Evolution of Nervous Control from Primitive Organisms to Man

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Preface

From the very beginning, living things were able to survive only because they had developed control systems which enabled the individual organism to respond to changes in the outside world. Responsiveness to stimuli is a characteristic of life and may be defined as behavior. Even the lowly unicellular organism, though it lacks a nervous system, can "behave"; it makes adjustments in the face of an inconstant external environment, responds positively to stimuli, and even displays a crude type of learning process. Its receptors provide a flow of information about the world around it; in some fashion the cell decodes the information and sends out appropriate responses. We know little or nothing of the nature of the regulating mechanisms in these primitive life forms. It is not surprising therefore, that we know so little about the working of the human brain—that marvelous apparatus which not only controls the constancy of the internal environment and all the instinctive patterns of unconscious behavior, but also has the unique capacity for abstract thought and the mysterious inward awareness which we call "mind."

Man cannot extricate himself from his remote ancestors, for his development from lower forms has been a slow summation of continuous changes. Therefore, understanding the nature of behavior in lower forms may well be a key to understanding of nervous control in man. Granted, there is a vast difference between the proliferation of functions in man's nervous system, and the limited functions of the non-nervous control mechanisms in unicellular organism. Yet, in the course of evolution, Nature improves but does not necessarily discard. For example, the biochemical energy mechanisms developed some thousand million years ago in unicellular organisms still have their close counterpart in our bodies.

Similarly, the response mechanisms in the one cell of the amoeba may be activated in basically the same way as each of the billions of cells in our brains. Plants, too, respond to their environment despite their having no nervous system, and studies of their responses may well help in a better understanding of the brain.

This book portrays the impact of the evolutionary process upon the brain. The various papers represent a variety of disciplines and viewpoints which are presented by a botanist, an embryologist, a neurologist, a neurophysiologist, a physiologist, a psychologist, and a psychiatrist. I was greatly stimulated by the various presentations, and they have given me a sense of perspective as well as humility in studying the brain. I hope that other readers of this monograph will be similarly affected.

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A Common Basis for Development and Behavior in Organisms

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The purpose of this first paper in our symposium is not to discuss any aspect of the nervous system as such but rather to introduce the problem of the nervous control of organic activity by relating it to other activities of the living organism and thus setting it up against the background of biology as a whole.

In all higher animals, behavior is obviously under the control of the nervous system; but in the simplest ones, such as protozoa and sponges, though behavior obviously is controlled, no nervous system is differentiated. In plants, many of which show behavior of a primitive sort, there is not even a suggestion of a nervous mechanism. Evidently behavior does not always depend upon the activity of nerves. As Bergson (2) says: "Neither mobility nor choice nor consciousness involves as a necessary condition the presence of a nervous system. The latter has only canalized in a definite direction and brought up to a higher degree of intensity, a rudimentary and vague activity, diffused throughout the mass of the organized substance."

The fact of biological organization which Bergson here emphasizes is the basis, I believe, of the control of all vital activities. It produces the *organism,* a distinctive feature of life. Organization can be seen most directly in development and embryology. Organic form is its visible expression and morphology, which Darwin called the soul of biology, may claim a fundamental place in the hierarchy of the sciences.

Two facts about organic development are particularly important: first, it moves toward a precise end, the completed structure or the mature organism. This is familiar to students of embryology and to all who have studied any aspect of development, such as the growth and unfolding of a flower from a tiny primordium, or the orderly metamorphosis of an insect.

Second, if this normal development is blocked, the organism tends to restore it by processes of self-regulation. Regeneration is a familiar phenomenon. A single isolated blastomere may produce a whole individual. So may single cells from various parts of a plant. A sponge, completely disorganized into a mass of separate cells, will reorganize itself again. It is as though the whole organism, in a sense, was present in each cell, as it is in the egg.

Driesch here called attention to what he termed *equifinality*, the fact that the same developmental end may be reached by various routes and that the constant end rather than the various steps by which it may be attained is the unifying factor. Development seems to be essentially teleological and organism a teleological concept. This implies no "final" causation but simply self-regulation to a norm or end. As the result of natural selection most developmental ends are favorable for survival, but there seems to be no inherent tendency toward favorable ones; and many, especially those newly produced by mutation, are deleterious and would disappear under natural conditions.

The self-regulation evident in developmental processes is paralleled by the regulatory character of most physiological ones, as evident in the countless cases of homeostasis.

It is difficult to make a sharp separation between these more strictly biological processes of embryology and physiology and those psychological ones called behavior. All three are manifestations of the regulatory action of protoplasm: embryology, in the orderly construction and repair of the bodily organism, moving toward a specific norm; physiology, the control of processes taking place within the organism in conformity to a functional norm; and behavior, the regulatory activities of the organism as a whole. Instincts, the simplest sort of behavioral controls, are directed toward specific goals, which change as conditions change. They regulate behavior in conformity to norms set up in the nervous system. We may regard such norms as primitive purposes, the simplest of psychical phenomena. That even these lowest levels of behavior involve what may be logically called purposiveness is well argued by Agar (1). Says he, "The chief objective indication of purposiveness in the behavior of living organisms is the familiar fact that the sequence of acts by which the goal is attained is not always the same. On different occasions, the organism reaches the same end by different routes. It must fit the details of its action to the special situation. The completed nest, the spider's web, the act of mating, is attained by a train of acts different in detail on every occasion." It is the end, the purpose, which is important. This remains constant, but it is not reached by any single, linear path.

It is evident that in all animals above the simplest ones this self-regulatory character is canalized in the highly differentiated nervous system. This makes possible a far more complex behavioral control and thus a far more specialized behavior than where this control is centered in cells which have many other functions. The study of behavior has therefore become chiefly a study of the activities of the nervous system. We should remember, however, that this control is a specialized case of a generalized quality of all living stuff which directs the growth, functioning, and behavior of the organism in conformity to norms within it.

If a behavioral norm, set up in the nervous system, is a primitive purpose and thus a psychical phenomenon, this idea has important implications, for it suggests how a mental act may be related to a bodily one. Mind may thus be regarded as the control of behavior in conformity to norms or purposes set up in the organism. All ideas at first were purposes and from these simple organic regulations have come all other phenomena of mental life. Here is a biological basis for the evolution of mind. As the form and structure of the adult in some way is immanent in the egg from which it will grow as a pattern, so to speak, toward which development is regulated, so a purpose, to which behavior will be regulated, may be said to be immanent in the cells of the brain. A conscious purpose is the subjective *experience* of this regulation, but primitive purposes are presumably unconscious.

If mental processes are primarily regulations, this introduces an element in the nervous control of behavior that is sometimes overlooked. Behavior is more than a specific response to a specific stimulus, a reflex act. I hope I am not overelaborating the obvious in saying that the response an organism makes is not direct but depends on the state of the organism. The response will be such that it will tend to reach or maintain a norm or purpose set up in the brain, the integrating organ. Behavior is normative. Between stimulus and response is the organism itself, the state of which has much to do with what the response will be.

In emphasizing the basic biological character of nervous activity and its essentially self-regulatory quality, it is obvious that the final problem is to find how this regulation is brought about and what are its physical correlates. What in the fertilized egg "represents" the adult organism which will be produced, and what in a brain cell "represents" a purpose yet to be realized in behavior? Presumably there is involved in both cases a pattern of particles and processes in its protoplasm, but what this is and how it is maintained are quite unknown. Clues may perhaps be obtained through a study of electronic calculators and their feedback mechanisms. Information theory and its systems of coding may suggest something. Pauli's exclusion principle may represent the simplest sort of organization. Bioelectric fields, if they exist, and if we could find out how they operate, might provide what we seek. Even the principle of Le Chatelier, that a system under stress tends to return to its original state when the stress is removed, might prove important. Probably the self-duplicating and reproductive powers of living things are related to their capacity for organization and regulation.

If the ideas here discussed, which have been proposed by a number of biologists, are correct, it is clear that the nervous control of behavior is the same *sort* of phenomenon that is manifest in the control of development and of physiological activity. The control of behavior is simply general protoplasmic control raised to its highest level. In studying its evolution, this should be remembered.

This problem involves the nature of life itself. In seeking its solution perhaps the biologist, in his study of morphogenesis and in other ways, may make a contribution to our knowledge of psychological processes. He may not have much to offer at present but in the end, since what is here involved is life at every level, he should be able to join his colleagues in other sciences in contributing toward the solution of a problem that is not only a basic biological and psychological one but has important philosophical implications as well.

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Current Evidence Concerning Chemical Inducers*

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In 1924 Spemann and Mangold (46) transplanted a piece of tissue from the dorsal lip region of the blastopore of an unpigmented amphibian gastrula, *Triton cristatus,* into the ventral ectoderm of a pigmented form, *Triton taeniatus.* Owing to the graft's potentiality to invaginate and the formative movements of the host, it soon disappeared more or less completely into the interior. As a harmoniously coordinated unit the implant and the overlying ectoderm developed into a whole, secondary embryo. By virtue of the color difference between the host and the implant, their contribution to the secondary embryo could easily be traced. Cross sections revealed that the ventral ectoderm which normally develops into epithelium of the skin, was induced to form most of the neural tube and a small part of the somites and notochord, and the implant self-differentiated mostly into somites and notochord, as well as a tiny strip of the neural cord. This showed that the implant of dorsal lip tissue served not only as an inducing stimulus, but also contributed materially to the substance of the extra embryo. Because of this special capacity, Spemann designated the tissue that occupies the region of the dorsal lip as "the organizer." It was soon found that embryonic, adult, and even dead tissues of various kinds were capable of performing some functions of Spe-

* Part of the experimental results was presented also in Scotland at the St. Andrews meetings of the 9th International Congress for Cell Biology, August 28–September 3, 1957.

mann's "organizer" (27). All these tissues are now generally referred to as inductors.

As the study of embryonic induction progressed embryologists and biochemists turned their attention to the chemical nature of the inductor tissue. It was discovered that inductive action could not be abolished by either alcohol, cold or heat treatment (4, 28). Fischer and co-workers extracted amphibian embryos with ether, acetone, or alcohol and found both extracts and sediments to be inductive (21, 22). Activity of the extract was traced to fatty acids, and of the sediments to nucleoproteins. For instance, desoxyribonucleic acids from thymus, pancreas, and even muscle adenylic acid were active. Independently, at the same time, the Cambridge group (58) was able to trace the activity to the unsaponifiable fraction of the ether extract from *Triton* embryos and calf liver. This, together with the findings that estrogen and carcinogenic hydrocarbons were inductive, led this group to believe that the inductive substances were steroids (40). Strong support for this claim was found when it was demonstrated that a very dilute solution of 1, 2, 5, 6-dibenzenthracene-endo-α,β succinate was capable of inducing neuralization of the presumptive gastrula ectoderm (44).

About this same time there were many diversified claims being made regarding the chemical nature of the inducing agents. Barth found that neuralization could occur without an inductor (3). Prompted by this discovery, Holtfreter conducted a series of investigations (29–31) in which he was able to show that Barth's inductions were actually due to an indirect effect. The pH (8.2 to 8.4) of the culturing medium was found to be a little too high for the ectodermal explant of *Amblystoma punctatum,* with the result that some cell injury and death occurred. The products released into the culture medium by such cytolyzed cells, in turn, induced adjacent living cells to undergo neuralization. This discovery has helped to explain some of the diverse results reported in the late thirties. Many substances described as having an inductive capacity in earlier studies probably have no relation to the inductor substances responsible for neural formation in normal development, and are misleading in the attempt to identify specific inducing agents.

In addition to the general "organizer," regional specificity of induction was first shown by the presence of head and tail "organizers" (see ref. 45), and then by many examples of secondary or tertiary inductions, as well as by homeogenetic induction (39). The discovery that different adult tissues could induce the presumptive ectoderm to develop into different structures was a great stride toward understanding the complexity of the induction problem. According to Toivonen (50, 53), who implanted guinea pig tissue into the blastocoel of *Triton* gastrula, kidney regularly induced a tail-like structure (spinocaudal), whereas liver induced a head-like structure (archencephalic), and bone marrow induced mesenchyme and pronephros (mesodermal). In order to avoid regional host effects, Chuang (16, 17) explanted mouse kidney and newt liver into a folded strip of ectoderm (referred to later as the sandwich technique) and found that the former was an archencephalic inductor whereas the latter could induce tail as well as head structures. The differences in the inductive activity of homologous organs among guinea pig, mouse, and newt are not altogether clear and are difficult to interpret, especially in biochemical terms. However, these experiments did demonstrate the presence of qualitatively different inducing agents. Analyses showed that the archencephalic agent was dialyzable, thermostable, and ether soluble, whereas the spinocaudal agent was thermolabile, and not extractable in ether (51, 52, 54). Further studies failed to give a clear-cut chemical separation of these two agents (36).

Brachet (5–7) was the first to demonstrate the abundance of RNA-rich cytoplasmic granules (microsomes) in the upper blastoporal lip. During gastrulation, these granules of the invaginated chordamesoderm decreased while the amount increased in the overlying nerve plate. This suggested that a transfer of RNA-containing particles from the inductor to the reacting ectoderm might have occurred, thereby resulting in the determination of the nerve plate. To test his contention that these RNA-containing particles were responsible for induction by both normal and abnormal inductors, he isolated RNA-rich cytoplasmic granules by differential centrifugation of homogenized embryonic and adult tissues (8). These preparations, as well as tobacco mosaic virus, were found to be inductive. The probability that the RNA was the active agent was strengthened by the fact that treatment of "organizer," microsomes, adult organs, or tobacco mosaic virus with ribonuclease resulted in a conspicuous decrease or complete loss in their inductive capacity (9). Moreover, there was a direct correlation between the RNA content of the implant and the percentage of the inductions obtained (10, 11).

In view of the great significance of nucleic acids in modern biological concepts, Brachet's hypothesis of the RNA nature of inducing agents has attracted particular attention, with some investigators favoring and others rejecting this view (32). Criticism has been leveled for three reasons. First, there was no quantitative relation between the RNA content of the granular fraction isolated from guinea pig liver and its capacity for induction (36). Secondly, air-dried RNA isolated from guinea pig kidney was not inductive (61). Thirdly and finally, treatment with ribonuclease of the adult organs or their RNA-containing granular fraction and tobacco mosaic virus failed to reduce inductivity both in a quantitative and in a qualitative sense (18, 25, 36, 56). As a matter of fact, there was an increase in inducing power of the various tissues after RNAase treatment (19). We will return to this later on. However, the last objection is of questionable significance when one also takes into account the inefficacy of RNAase to remove the RNA content in tobacco mosaic virus, or in the isolated materials (38, 62). At this point, Brachet seemed to have made a concession and tentatively accepted the evidence as an indication that the protein fractions from the tissues and virus were of primary significance in induction (14, 36, 37, 59). Later, in 1956, Tiedemann and Tiedemann (48) published evidence showing high inductive activity in the phenol-extracted proteins from 9-day chick embryos and a low inducing ability of RNA from the same source (49). According to Brachet (12, 13), however, these substances were abnormal induc-