids. It seems possible that primitive forms based on inorganic catalysts might have been primarily responsible for the synthesis of the pool of amino acids required by Oparin's theory.

Some recent experiments by Fox indicate that proteins might have arisen spontaneously in an amino

acid pool simply by exposing the mixture of amino acids to heat. Subsequent to the accumulation of a protein-pool, a second, protein-based phase might have developed in which the catalysts were primarily polypeptide chains, and in which adaptability, hereditary stability and mutability depended on a folding process. But one might suppose that during this second phase the protein-based bionts were exceptionally sensitive to environmental effects and, hence, exceptionally unstable.

The development of a third phase in which the living state was more stable because it was based on nucleic acids must have followed rather than preceded the protein-based system, because the requirements for proteinaceous enzymes which are imposed on an organism for the implementation of nucleic acid syntheses are so imposing that a pool of available proteinaceous enzymes must have been present before a nucleic acid-based system could have been initiated. But even the most primitive nucleic acid bionts would have possessed two important advantages over (and would readily have replaced, or rendered dependent, i.e., parasitic) even the most advanced protein-based competitors; firstly, because the reproductive systems of nucleic acid-based bionts are both more stable and more precise and, secondly, because nucleic acid-based systems are able to store capacities to synthesize adaptive enzymes in the form of "self-reproducing" nucleotide sequences over long periods during which these capacities are not used. According to the receptor-hypothesis all the cellular proteins of an organism derive from DNA and are assumed to be synthesized on RNA templates according to current theory. The adaptive enzyme-proteins originate from genes in the euchromatic DNA, but the RNA templates for the proteins found in ribosomes or mitochondria, or similar very ancient and widely disseminated cellular organelles, are assumed to originate from RNA transcribed by the gene-free, heterochromatic DNA.

Might the Nervous System Exercise Control Over Evolutionary Change?

Since the simplest animal with a nervous system is incomparably more complex than any plant, it seems reasonable to assume that evolution in plants and in animals has occurred by quite different mechanisms. When one considers, as Martin points out, the enormous number of structures which have to be changed to make the slightest alteration in a muscular organism, it seems almost impossible that accidental mutations could produce genes which could effect all the necessary and essential changes that such an adjustment would require. In discussing evolution of the upright posture, Martin says:

... as the higher animals evolved and took on new ways of living, the function of many muscles, or parts of muscles, changed; they were called upon to take on new tasks and to abandon their former ones. This was especially the case when the ancestors of man adopted an upright posture and bipedal locomotion. Some muscles therefore have become enlarged in man and this gave rise to new muscular ridges on the bones to which the muscles are attached, or to the greater development of old ones, e.g., the linea aspera of the femur and the anterior, inferior iliac spine. Other bones acquired new curves from the new or greatly increased action of certain muscles upon them, e.g., the angle of the human ribs from the pull of ilio-costalis. Possibly none of these bony features is as yet truly hereditary, but, what comes to the same thing, the tendency of the bones to form them in response to the muscular stresses certainly is hereditary. Other muscles or parts of muscles were required to undertake a static role in the place of their former active one; they were required to act as intermittent and frequent resistances to stretching and to surrender their capacity to act as contractile organs. Every one of these muscles has been converted into ligament exactly in proportion to the change of function which it sustained. This is well seen in the intertransverse muscles of the vertebral column in man, for the degree to which these have been converted into ligament in different regions of the column parallels the limitation of movement which the vertebral column of those regions has sustained in man. There can be no doubt that the conversion originally began in post-natal life, for many of these ligamentous structures are still muscular in the human foetus. Nor can we doubt that many of the conversions are now hereditary, for they occur before birth. It also seems evident that each conversion took place by a succession of small steps or even continuously, for wide though continuous individual and racial variations still exist in them all. Of course muscles are not the only elements that entered into the formation of ligaments but there is not any doubt that many ligaments are derived in part of wholly from former muscles. It would be fantastic to suggest that a mutation causing a small step in one of these conversions could possess the slightest survival value or enter in any way into the survival value of a whole gene complex, and we can invoke neither pleiotropisms nor genetic drift to explain universal happenings.²

It is important to realize that Martin is not discussing a subject with which he has merely a passing acquaintance. These are the comments of a seasoned anatomist who speaks with authority upon a subject of which he is an acknowledged expert.

The autonomous nervous system exercises a considerable control over the bodily mechanism, and, certainly, only a very small fraction of the controls which are exercised ever reach the consciousness. Most of the solutions to problems appear to me suddenly upon awakening from sleep and, hence, appear

to have been worked out by a mechanism to which I merely fed data and in which my volition was not exercised, except in the selection and observation of the data. The brains of most animals, for example, frogs, appear to be enormously overdeveloped insofar as their immediate needs are concerned; the obliteration of the cerebral hemispheres produces a frog which is deaf and blind but otherwise indistinguishable from his fellows. Is it not possible that there are mechanisms in the brain which have something to do with the adjustment and adaptation of the animal toward its environment? Hence, one returns to Lamarck's original idea that an animal achieves at least somatic adaptation because he tries. The inadequacy of the mutation-selection theory of evolution makes it important to consider the possibility that some internal mechanism, possibly something in the brain might exert an effect upon the genome. The occurrence of psychosomatic disease means that the psyche can produce a diseased condition; why should it not be possible to make other adjustments as well? This does not necessarily mean that the adjustments would be conscious, or even what a conscious planner would consider reasonable, but it does suggest the possibility that a planned program, such as one could write into a calculating machine, might be written into the brain and that this plan was in some way being followed. The enormous speed of the evolution of animals in contrast to that of plants favors such a view, especially since the brain seems to be enlarged considerably beyond the requirements of the organisms, or at least beyond any obvious use which most relatively primitive organisms make of it.

In most multicellular animals the germ track is isolated and protected from the changes which occur in development. Such protection seems essential in animals since the experiments of Briggs and King show that the changes that occur during development produce irreversible changes in the cells involved. But in plants the germ track can be developed from vegetative cuttings, and hence, the germ track is not protected from the shocks of the environment in plants. Plants which grow from these vegetative cuttings produce seeds as normal as those produced by plants grown from normal seeds. Hence, the difference between plants and animals in this respect is basic. The idea that nervous tissue may play a large part in the control of epigenetic development has the value of being readily testable. It should be possible, by interference with the nervous mechanism, or the destruction of small, isolated sections of nervous tissue, in embryo, to determine whether or not, and how much, such changes can affect development.

Martin has pointed out that it seems almost inconceivable that the adjustment of a human to the upright stature could have been effected by gene mutations, because all of the alterations which were involved in making the changes needed to be precisely coordinated, and each small individual change could not have had a survival value, as a single change, at the time of its origin, since the entire structure had to alter in a precise and a coordinated manner. These difficulties disappear if one supposes that the brain functions as an epigenetic controlling agent during development to coordinate the different necessary adjustments. According to this theory, during the formation of the nervous tissue, the brain could play a major part in the process of development of the fertilized egg into the adult. The mechanism would be epigenetic since it would require the completion of one structure before the next could be organized. Very few changes in membership of the social system comprising the living state might produce an effect. It might not be possible to identify the changes as either nuclear or cytoplasmic; either kind might be equally effective.

Lamarck insisted on the importance of an organism's striving to achieve a change and supposed that the strivings of swans to make their necks longer or of cranes to make their legs longer had an effect that carried over into the next generation, hence, that striving produced at least a lingering modification. Martin has pointed out, in a consideration of the evolution of flightless birds, that the difference between the flightless birds on isolated islands, as compared with their progenitors who were capable of flight, was that the flightless birds were derived from progenitors which had been reluctant flyers. When reluctant flyers and eager flyers were isolated in an environment in which there were no predators, the eager flyers retained their capacity for flight while the reluctant flyers became flightless. These observations together with the proposal that the nervous system may function in development suggests a new kind of pangenesis in which the nervous system controls a feedback mechanism to the germinal cells which directs the development of hereditary material.

The enormous enthusiasm for calculating machines which has impelled many theorists to look upon them as equivalent to living organisms would tend to support the argument that the brain might control development since it is generally agreed that no calculating machine has ever been devised which approaches the brain either in complexity or in capacity. If (a) the different members of the cell-society are not particularly dissimilar and if (b) most of the differences are mainly due to changes in their proportions and, hence, to the interactions and balances between the members of the cell-society, rather than to changes in the kinds of organelles, then the problem of epigenetic feedback to the gonads would be considerably simplified. According to this theory, one would suppose that all the

different kinds of original members of the cell-society of animals' cells had been developed to a specific balance in the early stages of each phylum and that many of the differences in evolution might result from environmental influences which led to adaptations effected by changes in balance under the control of the epigenetic action of the nervous system. If the effect had been intensified in succeeding generations by epigenetic feedback to the sex cells, many major changes might be achieved with a cell-society to which no new kinds of members had been added but in which a variety of new kinds of balances had been achieved by shifting the proportions of standard components present both in the genome and the plasmons. (This proposal has its parallel in Goldschmidt's proposal that no new genic material has been added to a phylum but the preexisting chromosomes have only been rearranged.) It may be important to test this proposal by concentrating more on the transplantation of material from the cytoplasm (rather than nuclei) of related organisms and observing the changes which occur in development. The highly stratified eggs of some of the amphibians suggest that one might remove material from different strata and replace it with similar material from a different but relatively closely related form.

If one considers the cell to be a society composed of an enormous variety of different kinds of autonomous organelles embedded in an autonomous cytoplasm and associated with an autonomous nucleus, then the interpretation of heredity, development and evolution becomes very different from the interpretation which one would make if he considered the cell to be a unit in which a nucleus controlled all activity and in which the nucleus was the only autonomous structure. For if the nucleus is the only autonomous member of the cell's society, then problems of evolution become problems of mutation, addition, subtraction or rearrangement of genes.

Goldschmidt has pointed out that the size of the genome has not changed significantly over extremely long periods of time. According to him, the nucleus in the protozoan contains practically the same amount of chromatin and nearly the same kinds of genes as those present today in the nuclei of metazoa. Generally speaking, there is very little difference between the appearance of the nuclei in all the wide variety of protozoans and metazoans. Goldschmidt has proposed that the principal difference between the nuclei is in repatterning of the gene arrangements. He has stressed the importance of the interaction of gene products and believed that major repatterning of the chromosomes could lead to the macromutations which he considered essential for evolution. He rejected the mutation-selection theory of evolution since he held that the "micro-mutations" of the Mendelists could not explain evolution. Because Goldschmidt was actually a Mendelist and only dissented in part, he did not propose that the cytoplasm might play a major role in evolution. But if the nuclei are all as similar as Goldschmidt thought, it seems possible that the principal difference between the different species might be in their cytoplasm and the substances contained in the cytoplasm. However, those few components of the cytoplasm which electron microscopy has revealed seem to be remarkably similar, namely, the microsomes, the mitochondria and the chloroplasts.

For Higher Objectives in Biology

When Jacques Loeb, the dilettante son of a wealthy banker, entered science, he chose as his objective the discovery of the biochemical basis of conscious thought, and finally achieved the discovery of artificial parthenogenesis. Although Loeb failed to fulfill his highest hopes, he managed to lower the status of the virgin birth of Jesus from the height of a holy miracle to the more commonplace level of a biological accident. Biologists must set as their objectives higher goals comparable to those which Loeb set for himself. There is a tendency now to search for the solutions to the problems of life in the analysis of the mechanism controlling the production of an enzyme by a gene, and, although this is an endeavor worthy of the greatest effort, it would be fatal to lose sight of higher goals and to assume that the molecular biologist could achieve even a modicum of success without the help of the anatomist, the ecologist, the physiologist, the taxonomist, the cytologist, the immunologist, the psychologist, and above all the philosopher.

FOOTNOTES

1. T. Dobzhansky, *Genetics and the Origin of Species*. (New York: Columbia University Press, 1951).
2. C. P. Martin, *Psychology, Evolution and Sex*. (Springfield: Charles C. Thomas, Publisher, 1956), pp. 113-115.