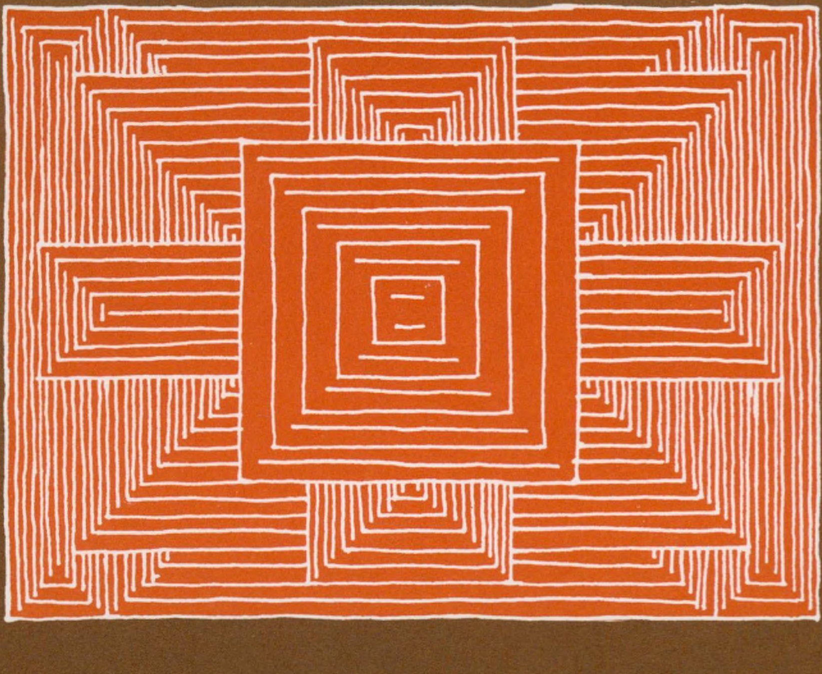
Citizen of Science

RALPH WALDO GERARD

A Guide to the Gerard
Microfiche Collection, 1927–1975



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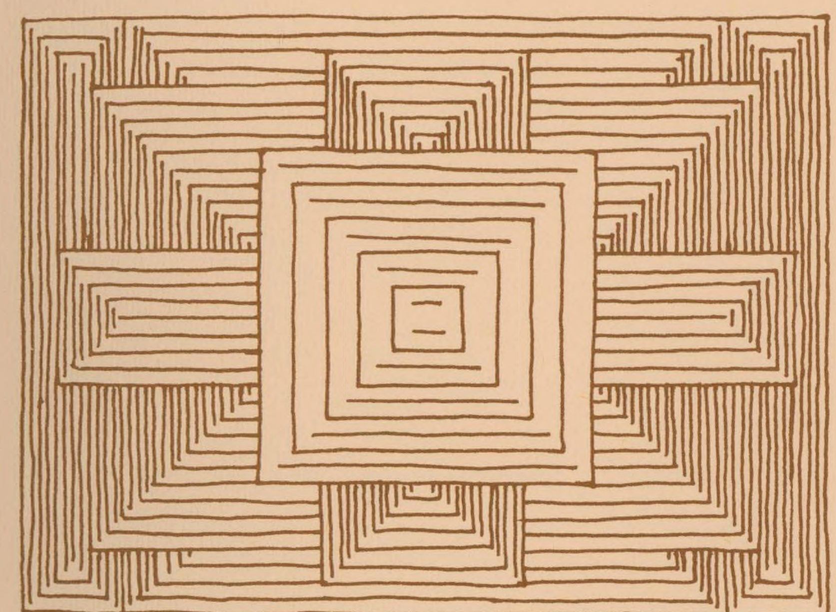

CONTENTS

Leona Bachrach Gerard

FOREWORD

It does not often happen that a person is consumed for more than a half century by an unquenchable curiosity about the universe, ranging from biology, medicine, human and animal behavior, the nature of science itself, education, computerism, interdisciplinarity, to ethics. But such a one was Ralph Waldo Gerard. He perceived the search for scientific truths to be forever unfinished, the shoulders of one scientific generation affording a firm footing for the questing minds of the next.

In his last published paper, Ralph Gerard characterized himself as "a generalist (different from a generalizer) [who has] earned the right to this broad approach by meticulous devotion to many particular areas of research, and by the exploration in simplified systems and with micromethods of the precise mechanisms involved in their operation. . . . I have been committed to the minute experiment and the large picture." Behind this statement lies the fact that from his early student days at The University of Chicago, he made a point of taking a course in every science offered on the campus and in most other departments there, so that he came to know at least the elements of philosophy, comparative religion, cultural anthropology, psychology, mathematics, literature, history of art, etc. His familiarity with the concepts, vocabulary, methods and approaches of so many fields accounts for his fascination and ease in seeking inter-relationships—similarities and dissimilarities—among apparently disparate phenomena. It seems therefore an appropriate memorial to him and a worthwhile use of his scholarship and insights to make them convenient to students today through research libraries, an important interface between science and society.

The *Introductory Essays on the Life Sciences,* included in this index volume, Ralph Gerard wrote during December 1973, a few months before his death. Unpublished until now, they were to have accompanied the republication of his reprints under a different format. The essays sought to place in related intellectual scaffolding, an overview of current thinking in such diverse fields as the nervous system, mental disease, aging, science, education and society.

The University of Chicago has produced microfiche sets of Ralph Gerard's reprints and several unpublished manuscripts, which are being made available to research libraries throughout the world. These sets are a gift from the University, the total cost of publication being borne by the institution as a public service. I deeply appreciate the generosity of The University of Chicago, and the kindness of Theodore Hurwitz, its Director of the Office of Gift and Estate Planning, whose responsibility it has been to coordinate all aspects of this project. I am grateful to the University of California, Irvine, for enabling Roxanne-Louise Nilan, Curator of the Gerard Collection that is housed in the U.C. Irvine Archives, to compile the index contained in the volume accompanying the fiche; and for Dean Howard Schneiderman's assistance in identifying major research libraries the world over. David Novick, Ralph Gerard's grandson, designed the cover of the index volume.

Perhaps a last acknowledgement is in order: Ralph Gerard during the nearly twenty years of our marriage and until the very end of his life remained an affectionate, considerate, most interesting and imaginative companion.

Leona Bachrach Gerard
February 1976

Ralph Waldo Gerard

INTRODUCTORY ESSAYS ON THE LIFE SCIENCES

I

As an undergraduate at The University of Chicago my main subject was chemistry, but I was always attracted by the problems of behavior. When I finally came to take an elementary course in psychology, however, the young instructor solemnly assured the class that the nerve impulse was a sort of electrical current which crossed synapses by the process of osmosis. This impossible juxtaposition so offended my budding knowledge of physics and chemistry that it was a couple of decades before I actually ventured into studying the brain and behavior, but it also sharpened my interest in the problems of nerve activity. When, in the mid-twenties, after completing my Ph.D. (on a problem concerned with the chemical cause of death in an intestinal obstruction) and my M.D., I was given the opportunity to spend a couple of years in Europe as a National Research Council fellow, I chose to work first with A. V. Hill in London, who was about to turn his splendid myothermal techniques and analyses to the problem of nerve, and then with Otto Meyerhof in Berlin, whose chemical studies had paralleled Hill's physical ones in so effectively elucidating the processes involved in muscle contraction that they were jointly awarded the Nobel Prize in the early twenties. They graciously welcomed me into their laboratories and minds and so launched me into nearly half a century of research in my chosen field.

My infatuation with the nerve impulse began, I think, in relation to a standard class experiment in neurophysiology, demonstrating the non-fatiguability of nerve. A discussion of this with the professor, A. J. Carlson, led to our becoming good friends and I ended up as a physiologist rather than a chemist. I also returned to Carlson's department at The University of Chicago after two highly educational and productive postdoctoral years.

Reviewing half a century and a half a thousand articles later my scientific life trace, it has proved gratifying on rereading even these earliest papers to find that the work was carefully performed, with complicating factors recognized and controlled and with the reasoning and analysis essentially sound, even though the conclusions and interpretations had in many cases been superseded by the onward sweep of neurophysiological research. With relatively few rotten apples to be easily discarded, it has been correspondingly difficult to select an appropriate sampling for the present purpose. I have reluctantly, for example, omitted the first paper on the measurement of nerve heat (by Downing, Gerard and Hill) because this was so largely devoted to the development of the extraordinarily difficult instrumentation, to which I contributed only modestly and of which I was primarily the happy beneficiary. I have included the immediately related paper on delayed nerve heat, since this was definitely my discovery and also effectively presents the essential findings of the omitted paper. The fourth study performed in Hill's laboratory, on the influence of anoxia on nerve heat production, and the first paper done in Meyerhof 's laboratory, moving on to the direct measurement of gas exchange in the resting and active nerve, are included, as is the first major paper after my return to Chicago, an exhaustive study of the electrical responses of nerve in oxygen and nitrogen and an effort to tie together the different approaches into a coherent picture.

The investigations on nerve heat and metabolism were carried out, in each case, at the very limits of the methods available or developed for these studies—as is probably the case in all pioneering into new territory. The paper on electrical activity, by contrast, attempted by fine analysis to tease information from a well established technique, findings that fell out easily as amplifiers and oscilloscopes later became commonplace.

Perhaps this is a good place to interrupt my more personal chronicle and briefly review the status of neurophysiology before the 1920's.

Although Galvani and others had established a relationship between current electricity and nerve and muscle at the start of the 19th century, it was not until nearly the middle of this century that DuBois Reymond and Helmholtz, both young men working in the preeminent Institute of Physiology of Müller in Berlin, made two major discoveries that brought the nerve impulse within reach of experimental science. That nerve was directly irritable had been established earlier, but the only evidence that some message had travelled along a nerve fiber was the resultant contraction of an attached muscle or the production of a central response of some sort or a reflex action. Whatever message travelled along the fiber moved extremely rapidly. Müller had predicted that the speed would never be measurable in the short distances

of nerve available, and no change within a nerve had been unearthed as messages travelled along it. Then DuBois Reymond succeeded in demonstrating a small change in the injury current, between the intact side of a nerve and the cut end, as a rapid series of impulses was sent along the nerve trunk. This so-called negative variation became measurable with improving instrumentation until, at about the time these researches were begun, Gasser and Erlanger in this country succeeded in amplifying these minute potential changes with the then new triode amplifying techniques sufficiently to activate the also new cathode ray oscilloscope, thereby combining the sensitivity and speed of response necessary to directly observe the single nerve action potential. Helmholtz, a fellow student with DuBois Reymond who became one of the towering figures of science, reasoned that the existence of an electrical change indicated that some material alterations must occur with nerve conduction and that this could therefore not move at the speed of light or electricity, and he proceeded to measure the conduction velocity of the nerve impulse. This proved to be rapid, from 30 to over 100 meters a second in different nerves and at different temperatures, but in a different velocity universe from what had been assumed.

The nerve could thus no longer be regarded as a passive conduit for something put in at one end and emerging at the other and, in fact, this was completely excluded about the end of the last century by the discovery of the all-or-nothing law in nerve, following its earlier recognition in the heart. This states that the intensity of a nerve impulse is entirely independent of the intensity of the stimulus that initiates it (providing this latter is strong enough to initiate it) but varies only as the condition of the nerve fiber through which it is passing. The picture then was comparable to a spark burning its way along a fuse, except that the agent by which an active region activated a succeeding stretch in the nerve was an eddying electrical current rather than an igniting temperature.

Whatever the mechanism of propagation, however, if it was actively generated within the nerve, energy would be required and an active nerve should produce extra heat and increase its metabolism as compared to a resting one. Various efforts in the first quarter of this century had failed, however, to show any increased oxygen metabolism or other metabolic change in active nerve and Hill had failed to demonstrate an increased heat production with the methods that had been highly successful in the case of muscle. The notion still prevailed, therefore, that nerve activity was somehow in a unique category and, indeed, an authority in the field of metabolism had made the solemn pronouncement that an hour's hard thinking would require less energy than would be obtained from half a peanut. The experiments with Hill, which finally did succeed in establishing a minute but entirely meaningful heat production with nerve activity, and the following demonstration in Meyerhof 's laboratory of a corresponding increase in oxygen consumption and carbon dioxide and then of a variety of other chemical changes in active nerve did bring neural tissue into line with the other tissues of the body.

Work continued on neurothermic measurements for some years, primarily in Hill's laboratory, although extended elsewhere to the central nervous system; but once the magnitudes and time relations of the heat production were well established it was obviously more fruitful, and certainly much easier, to push the further studies along the lines of metabolism by measurement of changes in the actual substances undergoing change. This remained the focus of attention in my laboratory and in others for perhaps a decade, by which time a new sub-specialty, neurochemistry, had become well established and when chemical and pharmacological studies on the nervous system took a new direction as a result of the discovery by Loewi and by Dale of neurohumoral substances that served as transmitters between nerve and effector or neuron and neuron.

Today this field of neuropharmacology is especially active and productive and is tying back to more familiar neurochemistry and to neural function in general. After acetylcholine and then noradrenaline and the other catacholamines and then other amino acid derivatives were identified as effective transmitters at excitatory or inhibitory junctions, and a number of these had been related to disturbances in junctional transmission and in central functioning, they are being used with increasing success in the treatment of myasthenia, parkinsonism, and other neurological and even psychiatric disorders. Neurochemistry, in this same period, has moved along with biochemical knowledge of other tissues, with much current attention to nucleic acids and other nuclear and genetic chemistry, to the lipids, in many cases unique to neural tissues, and to an array of equally unique neuroproteins. Some further words on this will be appropriate to the second essay in this series.

Thermal and chemical measurements of nerve activity were of limited value unless they could be related to another well established indicator of the level of activity attained, such as the electrical changes. I was thus soon led into electrochemistry as well as neurochemistry and, when we developed the capillary microelectrode in my laboratory, the much larger striated muscle fiber offered an especially favorable material on which to study the membrane potential by impaling a single cell with this gadget. This microelectrode has

proven to be remarkably productive in laboratory and clinical research and has been used for intra and extra cellular recording with single axons (such as the squid giant axon), single neuron cell bodies or dendrites and synaptic fields, skeletal and other muscle, especially the conducting system in the heart, in receptor cells and organs, glands, and other body stuctures.

II

For some years I limited our research to peripheral nerve, despite the obvious lure of the central nervous system, partly because much still demanded attention in the simple nerve preparations, but more because the central nervous system seemed too messy for meaningful quantitative or even qualitative studies of metabolism; since glia were mixed with neurons and many different types of neurons existed and since any manipulation produced an unknown mixture of excitatory and inhibitory changes. The riches to be mined, however, overcame our doubts and my laboratory as well as many others around the world plunged into biochemical and electrophysiological studies of the central nervous system. The micro pipette served not only to pick up or apply potentials and currents to minute neural structures, but also to administer drugs locally and even to obtain small localized samples of brain tissue for chemical study. The growing availability and refinement of radioactive tracer techniques and of other cytochemical methods, especially for enzyme determination, soon enabled neurochemists to study single neurons or even parts of neurons and to deal separately with glial cells and with the various species of nerve cells.

Cholinergic neurons and pathways with junctions could be separately identified, and even various types of cholinesterases distinguished. Similarly, adrenergic elements or, more generally, aminergic ones were identified cytochemically and by their enzyme actions and especially the indophenol family could be vividly exhibited in sections by a fluorescence that developed after treatment with formaldehyde. Adrenalin, noradrenalin, dopamine, copa, tryptamine, tyramine, GABA and still other monamines and other amino acid derivatives were intensively studied. Further, techniques for manual dissection of single neurons or even of their nuclei, plus the development of ultramicro chemical methods, permitted the Swedish workers, in particular, to follow neurohumors, nucleins, and other important agents in and about the central nervous system and along peripheral nerves.

My own early interest in why a severed nerve fiber should degenerate led us to the finding that materials move along axons. This phenomenon, as is so often the case, turned out to be a complex one, with clear evidence today of movement of particular substances at the slow speeds originally demonstrated of some three millimeters a day and at fast speeds some hundred times greater. There is also a movement of the entire neuroplasm mass from the cell body peripherally at a slow speed; electron microscopic studies have revealed neurofibrils and neurotubules extending the length of nerve fibers, perhaps serving for the rapid movement of substances, and vesicles have been shown to move along the axon and accumulate in the presynaptic knob, from which they are released by nerve impulses into the synaptic cleft, to release neurohumors which act upon the post-synaptic receptor elements. The various subcellular elements have been freed by appropriate breaking up of neural tissue and the differential centrifugation along specific gravity gradients obtained by different concentrations of sucrose or other substance—mitochondria, membrane, endothelial reticulum, synaptosomes, vesicles, and other elements have thus been segregated in reasonable quantities in different layers and subjected to individual chemical and metabolic studies. Not least, studies on the membrane itself, of nerve and other cells, have led to detailed knowledge of its properties—including the permeability changes with functions, the binding of agents on receptor sites, etc.

Our interest in degeneration early led us to an examination of the supposed impossibility of regeneration of damaged fibers in the central nervous system. We were able to demonstrate that fiber growth and physiological function could be reestablished across a complete transection of the spinal cord, but to a limited extent except in perinatal animals. Since the clinical importance of successful central regeneration is enormous, it is encouraging that efforts in this direction are now being renewed vigorously, with the strong encouragement of the National Paraplegia Association, and a number of encouraging leads give promise of great improvement in central regeneration in future years.

Turning to the electrophysiological area, the reactivation of the Horsley-Clarke stereotaxic instrument and our combining it with concentric electrodes to lead off activity from known small regions throughout the brain mass made it possible to demonstrate spontaneous rhythms of a great variety and to follow evoked potentials into neuroanatomical regions which were known to receive the various inputs and also to many others presumably barren of these. Experiments along these lines have been vigorously pursued by many laboratories and today the neural traffic throughout the central nervous system is being clarified in considerable detail, not only as to where nerve messages go, but also how the critical information is coded in

various patterns of nerve impulses and how it is processed back into meaningful experience or behavior. Recent experiments on conscious humans (in connection with legitimate neurosurgery) have shown, for example, that the various particular modalities of cutaneous sensation can be evoked by near threshhold stimuli of one or another region of the post central gyrus. Similarly, although electrical activity in this region appears within ten or fifteen milliseconds after a peripheral stimulus, local stimulation of the cortex as much as half a second after the peripheral stimulus is given can completely inhibit conscious sensation.

It has been possible and profitable to relate brain activity to behavioral attributes in general. Our early studies on memory, indicating that an interval of minutes or hours must elapse between an experience and the establishment of a permanent memory of it (the fixation or consolidation period) has also effluoresced into a rich sub-field of research and many workers are now studying the factors that influence memory and recall. At least two and probably three or more processes of greatly different time scales are involved in establishing an enduring memory, and the agents that successfully interrupt these processes, such as chilling or electric shock which presumably stop the normal passage of nerve impulses, are being explored in some detail. Further, a variety of agents which slow or accelerate nucleotide or protein formation in neurons are being explored for their ability to slow or accelerate the fixation and learning processes.

In another direction, great advances are being made in finding and using simplified neural preparations. We went to the isolated frog brain and to the rat spinal cord; others have turned to the smaller and simpler invertebrate nervous systems, where it has been possible to identify structurally and functionally every neuron in a major ganglion or system. Such preparations have lent themselves especially well to the study of learning, which clearly can occur in small neural masses far from the cranial ganglia.

The phenomena of attention and habituation have also come in for intensive and successful study, in mammals particularly, and related to the reticular and other systems; and various drives and emotional experiences have been successfully modulated by manipulation of hypothalamic and other limbic structures. One productive approach has been allowing animals to self-stimulate particular brain regions, by pushing a lever; brain regions related to rewarding or aversive experiences have thus been identified and single neurons have even been conditioned to increase or decrease their activity in comparable manner.

III

With the almost explosive increase in knowledge of neural metabolism and of anatomical connections and, particularly, physiological mechanisms of neural interaction, it was inevitable that clinical neurology and neurosurgery, and eventually psychiatry, would also make great strides forward. The EEG has become a universal diagnostic tool in the clinic, and more discrete electrical recording —including that from deeper structures—is also used not infrequently. These resources have proven especially valuable in dealing with epilepsy and, indeed, have given strong clues that the overexcitation of the brain in this illness is associated with defective inhibitory mechanisms. Several effective drugs, specific for one or another form of epilepsy, have proven highly valuable in handling this disorder. The almost convulsive pain states of causalgia, tic douloureaux, and related clinical entities were seen early also as involving a disturbance in inhibitory control, in this case at the level of incoming messages to the brain stem, and a direct inhibitory connection from the large diametered "epicritic" sensory fibers and their dorsal route processes, leading to a clear inhibition of the pain and other protopathic inputs at the same segment, has since been demonstrated. More generally, reflex loops from central nervous system to receptors, from muscle to cord and back, and at practically all relay levels up and down the neuraxis have been demonstrated. Further, various types of lateral inhibition at a given level in the nervous system have been shown for sensory inputs (as in activation of cortical projection neurons from particular photoreceptors) and for motor outputs (as in the sharp delineation of active motoneurons within a total motoneuron pool); and comparable sharpening of sensory inputs, as by lateral inhibition within the retina itself, is also clear.

A chemical negative feedback, first demonstrated by the action of thyroid hormone in decreasing the metabolism of thyroid gland, in contrast to its increasing cell metabolism in general, in this case now known to involve an intermediary link through the anterior pituitary, has also been generalized to a number of hormonal systems and shown to operate intracellularly as well in the control of enzyme activity and in the activation and suppression of particular genes in the genome.

Inhalation therapy has developed into an important clinical subspecialty, especially involving the breathing of carbon dioxide to dilate blood vessels and so to abort or reverse vascular spasms in brain vessels to protect against ischemic destruction of neural regions and the attendant "strokes".

Parkinsonism is now effectively controlled in many instances by administering L-dopa which, after penetrating the blood-brain barrier, is changed within the central nervous system to dopamine and noradrenaline, which appear to be deficient in this illness. It is perhaps significant that chlorpromazine and other psycho-active drugs tend to produce Parkinson-like side effects and some workers tend to implicate the dopamine-noradrenaline system in the disturbances of schizophrenia. More and more evidence is building up to implicate a biochemical disturbance in this illness and to base this increasingly on a genetic background. Our own studies, separating schizophrenics into seven subpopulations, largely on the basis of physiological and biochemical measurements but correlating well with established clinical categories, have not yet been followed up extensively, although there is an increasing interest in the nosology of this group of disturbances. Considerable attention has been given to the somewhat spurious problem of functional versus organic in mental illnesses; and even more to the usually misunderstood and polarized question of the roles of heredity and of environment in contributing to normal and abnormal behavior. The nature-nurture issue has become especially acute and highly emotional, in connection with the problem of intelligence variation between races. Incidentally, a growing recognition of the importance of very early environment, especially the richness of biochemical nutrition on the one hand, and of psychosocial "nutrition" or sensory input on the other, is contributing to large scale social experiments, especially in education, and at the same time complicating interpretations.

Finally, interest in the aging process and an aging human population is rapidly increasing. Gerontology and geriatrics are now well established in biological science and medical practice, respectively. The creation of new research institutes and national associations, plus the intense concern of government with these problems, bodes well for the improvement of dealing with our aged.

IV

The papers in this segment present the author more as a citizen and a total person than as a neuroscientist, but many of them are dependent on general biological or even neurological thinking. The steady accretion of knowledge, or even of wisdom, is less evident in the broader arena of human affairs and the application of science to them than in the narrower domain of science itself, so it is not especially appropriate to attempt brief updating summaries of developments following these publications. This caveat is perhaps less applicable in the area of computer-aided learning; the predicted developments in applying computers and other technologies to enhancing the educational experience have indeed occurred or are occurring, although mostly at a rather slower rate than expected. Similarly, the more general proposals regarding higher education in general and health education in particular, along with corresponding shifts in health care delivery organizations and attitudes, have also become the more and more accepted directions of contemporary thought and action. Greater attention to education as well as research and to preparation for effective teaching during the graduate years has had great attention, and even the specific urging that these two functions be separated administratively and not lumped in single entrenched departments which easily become archaic is beginning to have some takers. A shift from lockstep passive learning toward active progress along individualized programs is now given wide lip service and considerable implementation; and the individual project seems firmly established, at least in the science education sector.

Much attention is today devoted to the penetration of science and particularly of its offspring, technology, throughout human affairs; and for some years there has been developing an anti-intellectual backlash in our society so that the prestige of scientists and the support of scientific research have suffered considerably. To many, technology has become a dirty word. Yet it must remain true that man's large cerebrum and the capacity for reason that this engenders is responsible for the achievements of mankind, expressed in human creations in art and social organization no less than in intellectual understanding and its outfall in operational instrumentation and procedures, all of which constitute the human estate.

Other interests that have been developed in these essays deal with the nature of science itself, the potential scope of this approach in dealing with other areas of human affairs and its relation to art and literature, the international aspects of the scientific endeavor, the nature of universities and other institutions of higher education and research, and the history of some of these developments.

It has proven profitable to examine systems at different levels of organization and complexity, and particularly to consider societies as epiorganisms, composed of organisms as units, as most of the plants and animals we know are multicellular organisms composed of single cells as units. The evolution of organisms and epiorganisms, or orgs in general, towards highly integrated systems with specialized differentiated units suggests probable directions of social evolution, including the progressive emphasis on cooperation and related ethical and moral values. A society and several periodicals are now devoted to general systems problems. On the other hand, the frictions that have long

existed between beliefs grounded in faith or in observation and experiment have shown a recrudescence in the last decade or so; and the teaching of evolution in our public schools, notably in California, has been challenged by individuals and groups of fundamentalist religion orientation. When the California Board of Education inserted a statement about special creation, as an alternate "theory" to that of evolution, presented in the scientific framework document prepared by a blue ribbon committee of scientists and educators at the request of an earlier Board of Education, the committee protests at least led to this insert being identified as not acceptable to the writers of the guideline material. Interestingly, a number of religious groups lined up with many scientific ones in opposing this violent miscegenation.

Inevitably, problems of biological and social evolution have undergone critical examination; and the problems of heredity and environment and their interactions, referred to in an earlier volume, have had extensive—but not always logically critical—attention in the scientific and public arenas. Particularly when racial differences have come into question, the evidence and arguments of scientists favoring an hereditary component in intelligence differences have hardly been given an objective and fair hearing by their colleagues and often have been denied any hearing on public platforms by obstreperous protestors. The mood of exaggerated individual protest in society is perhaps waning but is still clearly present in the attitudes of the 70's.

A final note may be in order about my papers on the biology of imagination. These have been widely quoted and reproduced and I like to think of man's imagination as the culminating effluorescence of the process of evolution up to the present time.

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JOINT AUTHOR INDEX

TITLE INDEX