Experiments in Microevolution*

R. W. Gerard

Neuropsychiatric Institute, Division of Psychiatry, Medical School, University of Illinois, Chicago

Foreword. In summarizing this symposium, I expressed to our hosts, the Office of Naval Research and the University of Pennsylvania, our deep appreciation for their hospitality and for what all agreed was the great success and stimulation of this meeting. It was rather good to see Government, and particularly military science, tied up with civilian science. It was also good to see the applied so deeply woven with the theoretical. We were concerned, of course, on the one hand, with the enormously important specific problems of the antibiotics, herbicides, and insecticides, with drug resistance and addiction, with the development of resistance to epidemics due to bacteria and other organisms. Yet, on the other hand, these very practical matters do reduce, I think, to the general theory of the interaction of systems with their environment over the course of time; and this is a problem of microevolution. So we were dealing, for those 2½ days, with modern experiments in the general field of evolution.

THE conditions of this summary precluded a talk prepared before the symposium, so I avidly collected notes and ideas as the talks proceeded. By the first evening I had much to say, but, alas, one point after another was disposed of by successive speakers and by the second evening my bag was again empty. Let me give some examples, a little in my own defense, but also to point out something later.

Scope of the Subject

H. B. Newcombe started with the question of whether the presence of specific drugs could not merely increase mutations but might actually direct them, so that specific resistant strains developed rapidly. I made a quick note, "Lamarckianism raising its head, something worthy of discussion." It surely was, and C. P. Martin's evening lecture constituted a courageous modern defense of this presumably defunct view. Also I had an idea: The presence of a nonspecific mutagenic agent ought to hasten the development of specific drug resistance in organisms, if this depends on selection from random mutations; so exposure to a combination of drug and radiation should bring about resistance faster than exposure to drug alone. As later appeared, this experiment was in the unpublished part of Newcombe's paper, and I am glad to know the results are positive.

The problem arose, in V. Bryson's comments, of the time lag between the genetic mutation in bacteria and the appearance of the induced phenotypic change—a lag covering some generations. I thought, "Well, this is the occasion to expand on the time aspect of these problems, on the importance of process in the interaction of a gene with its environment." I thought of emphasizing congenital as intermediate between genetic and subsequent environmental effects and of the varied consequences of a given change at various times. Thus, Mongolian idiocy seems to result from anoxia at an early stage in the development of the embryo, from damage to the placenta, and cataract results from German measles at a certain time in gestation. Then W. E. Loomis spoke about herbicides and corn and pointed out just such things. The time of application of 2,4-D in relation to the morphological stages determined, for example, whether tassels disappeared or ears lost their kernels.

A. C. R. Dean raised the problem of the actual molecular basis of adaptation: whether it be called a gene change or an enzyme change, whether something happens in the substrate-enzyme interaction or interavailability, whether accelerators or inhibitors are involved, or what not. I decided to direct attention to the fact that a basic molecular change must be involved —and M. G. Sevag developed that theme extensively and effectively.

From vigorous discussion involving the fluctuation test, applied to bacterial cultures, the fact emerged that the results could be reconciled with either one of the theoretical interpretations—a genetic mutation or a physiological adaptation leading to resistance. Indeed, this was true for much of the evidence presented on both sides of the genetic-adaptation argument. And I thought: "It will be nice to point out that, since the consequences of two different theoretical interpretations are so nearly identical that it is practically impossible to devise experiments to discriminate crucially

* This was the last of the three papers presented during session V of the symposium on the *Origins of Drug Resistance and Related Problems* (microbicides, herbicides, insecticides, narcotics, alcoholism, carcinogenic and living agents). Session V aimed to integrate and summarize various points of view expressed during preceding sessions. The symposium, organized by M. G. Sevag (University of Pennsylvania) and Roger D. Reid and Orr E. Reynolds (Office of Naval Research), took place 25–27 March 1954 at the Hotel Statler, Washington, D.C., and 25 papers were presented by invited speakers from Europe, Canada, Japan, and U.S.A. The entire proceedings are being published by the Academic Press, New York. In view of the fact that "Experiments in microevolution" develops and integrates various topics of the symposium in an eloquent manner, the committee believes that its publication also in *Science* will serve a useful purpose.

between them, it does not make too much difference, unless the theories are basically different in the first place. I will show that the theories are not basically different, so the whole debate resolves to an operational problem." Then the operational approach was expounded with vigor by H. A. Schneider.

Loomis talked of the problem of finding herbicides to kill the weeds but spare the corn in a plot, and I thought of the comparable problem of killing cancer cells by circulating chemicals while sparing normal ones, but M. K. Barrett considered just this and explicitly posed the problem of the evolution of two interacting populations. The course of change when the interacting systems are each modifiable, as in the development of resistance or susceptibility of one organism to another, is, of course, a more difficult and exciting problem than is the modification of one organism in developing resistance or addiction to some fixed agent, such as a drug. But after this is pointed out, the rest is detail.

C. W. Kearns spoke of the enzyme that removes hydrogen chloride from DDT in resistant flies. "Aha, I shall relate this to immune phenomena, to the genetics of blood groups, the different lysins, agglutinins and all the rest." Barrett did just this with his report on cancer immunity, and he also anticipated my comments on the individually unique metabolic patterns, described by R. J. Williams. These also relate to immune factors in individuality, exemplified by Leo Loeb's lifetime work on tissue grafts, which showed that the success of takes parallels the blood (or genetic) relationship between graft and host.

At last it dawned on me that I was on the wrong track; I was, in effect, trying to out-plan the planners of this symposium. I submit as a remarkable fact that, in anticipation, they had clearly recognized the ramifications and implications of their problem, had already thought of all these points, and had invited appropriate speakers to develop and analyze these many aspects of the whole. I do warmly congratulate them upon their conceptualization and foresight.

Particular Problems

There remain, however, a few things that I can, with some profit, take up further. First a few particular comments on items, mentioned during the symposium, which did not have all the attention they deserve. When Martin said he knew of no mutation that had actually led to the selection of the species, I thought of an old experiment with a blue green mutation in caterpillars. The grass greens and blue greens kept their proper genetic proportions while grown in the laboratory; but on the open roof, with green plants as a background, the blue green caterpillars were quickly eliminated by hungry birds.

Martin also considered the role of temperature in determining whether or not white coat color actually appears in animals that tend to turn white in winter but do not always do so. The influence of temperature on animal and plant coloration has, of course, been widely studied; the interesting point he made was that, once a severe winter had induced a white coat to appear in an animal, whiteness recurred in subsequent seasons, even though the temperature remained moderate. I wonder whether a hormonal mechanism might be involved, the thyroid being activated by cold and the cycles running over a bit from one season to the next. Such a piling up of residues seems involved in the enlargement of the adrenal cortex with repeated stresses and outlasts the stress period by considerable time.

On the interaction of two populations, I cannot resist mentioning some work of a group in which I have participated, the Behavioral Science Group at the University of Chicago, with members ranging from mathematical biologists to political scientists. This group has considered with some care, during the past year, the predator-prey relationship, and has examined the phenomenological consequences of a variety of assumptions concerning the parameters and boundary conditions of the formal equations defining relationship. With rather small changes in conditions, one can get the full scale of time relationships between the predator and prey populations: increase of either to a maximum, or fall to a minimum, or moving to a steady equilibrium or to an oscillation with decrementing waves, or one incrementing to an "explosion" or, perhaps most interesting, to an oscillation with a "beat" of its waves. The most intricate population cycles are thus predicted from straightforward assumptions concerning the rules of interaction.

Williams emphasized the individual, uncontrollable drives that constitute alcoholism, the craving for alcohol, and related these to particular biochemical individual characteristics, perhaps genetically induced. I thought, in that connection, of much neurophysiological work on the problem of drives. Quite discrete lesions, placed in the appropriate parts of the lower brain, the hypothalamus, can induce in a variety of animals an irresistible craving for water, for food, or even for a particular kind of food, as in salt hunger. One can, with lesions or stimulations, as the case may be, induce a goat, for example, to drink a tub of water, even enough to kill itself, or can cause rats, supplied unlimited food, to eat themselves into spheres of fat. It would be interesting to examine the hypothalamus in human cases of chronic alcoholism and also to compare the food and water drives of operated animals with alcohol added or absent.

Having introduced the nervous system, as did N. B. Eddy and M. H. Seevers in discussing morphine addiction, I shall continue with some items that seem to me to involve this little-mentioned entity. Does morphine addiction involve rather specifically the most recently evolved part of the nervous system, the cerebral neurons, or is it a universal effect involving all kinds of cells? Evidence was cited both ways. The differential acquisition of resistance by the medulla so that respiratory failure ceases to be a danger, and by cells in tissue cultures so that they grow in considerable concentrations of the drug, cited by Eddy, certainly support the more general character of morphine resis-

tance. On the other hand, Seevers' statements that true addiction can be obtained only in animals with a large cerebrum and that acute toxic doses of morphine produce demyelinization only in this part of the nervous system favor the more specific locus of action.

It is interesting that prefrontal leucotomy, topectomy, and other operations to remove the frontal poles of the cerebral hemispheres or to separate them from the remaining brain parts—operations now widely performed under the general terms of psychosurgery, to relieve severe psychotic behavior or intractable pain—rather regularly eliminate any narcotic addiction that had been acquired during the painful period. The addiction is eliminated in the sense that the individual no longer craves morphine, but not that withdrawal symptoms fail to appear when the drug is stopped. An addicted dog can die on morphine withdrawal, even if decorticated.

If specific neurons are involved in morphine addiction, as some of these facts suggest, then one would guess that the mechanism could not be an extremely basic or general one. That is, if an agent such as morphine, is able to produce changes involving interneurons or cerebral neurons, but not other kinds of neurons, then the agent must act on something fairly specific to the sensitive cells and not on universally present enzymes, or the cell membrane, or anything common to all cells. Yet, much of the work on morphine addiction suggests to me that an adaptive enzyme develops under the action of the morphine, a general cellular response. Nalline, quite specifically, acts as a competitive inhibitor of this morphine-altering enzyme, so that nalline can precipitate the withdrawal symptoms of morphine even when morphine is present.

Another interesting point: one can induce a high resistance to the lethal action of epinephrine, in dogs particularly. This was shown first by Essex, who adapted animals over a period of several days, and we were able to establish the same tolerance to manyfold lethal doses by infusing dogs over an 8 hr period, increasing the dose every few hours. Now the signifficant point is that an animal able to stand, say, a fourfold lethal amount of epinephrine shows no adaptation to its pharmacological action. The same small dose that initially caused vasoconstriction, change in heart rate, and so forth, still does so after adaptation. Apparently there are two different actions of the same drug in the same individual, one showing adaptation, and the other not.

A final particular item for comment has to do with the mechanism of action of various agents, the subject's reaction to the agent, the development of resistance, and so forth. What impressed me was that, one after another, the speakers outlined essentially the same list: Loomis for plants, L. E. Chadwick for insects, and Eddy and L. W. Law for man pointed to the same basic physical factors—penetration, absorption, spread, elimination—and the same chemical factors—inactivation of the agent by combination or degradation, inactivation of a particular enzyme by a change in the molecule, development of alternate metabolic paths so that the process can continue when the usual one has been blocked. Again, I could not help thinking that such common processes, common possibilities, appeared not only in the action of all sorts of agents on all sorts of organisms but also throughout biology. Exactly the same kind of problem arises in restitution, substitution, replacement, and elimination of all kinds. When the recovery of function, after a lesion has been made in the nervous system, is analyzed in terms of repair, or reeducation, or some other process, the same problems of the mechanisms of change appear in the same guise.

Yet, despite the intellectual satisfaction in seeing these likenesses over a wide range of phenomena and problems—indeed, the necessity of seeing them to achieve the basic orientation toward a problem that enables one to go forward in investigation—nonetheless, the real problems that have to be answered are always in terms of the particular facts in the particular case. It is fine to be able to interpret resistance in terms of changes in physical state, or changes in chemical state, or changes in enzymes; but one must finally specify which enzymes, which physical events, and so on, are the ones involved. It is only as these, often boring, technical details come into our ken and become a part of our armamentarium of knowledge that we can cope with the actual particular situation.

Flies develop resistance to DDT, by acquiring the hydrogen chloride-splitting enzyme of Kearns; in morphine habituation there may arise another enzyme, as already mentioned; chloretone and other narcotics may depress brain function by specific interference with carbohydrate metabolism or with phosphate generation, as argued between J. H. Quastel and W. D. McElroy; resistance to 8-azoguanine depends on the presence of a deaminase for this agent, as Law developed; DAB, the azo dye that generates liver carcinoma, is bound by specific proteins present in the liver, as J. A. and E. C. Millers reported, and the complex may be the carcinogen; the detailed interactions of genes and substrates, presented by H. K. Mitchell—such specific bits of fact enable their possessors to act intelligently in each particular case. So, although we certainly must paint the big picture, we must not forget that it, alone, will not take us far.

The last detailed point I refer to has to do with the question most vigorously discussed through the whole symposium: Is the development of resistance a matter of adaptation or of mutation, or is it a lingering modification somewhere in between? I kept score on the debate. There are 5 counts for adaptation; 3 clear-cut protagonists plus 4 halves, speakers "sort of on that side," as best I could judge. And there are 7½ for mutation; 5 clear-cut protagonists and 5 halves, not quite so clear. Two, I could not put in either category. This proves nothing, for the enthusiasm and the intensity of the adaptation protagonists more than overcame their weakness in numbers. They showed all the courage and the fighting qualities of the Scotch at Bannockburn and the Irish under any conditions!

Binding the Past

This brings me, then, to what seems especially important, the general problems that have come before us at this meeting. As I said at the beginning, we are, in effect, examining the problem of the interaction of two systems—or of a system and its environment, which still means two systems—in the course of time. Let me restate this in a number of different ways, to bring out some of the nuances and to make a few comments. Introducing a time factor inevitably brings up the possibility of change, the question of stability of the old and origination of the new. Saying this another way, it poses the whole problem of the storage of experiences by the system that has experienced them. We are asking, really, "How does process become pattern; how does a reversible disturbance become an irreversible state?"

I am tempted to talk at length on the record of a process left in a pattern, for I have had an exciting idea about it in recent months: When the formative processes are highly determinate the structures formed will be highly regular, and the greater the indeterminate, statistical, stochastic element in the processes, the more variable the resultant structures. Measurements, some of which are already in the literature, on the precision of repetition of structures should yield quantitative information on the degree of determinism in the underlying processes. The relationship between the mean and the variance of some structural attribute would show whether the processes were highly determined or highly chancy. As an example, compare the regularity of the hexagon in a honeycomb with the irregularity of the hexagons in squamous or cuboidal epithelium; or contrast the regularity of muscle fibers and fibrils in the longitudinal axis with their irregularity in cross section. It is interesting that the processes producing the honeycomb, though highly deterministic, are the actions of a group of individual organisms. But I must not pursue this theme now.

Another important question, which has kept bobbing up by inference, concerns the relationship between an individual as a complete entity, or *org* as I have sometimes called it, and that individual as a unit or member of some larger system, a group or a society or what I have called an *epiorganism*. This, also, I shall not go into, except to develop a bit the question of levels of organization—from the molecule or gene, through the organelle, the cell, the organ, the multicellular individual, the small group, the large group, the interbreeding population, or the social community, as the case may be. And, although this is repeating what others have said, I should like to restate it quite explicitly and to introduce this dimension of levels into our thinking.

Starting at the lowest level, a unit has its own past built into it in some set manner. This is now its heredity and is fully determined. What happens as a result of the behavior of the unit will depend, of course, on these inborn attributes and on the environment in which they operate. This is the point Mitchell made so fully with the *Neurospora* data. But just this activity of this subordinate unit in its environment forms substances or patterns that set the inherited character—or the given character, to avoid a word with other overtones—of the next higher unit. This new unit, in turn, reacts with its environment to determine a unit at the next level. So it is fallacious to place heredity at one locus and environment at another; a steady interaction between them occurs at each successive level.

For example, the protein molecule, with a given shape and side groups (the concrete entity that Sevag talked about, or that Pauling invoked to account for the production of a specific antibody, or even the interesting sickle cell anemia which apparently depends on an abnormal structure of the hemoglobin molecule) and depending on the medium in which it finds itself—what other proteins, what temperature, what *p*H, what substrates, and so on—will make certain other molecules. Now, whether it proceeds to make more of itself, in a general autocatalytic fashion, or whether it makes other molecules entirely, perhaps other enzymes, whether it reduplicates itself with some kind of spatial organization and makes only one replica, as in the template story, or whether it forms a mold against which an opposite kind of structural protein molecule will form—in other words, whether genes, or antibodies, or enzymes, or just other constituents or protoplasm are produced—will depend on the nature of that protein molecule and on the environment, the physicochemical medium, in which it is operating.

Once it has operated, there results a given cell organelle, say, with its fixed inheritance, with whatever it carries from its past history. The same thing recurs at the next level, whether it be a particular mitochondrium or microsome, whether plastids or plasma-genes are present, whether the killer factor in *Paramecium* is included or not, and so on. These then may multiply autocatalytically and reproduce themselves, either in more or less unregulated fashion or by rather sharp replication and with other associated properties of strict genic (cytogene) inheritance. E. D. DeLamater's pictures of bacterial structure came to mind here.

The whole cell is formed, in turn, by the action of these subordinate units and their environments; and the kind of cell produced is again determined by these given built-in components and their organization plus the environment in which it finds itself. Cells coming from a single dividing egg, with identical inherited genes, will form brain, or skin, or retina, depending on what other cells are near them; the endodermal anlage will form gut or liver, for example, depending on its proximity to an embryonic heart. This same situation occurs over and over again. Whether somatic mutations have occurred, which seems pretty clear in such cases as the pigment spots in piebald skin coloring or even the regular color patterns of feathers, or whether no mutation is involved, is perhaps not very important when looked at this way. Similarly for the cell foci which develop a lowered resistance—possibly favoring ultimate cancer development and certainly responding to chemical or other insult in their special way. Thus, a particular skin patch may redden and

desquamate each time a barbiturate is taken, although it is normally unidentifiable.

Moving to the organism level, from the fertilized egg to the newborn human baby is something like a 2^{43} increase in cell number; which means that more than 40 generations of cell division have occurred on the way from egg to baby. The attributes of the individual, of course, depend on the environments in which these cells multiply—at first intrauterine, which leads to congenital effects, but then those experienced on through life. Whether they are "inborn" skin ridges of fingerprints, or nail ridges produced by disease in the teens, or tree rings that show the climatic vicissitudes over a millenium, is not too important; all result from interaction of cell groups and their environment. It is often impossible to allocate the factors between cell or organ or organism levels, and to place their operation in time. For example, the aging process in multicellular organisms can be shown to be in the cells, since young ones grow faster in culture than do old ones, or in the body fluids, since young plasma promotes better growth than does old; yet the fluids are the collective product of the whole organism.

Finally, the same interaction pattern holds at the level of the epiorganism, or group. The kind of colony, the kind of population, the characteristics of the termite nest or of the metropolis and the culture that pervades it—these are the products of the organisms of which the epiorganism is composed, acting in their togetherness in response to the group environment and to their individual experiences during the formative period.

Perhaps this whole point is sufficiently made in the lovely couplet, "On Seeing Weather-beaten Trees":

> Is it with us as clearly shown
> By slant and twist, which way the wind hath blown?

Stability is obviously tremendous if a fertilized egg can go through 40 generations of cell division and come out an overwhelmingly stereotyped individual, billions upon billions of times. This must mean that enormously powerful homeostatic mechanisms operate at all levels: mechanisms for maintaining cell *p*H reasonably constant, for maintaining blood thyroxin reasonably constant, for maintaining hive temperature reasonably constant, and, no less, for maintaining cultural patterns of a group reasonably constant.

And there are no sharp discontinuities; from the perturbation or fluctuation, the reversible response to some environmental stress imposed upon the system and followed presumably by a full return to the *status quo ante,* there is a gradation to the modification, the irreversible material change. The phenomena present a spectrum, not a black or white dichotomy, and this I think is true even for the mechanisms. These are also not either-or. For example, one extreme is surely a gene mutation that, per se, gives a new phenotype. But then comes the gene mutation that enables the organism to show a new phenotype only when it is placed in some particular new environment, leaving it unchanged in the original environment. Here are the adaptive enzymes. Then comes a gene mutation that favors the appearance of other gene mutations in certain environments. Here the point is important that each gene is part of the environment of other genes. Next, there are genes that favor somatic mutations in multicellular organisms, and genes needed for adaptive enzymes to form in the presence of substrate. If such genes are lost by mutation, a strain of yeast, say, can continue to ferment galactose as long as the strain is cultured with galactose, but, once grown without this sugar, it can never recapture the ability to use it. This approaches the case of plasma particulates, with their complement of enzymes, which reduplicate or reproduce in a cell. The *Paramecium* killer factor and chlorophyll plastids come to mind as well as the example, presented by Mitchell, of cytochrome transmission in the breeding of molds. Next come cases of infection by viruses, carried along intracellularly during cell division and multiplication; of the intracellular HCl-splitting enzyme of DDT-resistant flies; of antibodies in tissue fluids of immunized multicellular organisms. We even find 2,4-D carried in the corn seed and inactive until germination and development produce the particular susceptible structure, kernel or silk, which is then mutilated.

At the behavioral level the same progression occurs from an early reversibility to a later irreversibility. Starting with repeated vasoconstrictions, spasms of smooth muscle of blood vessels stimulated to overactivity, there is the presumed sequence of hypertrophy, thickening, and finally calcification. A physiological contraction has become an irreversible constriction. It is clinically helpful, in cases of hypertension, to administer a drug, such as tetraethylammonium, that paralyzes the orthosympathetic constrictor nerves. If, when the impulses are blocked, a vasodilation results, it may be worth while to cut the nerves; but if the narrowing is no longer dependent on continued nerve excitation, surgical intervention will hardly help. Here the change from reversible to irreversible is very clear.

Irreversible changes can result, of course, from behavioral influences in relation to the external environment—the bowlegs of the cavalry man, the weathered skin of the outdoor person, even the reflection of an adult's temperament or character in the kind of skin folds in the face, whether frown or smile lines have become etched in. One example that has long intrigued me is the influence of alcohol and of mescaline on spiders. Under alcohol they weave their webs in an irregular fashion, as if the drunk were staggering home; under mescaline, which changes the time sense in human beings and apparently in spiders, a web is woven which is more perfect and with closer spirals than normal. Again, we see an irreversible structural manifestation resulting from transient and fully reversible physiological states.

The whole question of storage of experience, or memory, involves the same sequence from process to structure. Excellent neurophysiological evidence shows that memories in the brain, first in some dynamic form, require time to "set." Hamsters, given daily learning

runs through a maze and daily electroshocks, learn well enough when some hours elapse between run and shock, less well as the interval is reduced to an hour, and not at all when only a few minutes are allowed between experience and the disruptive shock. So something more than an hour is required for what is initially a passing ripple of nerve impulses to become solidified into a structural modification—whether chemical or morphological change at a synapse—of the nervous system. Conditioned reflexes, habits, are similarly fixed by repetition of a response to a recurring experience.

And I suggest that in the epiorganism of society the new idea is the cultural change, is something like the mutation or the adaptation we have been discussing. Several religions have in their records a description of a great flood. It has been interpreted by some as a folklore record of the inflow of the Atlantic into the Mediterranean basin. I have no idea how reasonable, theologically or geologically, this suggestion is; but I can cite a better proved instance of social fixation. An anthropologist noticed some years ago in a small Scandinavian village that the natives, going by a whitewashed brick wall, would make a small obeisance. There was nothing to be seen, and no one was able to suggest the reason for this local custom. He finally scraped off some of the whitewash and found underneath a religious painting, many centuries old. Obviously, in the past of that particular community there had been established the habit of making a little bow in passing this icon; and the bow persisted when even the object to which it was made was entirely forgotten.

When does one get an effective social mutation; what determines that a new idea "takes" in a community so that it becomes part of the culture? Maybe the word-of-mouth passage suffices in some cases even today; maybe now a written document is needed, or even a mass printing; or perhaps a nation-wide television program will suffice to imprint, with no direct record. But remember Don Marquis' poem about lost civilizations of the past:

> Their name? Go ask oblivion.
> They had no poet—and they died.

Cultural inheritance also passes from the evanescent word to the material record or ingrained attitude.

These fixations take time. There is a lag from the mutation to the phenotypic change, as Bryson pointed out. Williams spoke of the difficulty of inducing a vitamin deficiency in an adult animal that was well fed all its life, and Martin assured us that recently acquired racial characters fade out most easily. Similarly, recent individual memories are lost first, old learning being more stable than new, and even new learning requiring time to fix, as already mentioned. Races are almost annihilated by contact with new pathogenic organisms or drugs, but the great epidemics die out in time, and measles, for example, became a mild indisposition in populations that had long lived with it. The crucial point, of course, is: When does the system reach the point of no return; when has the reversible become the irreversible? Remember that the point of no return, even in modern aviation, is determined not only structurally, by the plane's position vis-a-vis the two continents, of origin and of destination, but also by dynamic factors, such as wind velocity and direction.

And since, as it has turned out, there is pretty good gradation in stability, in time, in mechanism, and maybe even in concepts, I again say there is no theoretical antinomy in the positions taken during this symposium. Each particular case has to be worked out on its own merits, in the light of experimental findings, to reach a useful result.

The Epochs of Man

It seems to me that one can think of three epochs in human affairs. Before the rise of biological science, man was pitting his own evolution as a biological entity, a very slow one, against the biological evolution of bacteria, insects, and other organisms that might be inimicable to him. Since they were moving faster in reproduction and modification than he, man was always getting the small end of the stick. Mankind was really ridden by pestilence and famine, by the horsemen of the Apocalypse; and Malthus was right not only in theory but in practice. A human's lot was not a happy one.

Then came the age of biological science, and we no longer had to pit biological mutations against biological mutations; we are now pitting social mutations of the human epiorganism, of man as a society, against the biological mutations of these other forms. And since social mutations, new ideas, give rapid evolution, and since science itself is a social mutagen that increases them, I feel reasonably confident that, however rapidly the organisms adapt or mutate into new and more virulent forms resistant to our existing agents, we will continue to find new means through our science, through our social evolution, of combating them effectively and keeping comfortably ahead.

The real problem, of course, is not any longer man against other organisms but man against himself. In social evolution, simpler natural science has grown more rapidly than social science and so has given a tremendous increase of power before the social organism has developed the coordinating homeostatic mechanisms necessary to control it. So we are now, all too clearly, in grave danger of wiping ourselves out. Here also, I have, if not confidence, at least hope that the further advance of the scientific mode—certainly not its abandonment—will solve these problems, too, before our brutish power destroys us.