Dynamism in Neuroscience

Francis Otto Schmitt

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A prominent molecular biologist, Professor Francis Otto Schmitt founded (in 1962) the Neurosciences Research Program at the Massachusetts Institute of Technology, an interuniversity, international research organization with experts in many fields studying physiochemical, biophysical, and psychological aspects of mental processes such as memory and learning. He has published extensively and is coeditor of *Neurosciences Research Symposium Summaries* and *The Neurosciences: A Study Program.* Professor Schmitt has been elected to the American Academy of Arts and Sciences, to the National Academy of Sciences, to the American Philosophical Society, and to the Swedish Royal Academy of Sciences.

The brain and its properties are perhaps best characterized as *dynamic,* but only in recent years have we been shown how ceaselessly active the brain really is. From their diagnostic and clinical studies, psychologists and psychiatrists have long been aware of this ongoing dynamic aspect of behavior and its conscious and unconscious substrates, but the biophysical and biochemical dynamism of brain cells and of the brain as a whole is an exciting discovery in neuroscience. Stimulus-response, reflexological research strategies and concepts—i.e., that the brain reacts only when acted on—missed essential aspects of brain dynamics. New approaches in neuroscience, based on principles of dynamic integration of brain activity at all levels—from molecules and cells, through brain circuits and behavior —have given us invaluable new insights into brain and behavior.

For this essay, I have chosen a few illustrations, at each level of organization, to depict some of the dynamic aspects of the functions concerned. Quite possibly, discoveries to be made in the near future make even the present description seem almost static.

Neuroscience may be thought of as the most central of all the sciences in its interest to man. This is because, if he were able to understand learning, memory, thinking, and emotion, to mention but a few mental processes, we should be in a position not only to improve our methods of alleviating functional and organic ills, but even to revolutionize science itself and thereby to improve man's interaction with his fellowman and with his environment. Such an advance may be able to help man gain insight into the biological substrates of those aspects of his own nature that are now comprehended only in terms of psychological data and concepts or in the metaphors of art, philosophy, and religion. [114]

The fearsome complexity of the brain with its billions of cells and connections has been the chief deterrent keeping gifted scientists in other disciplines from entering the field, but the complexity is beginning to show promise of unraveling, as more and more investigators from other fields are attracted to neuroscience.

A major difficulty in unifying the neurosciences and attempting novel theoretical approaches is that of meaningful communication between neuroscientists working at different levels of organization; each level has its own sophisticated vocabulary and conceptual framework. If it were possible for individual scientists to comprehend the major theories and tenets of *all* levels from molecular to behavioral, advance might well be spectacular. This is patently im-

possible, because it takes a lifetime to master portions of neuroscience even at the same organizational level.

To attempt a substantial step in solving this problem, a new experiment in interpersonal communication was undertaken by the writer in 1962. A group of Associates, who are eminent scientists from all disciplines relevant to neuroscience and with a high commitment to making original contributions in this field, were brought together, under the sponsorship of the Massachusetts Institute of Technology, to form the Neurosciences Research Program (NRP).[1] NRP surveys, evaluates, and innovates in the various phases of neuroscience; holds meetings, such as "Work Sessions," of the most gifted experts in each particular subject; and publishes a series of monographs[2] (and anthologies)[3] conveying the upshot of Work Sessions and also large volumes[4] resulting from triennial Intensive Study Programs held at Boulder, Colorado. In addition to these activities, and believing with Michael Polanyi that people know more than they can say, the NRP manages to achieve a kind of intellectual allosterism,[5] resulting from the group [115] dynamics engendered in its various meetings. The psychodynamics of this new form of group creativity, in itself, would constitute an interesting study.

The task of NRP at its founding in 1962 was to identify and define the several sciences relevant to brain and behavior and to help nucleate a coherent neuroscience field by building bridges between conceptually and methodologically disparate disciplines and subdisciplines. NRP planning and evolution was timely, occurring only a few years before the worldwide trend toward developing neuroscience gained momentum. Indications of the rapid expansion of the field are the recent appearance of a number of journals and book series with the terms "brain" and "neuroscience" in their titles and the formation of new multidisciplinary societies concerned with neuroscience, in addition to the International Brain Research Organization (IBRO), organized a decade ago as a participating member of UNESCO. New professional associations have been formed more recently, e.g., the Brain Research Association of the United Kingdom, the Society for Neuroscience of the United States, the European Brain and Behaviour Organization, and specialty groups like the International Neurochemical Society and the American Society for Neurochemistry. NRP, while continuing its major ongoing programs, seeks to provide theoretical formulations essential for the ordering of new data, methods, and concepts in a form catalytic for progress.

Illustrations of the dynamic processes of the brain described herein were taken, in the main, from meetings and publications of NRP during the past few years.

Molecular Neurobiology

Half a century ago biologists would not have been willing to attribute the enormously complex processes of heredity, development, and biosynthesis to a particular category of macromolecules. Nevertheless, through discovery of the way that DNA, RNA, and protein interact,

[1] The Neurosciences Research Program is supported in part by National Institutes of Health Grant No. GM10211, National Aeronautics and Space Administration Grant No. Nsg 462, Office of Naval Research, The Rogosin Foundation, and Neurosciences Research Foundation.

[2] *Neurosciences Research Program Bulletin.*

[3] *Neurosciences Research Symposium Summaries* (Cambridge: M.I.T. Press), vols. 1 (1966)-4(1970).

[4] *The Neurosciences: A Study Program,* 1967, G. C. Quarton, T. Melnechuk, and F. O. Schmitt (eds.), 962 pp.; *The Neurosciences: Second Study Program,* 1970, F. O. Schmitt (ed.), 1,068 pp. (New York: Rockefeller University Press.)

[5] Enzymes, in addition to their active site which binds and acts on the substrate, have another site which, by reaction with appropriate metabolite, can be caused to stimulate the enzyme to greater—or lesser—activity (J. Monod, J.-P. Changeux, and F. Jacob, "Allosteric proteins and cellular control systems," *Journal of Molecular Biology,* 6 [1963], 306-329). The model (J. Monod, J. Wyman, and J.-P. Changeux, "On the nature of allosteric transitions: a plausible model," *Journal of Molecular Biology,* 12 (1965), 88-118) views subunits of enzyme proteins as "molecular amplifiers" of highly specific, organized, metabolic interactions. Participants, like protein subunits, can be "turned on" by discussional "metabolites" and their discussional interactions amplified.

science has illuminated at least the basic processes in genetic dynamics.

Perhaps in the next half-century (or half-decade) historians may comment similarly on the reluctance of scientists of our day to attribute to macromolecular parameters—not necessarily coding as such—learning, memory, awareness, and consciousness emerging from human central-nervous-system states. Molecular coding, as the basic principle of genetics, may provide a conceptual model for related possibilities regarding the role of molecular processes in brain functions. For example, it is possible that new dimensions of understanding of the nervous system and behavior will [116] arise from the discovery of the functional significance of specific aggregations of macromolecules of various types in, or on, the neural membranes. The neuron may indeed wear important computational equipment on its skin!

The examples of molecular neurobiology to be cited exemplify the dynamic nature of brain processes; these citations, it is hoped, predict directions of future progress.

Molecular biology is a term that is frequently used synonymously with molecular genetics. The former is of course the broader, because it includes molecular genetics as well as molecular neurobiology, which deals with fundamental brain mechanisms at the molecular level whether or not they have to do with genetics or biosynthesis, and which is beginning to loom large on the horizon of neuroscience.

Enzymes and Brain Function

Some enzymes can act upon substrate more than a hundred thousand times per second; to achieve such high rates requires still faster intramolecular gyrations. An "induced fit" of enzyme upon substrate is accomplished by a portion of the polypeptide chain of the molecular whipping around, by fast configurational change, until a close fit is made. In the case of the proteolytic enzyme carboxypeptidase, for example, one particular group moves nearly half the diameter of the protein molecule, about 12 Angstrom units, and does so exceedingly rapidly. Recently the discovery by Storm and Koshland[6] of a second dynamic property further illuminates the process by which the reacting molecules align in precisely the best position for reacting, thus accelerating the reaction by some ten thousandfold and achieving greater molecular cooperativity: they utilize electron orbitals, i.e., the enzyme molecules "steer" their orbitals along a path that takes advantage of the strong directional preference. Storm and Koshland suggest that this "orbital steering" factor may bridge the gap that existed in our knowledge of enzyme catalysis.

It has long been known that, to accomplish a cyclic process involving several individual enzyme-catalyzed steps (e.g., the Krebs cycle of oxidative phosphorylation and the electron transfer chain of cytochromes on mitochondrial membranes), the enzymes are clustered in a precise three-dimensional array permitting allosteric interactions made possible through [117] supermolecular, quaternary bonding which allows control of the reactions by their products and by other factors in the environment. Aggregation of energy-transducing enzymes with additional molecular machines, such as transferases, on the neuronal membrane may well prove vital to brain cell function.

Like cells of other tissues, brain cells command a large repertoire of enzymes that can be induced, i.e., the gene necessary for making a particular enzyme can be "turned on" by various agents acting as derepressors. What makes this induction so important for neuroscience is that such enzyme synthesis can be triggered bioelectrically or by appropriate synaptic stimulation or action of transmitter. Axelrod, et al.[7] demonstrated that excitation of the neuronal input to an autonomically innervated tissue, e.g., the adrenal gland, accelerates synthesis of enzymes producing the transmitter noradrenaline. Similar processes have been demonstrated in other syn-

[6] D. R. Storm and D. E. Koshland, Jr., "A source for the special catalytic power of enzymes: orbital steering," *Proceedings of the National Academy of Sciences, U.S.,* 66(1970), 445-452.

[7] J. Axelrod, R. A. Mueller, J. P. Henry, and P. M. Stephens, "Changes in enzymes involved in the biosynthesis and metabolism of noradrenaline and adrenaline after psychosocial stimulation," *Nature,* 225 (1970), 1059-1060.

aptic situations.

McIlwain[8] (1970) points out that this ability to induce, by bioelectric and metabolic effectors of adaptation, a multiplicity of *enzymes* may be as significant for brain processes (such as ontogenetic specification, adaptation, and plasticity) as is the ability of the central nervous system to form a multiplicity of *synaptic connections* commonly considered the basis of physiological plasticity.

Brain enzymes are needed not only for the tasks common to tissue cells generally, but also for the special tasks related to high speed excitatory and inhibitory processes, and especially for the storage, delocalization, and fast retrieval of experiential information—a kind of temporal microminiaturization of the evolutionary process for which the enzymes were equally vital.

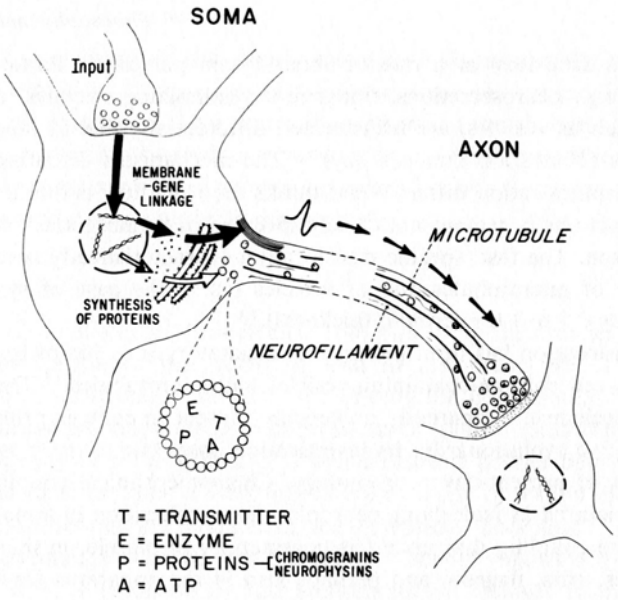

FIGURE 1 Linkage of gene expression with excitable membranes and with translocation of vesicle-bound transmitters and proteins.

Coupling Between Excitable Neuronal Membranes and Biosynthesis

The experiments of Axelrod, et al.[9] well exemplify coupling between excitable postsynaptic membranes and the biosynthetic centers of the cell. Incidentally, elevation of noradrenaline as Axelrod found for direct nerve stimulation was also produced indirectly by excessive crowding in a colony [118] of mice. One wonders to what extent similar factors in the human environment, as in the overpopulous teeming ghettos, may also lead to elevated production of noradrenaline, known to incite various kinds of affective and emotional behavior.

Another striking case of induction by presynaptic stimulation of postsynaptic synthesis, this time of RNA, was shown by Peterson and Kernell[10] and Kernell and Peterson[11] in isolated *Aplysia* abdominal ganglia. If RNA synthesized under these conditions generates specific proteins, a "permanent" response might result from synaptic excitation. If dicarboxylic acid transmitters (glutamate), which have inhibitory action on the cortex, are added to slices of cortex, a stimulation of protein synthesis is observed.[12]

FIGURE 1 portrays another coupling possibility; materials synthesized in the neuronal cell center, when deposited in or upon the membrane of the initial segment (axon hillock), may modulate the excitability of this membrane zone, hence the triggering of propagated action waves in the axon.

Highly suggestive is the situation in certain bacteria in which DNA and enzymes for protein synthesis and oxidative phos-

[8] H. McIlwain, "Metabolic adaptation in the brain," *Nature,* 226 (1970), 803-806.
[9] Axelrod, *op. cit.*

[10] R. P. Peterson and D. Kernell, "Effects of nerve stimulation on the metabolism of ribonucleic acid in a molluscan giant neurone," *Journal of Neurochemistry,* 17 (1970), 1075-1085.
[11] D. Kernell and R. P. Peterson, "The effect of spike activity versus synaptic activation on the metabolism of ribonucleic acid in a molluscan giant neurone," *Journal of Neurochemistry,* 17(1970), 1087-1094.
[12] F. Orrego and F. Lipmann, "Protein synthesis in brain slices," *Journal of Biological Chemistry,* 242 (1967), 665-671.

phorylation are all associated with the cell membrane. Because of this association, a single colicine particle, on impact with the bacterial membrane, can interact directly with the vital coding and synthesizing equipment and kill the cell.[13] One wonders whether in certain circumstances, DNA (and/or RNA) could be associated with neuronal membranes that are sensitive to electrical or transmitter stimulation. If this were the case, the coupling between stimulus and synthesis would be direct and require no diffusion or translocation of messengers or metabolites between membrane and cell center. Only recently has DNA been shown to exist in mitochondria and certain other "self-reproducing" organelles.[14] The DNA, present in low concentrations, is demonstrated chemically after extraction with phenol. This DNA [119] might not have been detected in mitochondria and localized by electron microscopic and histochemical means. The fact that DNA has not thus far been demonstrated electron microscopically or histochemically in excitable neuronal membranes is not definitive proof of its absence there. Quite possibly, after techniques are developed for fractionation and isolation of neuronal membranes, application of chemical tests for nucleic acids (and perhaps other metabolic systems) may prove them to be associated with or bonded to neuronal membranes. Such membrane-borne ensembles of nucleic acids and enzymes could conceivably provide a unique mechanism by which bioelectric factors might mediate gene expression *directly,* rather than through the transmitters, receptors, adenyl cyclase, prostaglandins, etc., as intermediates. If no such mechanism exists, we shall have to seek slower processes by which substances may be transported between the active neuronal membrane and the biosynthetic center—perhaps mediated by microtubules appropriately arrayed in initial segments or in dendrites.

Neuroplasmic Dynamics

It is now generally believed that neuroplasm is constantly synthesized in the cell body and moves as a gel down the axon (and probably also [120] along the dendrites) at a rate of about 1 mm per day.[15] Particular substances, e.g., neurosecretions, transmitter-synthesizing enzymes, and organelles such as vesicles, are translocated differentially and at much higher velocities (100—2000 mm per day).[16] The mechanisms actuating the two types of translocation differ. Weiss thinks the slow flow is due to peristaltic contractions in regions not closely specified in membranous investments of the axon. The fast, specific translocation characteristically occurs in the presence of microtubules and of vesicles (as in the case of sympathetic fibers only 0.5 to 1.0 micron in thickness).[17]

Translocation has been pictured as a saltatory, i.e., jumpwise, interaction between enzyme-containing vesicles and microtubules.[18] The translocating mechanism, apparently universally present in cells, is primitive and conservative evolutionarily. Its investigation poses one of the most exciting problems of present-day neurobiology. Chemomechanical coupling of energy is pictured as underlying neuroplasmic translocation in a manner similar to the coupling that underlies contractility in muscle, in microtubular structures, cilia, flagella, and perhaps also in the apparatus for the injection of nucleic acid into micro-organisms by viruses. In some instances, as in the unmyelinated neurons of lamprey, Smith,

[13] M. Nomura, "Mechanism of action of colicines," *Proceedings of the National Academy of Sciences, U.S.,* 52 (1964), 1514-1521.

[14] See J. L. Jinks, *Extrachromosomal Inheritance* (Englewood Cliffs, N.J.: Prentice-Hall, 1964).

[15] P. A. Weiss, "Neuronal dynamics and neuroplasmic ('axonal') flow," in *Symposium of the International Society of Cell Biology,* vol. 8 (1969), S. H. Barondes (ed.), pp. 3-34 (New York: Academic Press).

[16] S. H. Barondes, *Axoplasmic Transport,* in: *Neurosciences Research Symposium Summaries,* vol. 3 (1969), F. O. Schmitt, et al. (eds.), pp. 191-299 (Cambridge: M.I.T. Press).

[17] A. Dahlstrom, "The transport of noradrenaline between two simultaneously performed ligations of the sciatic nerves of rat and cat," *Acta Physiologica Scandinavica,* 69(1967), 158-166.

[18] F. O. Schmitt, "Fibrous proteins—neuronal organelles," *Proceedings of the National Academy of Sciences, U.S.,* 60 (1968), 1092-1101; F. O. Schmitt, "The molecular biology of neuronal fibrous proteins," in *Neurosciences Research Symposium Summaries,* vol. 3 (1969), F. O. Schmitt, et al. (eds.), pp. 307-332 (Cambridge: M.I.T. Press).

et al.[19] have observed vesicles closely applied upon and between microtubules in the synaptic region, supporting the view that such association may be functionally meaningful.

Another exciting line of investigation that may benefit from methods developed to demonstrate neuroplasmic flow and fast translocation is that dealing with the trophic relationship between neurons and the tissue they innervate, as, for example, in the neural regulation of gene expression in [121] muscle,[20] i.e., materials still poorly characterized presumably pass from the axon across the synapse into postsynaptic tissue and are required metabolically for that tissue. This is strikingly shown in the changes that ensue when fast nerves are sutured to slow muscles and vice versa. Recently, hypersensitivity to transmitter following denervation was demonstrated in relation to trophic processes by Fambrough.[21]

Membrane Dynamics

Because of the crucial bioelectric role played by membranes, the dynamic, fast processes that occur on and in membrane are of primary concern in neuroscience. Consideration of only the lipid-protein matrix of the membrane is likely to lead to impressions of static structural properties of a device meant to be primarily a semi-permeable barrier between cytoplasm and exterior; such a view misses the dynamic operation of the molecular machines that are mounted on the membrane "floor space."

It is commonly believed that the action potential's influx of Na + and efflux of K + is mediated by fast conformational changes in membrane macromolecules; fast and sensitive physical methods, such as polarization optics, light scattering, and fluorescent probes, are being applied in an effort to characterize these configurational changes.

Model systems of lipid biomolecular layers containing specific ion carriers suggest a solution to the problem that has eluded physiologists for generations, i.e., how the cell distinguishes ions so similar physically and chemically as Na+ and K + .[22] The ion carrier is pictured as an ion-specific peptide-cage molecule that engulfs the cation, desolvates it as it enters the opened cage, and closes by fast conformational change; then, facilitated by outwardly directed lipophilic side-chains, the ion-bearing cage-peptide traverses the membrane under the potential gradient and discharges the resolvated ion on the cytoplasmic side of the membrane.[23] [122] Isolation and characterization of the actual membrane carriers are difficult because of their low concentration in the neuronal membrane.

Dynamic Interactions at Synoptic Junctions

Arising from application of new electron microscope techniques, discoveries about the microstructure of the synapse[24] indicate that conventional notions are greatly oversimplified. Proteinaceous material constitutes a kind of "synaptic apparatus" that extends from presynaptic to postsynaptic regions across the cleft; this appara-

[19] D. S. Smith, U. Jarlfors, and R. Beranek, "The organization of synaptic axoplasm in the lamprey *(Petromyton marinus)* central nervous system," *Journal of Cell Biology,* 46 (1970), 199-219.

[20] L. Guth, *"Trophic" Effects of Vertebrate Neurons,* in *Neurosciences Research Symposium Summaries,* vol. 4 (1970), F. O. Schmitt, et al. (eds.), pp. 327-396 (Cambridge: M.I.T. Press).

[21] D. M. Fambrough, "Acetylcholine sensitivity of muscle fiber membranes: mechanism of regulation by motoneurons," *Science,* 168 (1970), 372-373.

[22] D. C. Tosteson (ed.), *The Molecular Basis of Membrane Function* (1969), Symposium of the Society of General Physiologists, Durham, N.C., August 20-23, 1968 (Englewood Cliffs, N.J.: Prentice-Hall); M. Eigen and L. C. M. DeMaeyer, *Carriers and Specificity in Membranes, Neurosciences Research Program Bulletin,* 9:3 (inpress, 1971).

[23] M. Eigen and R. Winkler, "Alkaliion carriers: dynamics and selectivity," in *The Neurosciences: Second Study Program,* F. O. Schmitt (ed.) (New York: Rockefeller University Press, 1970), pp. 685-696.

[24] F. E. Bloom and G. A. Aghajanian, "Fine structural and cytochemical analysis of the staining of synaptic junctions with phosphotungstic acid," *Journal of Ultrastructure Research,* 22 (1968), 361-375; K. Akert and K. Pfenninger, "Synaptic fine structure and neural dynamics," in *Symposium of International Society of Cell Biology,* vol. 8 (1969), S. H. Barondes, ed., pp. 245-260 (New York: Academic Press); F. E. Bloom, "Correlating structure and function of synaptic ultrastructure," in *The Neurosciences: Second Study Program,* F. O. Schmitt, ed. (New York: Rockefeller University Press, 1970), pp. 729-746.

tus develops when the synapse becomes physiologically operable and may prove an important part of dynamic synaptic processes.

The forming of ontogenetically and physiologically appropriate synaptic connections during development has been explained on the basis of molecular recognition by acidic glycoproteins through terminal groups of their carbohydrate moieties.[25] The same groups, by changing synaptic connectivity, may achieve the plasticity required for the consolidation of experiential information as learning. The transferase enzymes, which bring about changes in terminal glycosyl or fucosyl groups, act with ample rapidity, but it has been questioned whether such enzymes are present on the extracellular surfaces of the presynaptic and postsynaptic members.

The interesting possibility has recently been examined that macromolecules, which can be much richer informationwise than transmitters, may modulate transmission and synaptic function.[26] If this were the case, some type of plasticity might result. Actually, an acidic protein, *chromogranin A,* is present in the vesicles of adrenergic neurons along with noradrenaline, enzymes, and ATP; this protein is thought to be released from vesicles at varicosities and endings of sympathetic neurons. The function of the protein is unknown. [123]

Another exciting and dynamic biochemical process occurring at the synapse is the liberation of a substance called cyclic AMP (adenosine 3', 5'-phosphate), generated by action on ATP of the enzyme adenyl cyclase. This enzyme, located in the membrane, is thought to be in close interaction with receptor molecules, the crucial transducing molecules specifically binding biodynamic substances, such as hormones and transmitters, which, in extremely low concentrations (10^{-6} to 10^{-12} M), produce the appropriate response in the tissue. As the hormone (or transmitter) may be called the first messenger, the cyclic AMP is the second messenger,[27] triggering a number of vital intracellular reactions catalyzed chiefly by kinase enzymes. The mode of action is diagrammatically illustrated in FIGURE 2.

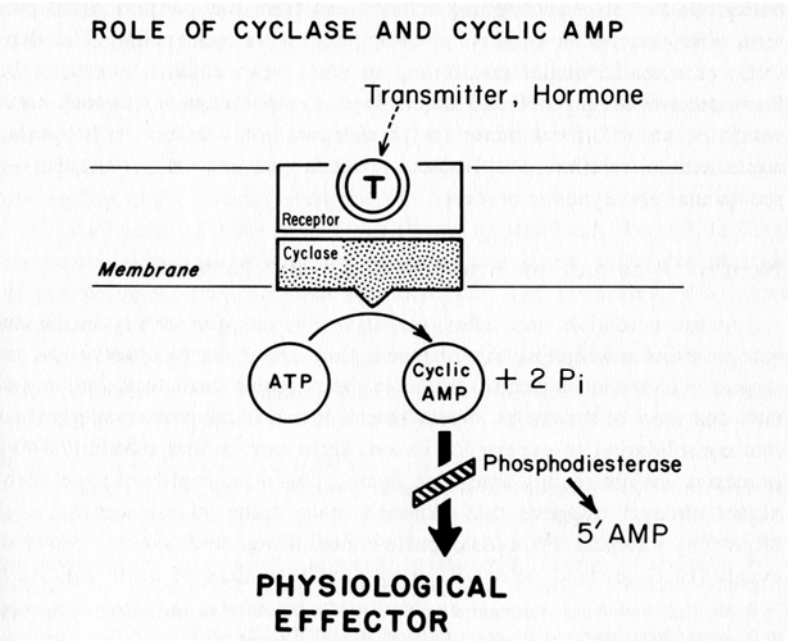

FIGURE 2 Diagrammatic representation of the role of membrane-bound adenyl cyclase in the postulated linkage between transmitter and intracellular effector (cyclic AMP).

Brain cortex contains the highest concentration of adenyl cyclase of [125] any tissue.[28] Synaptic

[25] S. Bogoch, *The Biochemistry of Memory,* London and New York: Oxford University Press (1968); S. H. Barondes, "Two sites of synthesis of macromolecules in neurons," in *Symposium of International Society of Cell Biology,* vol. 8 (1969), S. H. Barondes (ed.) (New York: Academic Press), pp. 351-364.

[26] F. E. Bloom, L. L. Iversen, and F. O. Schmitt, *Macromolecules in Synaptic Function, Neurosciences Research Program Bulletin,* 8:4 (1970), 325-425.

[27] E. W. Sutherland and T. W. Rail, "The relation of adenosine-3',5'-phosphate and phosphorylase to the actions of catecholamines and other hormones," *Pharmacological Reviews,* 12 (1960), 265-299.

[28] T. W. Rail and A. G. Gilman, *The Role of Cyclic AMP in the Nervous System,* in *Neurosciences Research Program Bulletin,* 8:3 (1970), 221-323.

transmission in the cerebellum is believed to activate adenyl cyclase, a finding that links transmitter action with the cyclic AMP system.[29] The concentration of cyclic AMP in the brain can be increased fortyfold by electrical or neurohumoral stimulation.[30] The adenyl cyclase-cyclic AMP system provides a dynamic dimension in neurobiology, discovered only a few years ago, but doubtless destined to prove even more significant as more information is obtained.

More than one hundred thousand synaptic terminals impinge on the dendritic trees of some neurons. It is hard to picture these as simple stimulus-response systems, even on the assumption of simple electrotonic additivity of multiple excitatory and inhibitory inputs, but the system seems rather to imply a computation by the postsynaptic cell to determine, on the background of its own ongoing activity and from the complex input pattern, what moment-to-moment output response is appropriate. The dendritic or somatic spatial positioning of each input could conceivably be fairly precise and is genetically determined. Temporal spacing of each input would be an additional factor in the computation, together with optimal adjustment in relation to diffusional, electrotonic, and other variables—a spectacular and dynamic process.

Neural Dynamics in Brain Systems and Subsystems

Action potentials and reflex arcs have figured prominently in the development of neurophysiology, because they are easier to observe and interpret than is the bioelectric traffic in the reticular formation, limbic system, and most of the cortex. Nevertheless, it is becoming increasingly clear that consolidation of experience in long-term storage and plastic learning processes are not readily assessible from classical neurophysiological techniques. Adey[31] suggests that although many transient phenomena, e.g., electrophysiological responses, pulse-coded firing, and slower, wavelike events (EEG, evoked potential), may provide indices of brain cell state, [125] they probably reflect transactional rather than storage processes. However, "slow electrical phenomena"—dc shifts across bulk tissue as well as across neuronal and glial membranes—reflect subtle but important plastic changes in long-term states that occur during learning. Gavalas, et al.[32] found that very small electric fields across the head produce measurable behavioral effects at levels of energy or gradients below that needed to stimulate synapses. Slow-wave phenomena have dynamic qualities, although they may seem less impressive than the major fast-wave grist of neurophysiology. Technical developments such as the remote monitoring of localized fields in brain regions[33] may help realize the promising potentialities of this aspect of neuroscience.

Steady potential gradients[34] may importantly affect memory storage processes; surface-positive transcortical polarization can induce the formation of cellular short-term memory by influencing neuronal responses to normal and established synaptic inputs. Anodal current fires cells otherwise below threshold to auditory stimulation. Pairing polarization with stimulation produces effects outlasting the stimulus by 20 minutes. Cathodal polarization tends to prevent or inhibit storage of training experience

[29] G. R. Siggins, B. J. Hoffer, and F. E. Bloom, "Cyclic adenosine monophosphate: stimulation of melatonin and serotonin synthesis in cultured rat pineals," *Science,* 165 (1969), 1018-1020.

[30] S. Kakiuchi, T. W. Rail, and H. McIlwain, "The effect of electrical stimulation upon the accumulation of adenosine 3',5'-phosphate in isolated cerebral tissue," *Journal of Neurochemistry,* 16 (1969), 485-491.

[31] W. R. Adey, *Slow Electrical Phenomena in the Central Nervous System, Neurosciences Research Program Bulletin,* 7:2 (1969), 75-180.

[32] R. J. Gavalas, D. O. Walter, J. Hamer, and W. R. Adey, "Effect of low-level, low-frequency electric fields on EEG and behavior in *Macaca nemestrina," Brain Research,* 18(1970), 491 -501.

[33] O. H. Schmitt, personal communication.

[34] V. S. Rusinov, "An electrophysiological analysis of the connecting function in the cerebral cortex in the presence of a dominant area," Communications at the XIX International Physiological Congress, Montreal, 1953; F. Morrell, "Effect of anodal polarization on the firing pattern of single cortical cells," *Annals of the New York Academy of Sciences,* 92 (1961), 860-876; F. Morrell and P. Naitoh, "Effect of cortical polarization on a conditioned avoidance response," *Experimental Neurology,* 6(1962), 507-523.

during flow of the polarizing current.

The obverse of these results was shown by Rowland:[35] small dc shifts measured in various parts of the brain are a neurophysiological criterion of psychological reinforcement for food, sex, and rewarding or aversive stimulation of the hypothalamus.

Another experiment of Morrell[36] deserves inclusion in our showcase [126] of examples of dynamic brain processes underlying psychological processes. Poststimulus histograms of unit cell recordings from the cat cortex demonstrate that the pattern of the unit's response changes with "experience"; in visual cortical neurons the simultaneous presentation of visual and auditory or visual and somato-sensory stimuli result in a pronounced alteration of subsequent responses to the visual stimulus alone. More recent work[37] shows the effect to depend on a real reorganization of the temporal pattern of firing; the response is abolished by barbiturates and is probably polysynaptic. Morrell is inclined to ascribe the phenomena to short-axon (Golgi Type II) cells which synapse on apical dendrites, fire with short spikes, and produce a field. Here is a truly dynamic neurophysiological response related to storage; Morrell's identification of the short-axon cells, diffusely distributed in the brain, as those responsible for the mnemonic response will await confirmation by other methods and in other laboratories.

Another neurophysiological phenomenon that is highly informative concerning the dynamic way in which information is processed is that of the conversion of incident light-quanta in the retina to the characteristic output of action potentials in the optic nerve. Through the application of new intracellular dye injection and histofluorescence techniques, together with electron microscopic and neurophysiological investigations of many vertebrate species, the five major cell types in the retina have been characterized structurally and physiologically. What has emerged is that the information processing in the retina is accomplished without generation of action potentials (spikes), but rather with slow-wave potentials.[38] Because the retina is an externalized bit of central nervous tissue, these experiments support the possibility that the slow-wave type of information processing may be more important in the central nervous system than is commonly supposed. One of the five types of retinal cells, the amacrine cells, which lack axons, apparently participates importantly in neurophysiological processing (as in the olfactory bulb) and does so without spike generation.[39]

Another window through which to view dynamic brain processes is by [127] examination of the integration and coordination involved in the central control and mediation of skilled motor movement, i.e., how the sensory input is translated into appropriately timed and patterned efferent output underlying motor activity.

Behavioral Dynamism

Dynamism is the *Leitmotiv* of behavior. One is at a loss to choose some subjects as meriting mention above others: wakefulness, sleep, dreams, and the role of serotonin; the neural correlates of conditioning and learning; perception; drive and motivation; all these might well be chosen for discussion. Perhaps the problem of neural regulatory mechanisms and their relation

[35] V. Rowland, "Steady potential phenomena of cortex," in *The Neurosciences: A Study Program,* G. C. Quarton, et al. (eds.) (New York, Rockefeller University Press, 1967), pp. 482-495.

[36] F. Morrell, "Information storage in nerve cells," in *Information Storage and Neural Control,* W. S. Fields and W. Abbott (eds.) (Springfield, 111.: C. C Thomas, 1963), pp. 189-229; F. Morrell, "Electrical signs of sensory coding," in *The Neurosciences: A Study Program,* G. C. Quarton, et al. (eds.) (New York: Rockefeller University Press, 1967), pp. 452-469.

[37] Morrell, personal communication.

[38] E. F. MacNichol, Jr., and H. G. Wagner, *Advances in Retinal Physiology, Neurosciences Research Program Bulletin* (in preparation).

[39] W. Rail and G. M. Shepherd, "Theoretical reconstruction of field potentials and dendrodendritic synaptic interactions in olfactory bulb," *Journal of Neurophysiology,* 31 (1968), 884-915; W. Rail, "Dendritic neuron theory and dendrodendritic synapses in a simple cortical system," in *The Neurosciences: Second Study Program,* F. O. Schmitt (ed.) (New York: Rockefeller University Press, 1970), pp. 552-565.

to phenomena for which the concept of motivation becomes usefully relevant epitomizes the neural and behavioral dynamics as well as any other. As neural mechanisms involved in regulation of temperature, hunger, thirst, and sex are increasingly discovered, it becomes clear that there is a hierarchy of mechanisms ranging from simple reflex mechanisms (e.g., sweating and piloerection in relation to temperature) up to behavioral phenomena with motivational qualities (e.g., increased behavioral activity to maintain temperature).

Epilogue

Ceaseless dynamic activity is the hallmark of the brain at each level: whole brain, systems and subsystems; neurophysiological, metabolic, biochemical, and biophysical. It has been the chief purpose of this essay, by describing some of the known dynamic properties, to point the way to other, perhaps even more significant ones yet to be discovered.

Gone are the days when the role of the central nervous system during sleep could be characterized, as did Sherrington.[40] Visualizing activity in brain tracts as little stationary or traveling points of light streaming in serial trains in the neural nodes and networks at various speeds, Sherrington describes events during deep sleep and in arousal therefrom. Except for flashes of light due to the superintending of the beating of the heart and breathing, there is mostly darkness. The brain is released from the waking day and marshals the factors for its motor acts no more. Then, where hardly a light had twinkled or moved, the brain [128] becomes now a sparkling field of rhythmic flashing points with trains of travelling sparks hurrying hither and thither. The brain is waking and with it the mind is returning. ... Swiftly the headmass becomes an enchanted loom where millions of flashing shuttles weave a dissolving pattern, always a meaningful pattern though never an abiding one; a shifting harmony of subpatterns.

In the history of neurophysiological research, some of the most outstanding work has been concerned with descriptions of stimulus-response type of activity, physiologic, anatomic, and behavioral; it is difficult because of technical limitations to investigate the brain in a more systems-oriented procedure. However, such work, even if vastly expanded and refined experimentally, could in its sum represent only an impoverished description of the brain as it really functions. What dynamic processes occur in addition to synapse-initiated neuronal firing in closed nets in the cortex, that thin outer layer of the brain which contains some 70 percent of all the neurons in the brain and which presumably accounts for at least some of its "higher" functions? The concept of connectionalism should be broadened to include the possibility of distributive pathways (perhaps numbering in the hundreds or thousands for particular tracts). In addition, the role of volume effects leading to global, holistic processes, including steady, polarization potentials and fields, oscillations, gradients, and other phenomena should be critically assessed.

In considering how excitation occurs in the sequential firing of neurons in the brain, we may tend to lose sight of the small nuances of changes of impedance, field, ion distribution and gradients, specific interactions of information-rich macromolecules with small molecules and with ions, and of other bioelectric parameters. These nuances may seem small when measured in bulk phase, but in microscopic compartments such topochemical reactions may be triggered and determined by strong and highly directional and specific forces.

If it were possible to analyze the brain—or perhaps at first only simplified systems, e.g., the *Aplysia* ganglion[41]—by systems and network theoretical methods, as have proved powerful in electrical engineering, we might get a glimpse of the significance of these topochemical and topophysical processes which, together with action waves and synaptic events in legions of neurons in nets, make up the ongoing activity of the brain. Without doubt, flows and forces

[40] C. S. Sherrington, *Man on His Nature,* 2nd ed. (Garden City, N.Y.: Doubleday &Co., 1955), pp. 183-184.

[41] E. R. Kandel, "Nerve cells and behavior," *Scientific American,* 223 (1970), 57-70.

could in principle be dealt with according [129] to Kirchhoff s laws, as generalized in theorems such as that of Tellegen.[42] Unfortunately, we are probably still far from the time when such theoretical and experimental analyses will prove profitable.

I leave the discussion on a note of optimistic expectation: solutions of complicated problems of the brain by rigorous systems-network theoretical analyses may not be achieved in the near future, but the experimental and theoretical search will go on for even more dynamic processes that may eventually account for the individual as a self-aware entity possessed of all those qualities which make him human.

[42] P. Penfield, Jr., R. Spence, and S. Duinker, *Tellegen's Theorem and Electrical Networks,* Research Monograph 58 (Cambridge: M.I.T. Press, 1970), 143 pp.