8. W. A. Berggren, *Micropaleontology* **15**, 351 (1969).
9. J. E. Andrews and K. Jinghwa Hsü, *American Stratigraphic Commission Note 38* (American Association of Petroleum Geologists, Tulsa, in press).
10. M. N. Bramlette, *Geol. Soc. Amer. Bull.* **69**, 121 (1958).
11. W. H. Berger, *Science* **156**, 383 (1967).
12. ———, *Deep-Sea Res.* **15**, 31 (1968).
13. M. N. Bramlette, in *Oceanography*, M. Sears, Ed. (AAAS, Washington, D.C., 1961), pp. 345–366.
14. M. N. A. Peterson, *Science* **154**, 1542 (1966).
15. J. D. Hudson, *Mar. Geol.* **5**, 473 (1966).
16. R. A. Berner, *Geochim. Cosmochim. Acta* **29**, 947 (1965).
17. C. Emiliani and G. Edwards, *Nature* **171**, 887 (1953); H. A. Lowenstam, in *Problems in Palaeoclimatology*, A. E. M. Nairn, Ed. (Interscience, London, 1964), pp. 227–252.
18. G. O. S. Arrhenius, *Rep. Swed. Deep-Sea Exped.* **5** (fascile 1), 1 (1952); W. R. Riedel and B. M. Funnell, *Quart. J. Geol. Soc. London* **120**, 305 (1964).
19. G. R. Heath, *Geol. Soc. Amer. Bull.* **80**, 689 (1969).
20. B. C. Heezen and M. Tharp, *Phil. Trans. Roy. Soc. London Ser. A* **258**, 70 (1965).
21. V. Vacquier and R. P. Von Herzen, *J. Geophys. Res.* **69**, 1093 (1964).
22. C. W. Stover, *ibid.* **73**, 3807 (1968).
23. E. Bullard, J. E. Everett, A. Gilbert Smith, *Phil. Trans. Roy. Soc. London Ser. A* **258**, 41 (1965).
24. W. J. Morgan, *J. Geophys. Res.* **73**, 1959 (1968).
25. X. Le Pichon, *ibid.*, p. 3661.
26. H. W. Menard, *Marine Geology of the Pacific* (McGraw-Hill, New York, 1964), chap. 3.
27. W. A. Berggren, in preparation.
28. M. G. Langseth, Jr., X. Le Pichon, M. Ewing, *J. Geophys. Res.* **71**, 5321 (1966).
29. J. Ewing and M. Ewing, *Science* **156**, 1590 (1967).
30. D. H. Matthews and J. Bath, *Geophys. J. Roy. Astron. Soc.* **13**, 349 (1967); C. G. A. Harrison, *J. Geophys. Res.* **73**, 2137 (1968).
31. E. D. Schneider and P. R. Vogt, *Nature* **217**, 1212 (1968).
32. X. Le Pichon, R. E. Houtz, C. L. Drake, J. E. Nafe, *J. Geophys. Res.* **70**, 319 (1965); M. Talwani, X. Le Pichon, M. Ewing, *ibid.*, p. 341.
33. K. J. Hsü, *Amer. J. Sci.* **263**, 97 (1965); K. J. Hsü and S. O. Schlanger, *Int. Geol. Congr. Rep. Sess. Prague 23rd* **1** (section 1), 91 (1968).
34. G. O. Allard and V. J. Hurst, *Science* **163**, 528 (1969).
35. M. N. A. Peterson *et al.*, *Initial Reports of the Deep Sea Drilling Project* (Government Printing Office, Washington, D.C., 1970), vol. 2.
36. M. N. Bramlette and J. A. Wilcoxon, *Tulane Stud. Geol.* **5**, 93 (1967).
37. W. W. Hay, *Trans. Gulf Coast Assoc. Geol. Soc.* **17**, 438 (1967).
38. The Deep Sea Drilling Project is part of the National Ocean Sediment Coring Program supported by the National Science Foundation. Contribution 2414 from the Woods Hole Oceanographic Institution.

Proteins in Excitable Membranes

Their properties and function in bioelectricity are discussed.

David Nachmansohn

Cell Membranes

During the last decade, the properties and function of cell membranes have been one of the most actively explored fields in biological sciences; much information has been obtained from electron microscopy combined with biochemical and biophysical analyses. The notion of a "unit membrane," which was based on the Danielli-Davson model, proposed a structure about 80 Å thick, formed by a bimolecular leaflet of phospholipids to which proteins are attached on the inside and outside by ionic forces (*1*). These views have been contested (*2*). Membranes appear to be a mosaic of functional units formed by lipoprotein complexes. The proteins apparently form the core of the complexes; phospholipids are attached on the outside, probably by Van der Waals and coulombic forces and by hydrophobic bonds (*3*). This idea has found much support, although it does not exclude the possibility of modifications, for example, lipid layers located between these complexes (*4*). While the precise molecular organization of cell membranes is far from elucidated, the most important change in the last few years has been conceptual. It is now well established that cell membranes are highly organized and dynamic structures, in which many proteins and enzymes are located and form by their activity an essential part of the control mechanisms effected by membranes. An illustration of the character and intensity of the chemical reactions taking place in these structures offers the well-explored mitochondrial (*5*) and other membranes (*6*). The central role of proteins and enzymes in cell membranes accounts for their great diversity of function, their specificity, and their remarkable efficiency more readily than the previous notions based essentially on the physicochemical properties of phospholipids. In view of the crucial role of proteins in membrane function, Sjoestrand and Barajas (*7*) have applied new procedures in preparing specimens for examination by electron microscopy aimed at preserving the conformation of proteins in their native state. Their pictures are quite different from those obtained with the standard procedures and offer evidence for the presence of globular structures.

Nerve impulses are propagated along nerve and muscle fibers by electric currents; bioelectricity is thus linked to one of the vital functions of the body. Since the turn of this century it has been widely accepted that ions are the carriers of these currents; the control of the ion movements was attributed to rapid and reversible permeability changes to ions of the excitable membranes surrounding the fibers. This special ability is a key problem for understanding nerve function. Hodgkin and Huxley proposed that the ion movements are a simple diffusion process and account exclusively for conduction (*8*). This view is difficult to reconcile with a variety of facts and has been repeatedly challenged (*9*). In contrast to conduction, transmission across the junctions from nerve to nerve or from nerve to muscle was proposed to be effected by chemical mediators, in many cases specifically by acetylcholine (AcCh). In view of basic similarities of the electrical properties of the membranes of axons and those at junctions, many neurobiologists questioned the transmitter theory, which was based on experiments in which classical methods of pharmacology were combined with those of electrophysiology (*10*). These methods, essential for the study of many aspects of biology and medicine, are inadequate for an analysis of the molecular events in excitable membranes.

A chemical theory, proposed more than two decades ago, resulted from a new approach based on the notion of

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the central role of proteins and enzymes in cell function. It appeared imperative for the study of the controversial problem of the role of AcCh in nerve activity to investigate the proteins and enzymes associated with its function. Four factors were decisive in the progress achieved since this approach was initiated three decades ago: (i) The information about biomembranes mentioned above; (ii) the development of highly refined methods and instruments for analysis of cellular function on the cellular, subcellular, and molecular levels; (iii) the explosive growth of protein chemistry, culminating in the elucidation of the three-dimensional structure of proteins and nucleic acids; and (iv) the availability of an extraordinary and uniquely favorable material for the analysis of the proteins associated with excitable membranes and with bioelectricity: the electric organs of certain fish. The electroplax, the single cells of these organs, have electrical parameters similar to those of other excitable cells; but they are arranged in series as in a voltaic pile. This arrangement accounts for the powerful discharge of 600 volts in *Electrophorus* (the "electric eel" of the Amazon River), whose electric organ is formed by 5000 to 6000 cells.

The most crucial feature of electric tissue for biochemical studies is its high degree of specialization for its main function, bioelectrogenesis. The metabolism of the cell is low except in the membrane. This aspect of the tissue provides a unique opportunity for the protein chemist, because membranes form a small fraction of the cell mass and their study in other tissues is very difficult. The distribution and concentration of acetylcholinesterase (E.C. 3.1.1.7), the enzyme that hydrolyzes AcCh, was studied in 1937 in a variety of excitable cells of many different species. A remarkable concentration was found in the electric organ of *Torpedo marmorata* and in the following year in that of *Electrophorus*; 1 kilogram of tissue hydrolyzes 3 to 4 kilograms of AcCh per hour in spite of the low protein (3 percent) and high water content (92 percent) of these organs. The use of this material in the next three decades was instrumental in the isolation, identification, and characterization of some of the proteins controlling the permeability changes of excitable membranes during electrical activity and in obtaining information about their function.

Role of Acetylcholine

As a result of the biochemical approach a modification of the original theory became necessary. Acetylcholine is not a chemical mediator between two cells; it is never released from the cell (see below); its action is intracellular, taking place within the excitable membrane. It is the trigger which initiates and controls the permeability changes permitting the ion movements during electrical activity. Its function is similar in the excitable membranes of fibers and in those at the junctions. This view is supported by a vast and, in the last few years, rapidly increasing number of experimental data. The picture of the role of AcCh that best fits the available data is the following. Excitation leads to the release of AcCh from its bound form in resting condition. It acts as a signal recognized within the membrane by a specific AcCh-receptor protein. The reaction induces a conformational change of the protein, thereby possibly releasing Ca^{2+} ions bound to the protein. Calcium ions are involved in the excitability of nerve and muscle fibers which become inexcitable in the absence of divalent cations and are distinguished from other divalent cations by several remarkable features and properties (*11*). Their release may induce further conformational changes of phospholipids and other polyelectrolytes. The end result of the sequence of chemical reactions is the change of the membrane permeability to ions, a change that permits the movements of many thousands of ions, possibly as many as 20,000 to 40,000 in each direction per molecule of AcCh released. These reactions thus act as typical amplifiers of the signal given by AcCh. Acetylcholinesterase rapidly hydrolyzes AcCh, thereby permitting the return of the receptor protein to its original conformation and reestablishing the barrier for the ion movements.

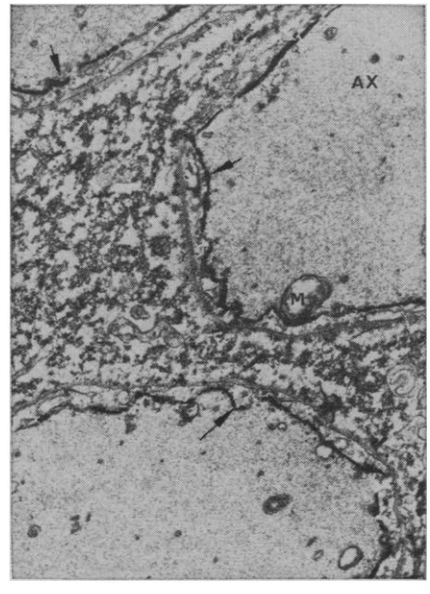


Fig. 1. Exclusive localization of cholinesterase (arrows) at the axon-Schwann interface of small nerve fibers (*AX*) which accompany the giant fiber in the stellar nerve of the squid. A mitochondrion (*M*) is located close to the axolemmal surface. A basement membrane surrounds the Schwann cell, separating it from the fibrillar material of the intercellular matrix. Incubated in acetylthiocholine and copper sulfate (× 4000) (with the permission of V. Tennyson).

Acetylcholine in its bound form and the two proteins reacting directly with the AcCh released, receptor and esterase, are presumably linked together structurally as well as functionally and form a protein assembly in the excitable membrane in a way comparable with other enzyme systems—for example, the electron transfer system in mitochondrial membranes. The structural organization of the system may account for the efficiency, the precision, and the speed of the events in the membrane during electrical activity. While an essential role of Ca^{2+} ions in the permeability changes of excitable membranes appears likely, their release requires a specific control mechanism. Among the cell components, only proteins are known to have the ability to recognize specific ligands and thereby provide the proper control for initiating and terminating a specific cell function. The early data supporting these conclusions have been summarized in a monograph (*12*), and the more recent advances in several reviews (*13*). A few features of the properties of the two proteins may be outlined.

Acetylcholinesterase

Localization. Acetylcholine, acetylcholinesterase, and acetyl CoA: choline *O*-acetyltransferase (choline acetylase) (E.C. 2.3.1.6), the enzyme that forms AcCh (*14*), are present in various types of conducting fibers and in a great variety of different species throughout the animal kingdom: in motor and sensory, cholinergic and adrenergic, and peripheral and central nerve fibers and in

muscle of both vertebrates and invertebrates. On the basis of a variety of biochemical data it was postulated that acetylcholinesterase is localized in or near the excitable membranes. This evidence was of necessity indirect. In the last 7 years direct evidence for the localization of acetylcholinesterase in excitable membranes has been obtained by electron microscopy combined with histochemical techniques (*15*). Figure 1, by V. Tennyson (*16*), illustrates the localization of the enzyme in the plasma membrane of unmyelinated fibers. The same localization has been demonstrated in a variety of other types of fibers and in the muscle membrane (*17*). On examination of myelinated fibers by similar methods, the enzyme was frequently absent, in spite of its regular presence when the esterase activity is determined in homogenized tissue. Even in a section 500 to 1000 Å thick, structural barriers may slow down or prevent the reaction between the membrane-bound enzyme and the added compounds required for its detection, especially in a tissue rich in lipids. Therefore, Brzin (*18*) applied a detergent, Triton 100 X, to sections of a single isolated frog sciatic nerve fiber and found that acetylcholinesterase was located exclusively in the plasma membrane between the myelin and the axoplasm (Fig. 2). In the electroplax of *Electrophorus* the enzyme is present in the membranes of the nerve terminal and in the synaptic and conducting membranes (*19*). Because virtually all of the enzyme is localized in the excitable membrane, a more correct value of the extraordinary enzyme activity in electric tissue is obtained when this activity is expressed as the amount of AcCh hydrolyzed per gram of membrane and not per gram of whole tissue. Since the membrane forms only 10^{-4} or less of the whole cell mass, 1 gram of excitable electroplax membrane hydrolyzes many kilograms of AcCh per hour.

Purification and crystallization. Studies on the properties of acetylcholinesterase started in 1938 when this enzyme was first obtained in a highly active solution by extraction from electric tissue (*20*). In the early 1940's a 500-fold purification was obtained, but the protein amounts available were small (*21*). The preparation was useful for kinetic studies and for analyzing many reactions of ligands with molecular groups in the active site and the

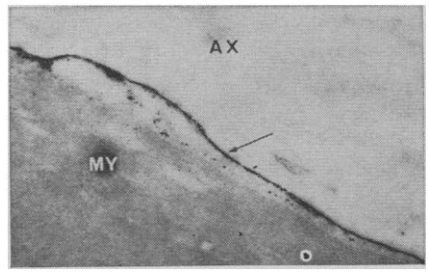


Fig. 2. Large myelinated (*My*) ventral root axon (*AX*) taken from a frog sciatic nerve. The fiber was treated with Triton 100 X, before the incubation for acetylcholinesterase activity, in the same way as in Fig. 1. Dense end product is present on the axolemmal membrane (arrow) (× 3200). [Figure reprinted by permission of Editor, *Proc. Nat. Acad. Sci. U.S.* **56**, 1560 (1966)]

mechanism in the hydrolytic process (*12, 22, 23*). The effects of potent competitive inhibitors widely used in neuropharmacology and medicine were explained in terms of their reaction with the molecular groups in the active site of the enzyme. Of particular theoretical as well as practical interest were the studies with organophosphates, potent inhibitors of acetylcholinesterase and other ester-splitting enzymes. Some organophosphates are potential chemical warfare agents, and many are widely used as insecticides. The fatal effects are due to the reaction with AcCh-esterase. The phosphorus atom of organophosphates forms a covalent bond with an oxygen atom of the serine residue in the active site of ester-splitting enzymes. The resulting phosphorylated enzyme is much more stable than the acetyl enzyme. The reaction was first thought to be irreversible, but this notion has undergone considerable modifications (*23–25*). The explanation of the reaction mechanism permitted the development of a highly efficient and widely used antidote against poisoning by organophosphate insecticides—namely, pyridine 2-aldoxime methiodide (PAM), which rapidly and quite specifically reactivates the enzyme by removing the phosphoryl group from the serine in a displacement reaction (*26*). Pyridine 2-aldoxime methiodide is much more efficient and less harmful than atropine, still frequently applied by physicians in organophosphate poisoning (*27*). The present trend against stable insecticides (for example, DDT) has increased the interest in unstable and more specific forms. Additional research on cells is required for designing more specific and efficient organophosphate or other types of insecticides, which are less harmful for men and animals and which would decrease the pollution of the environment.

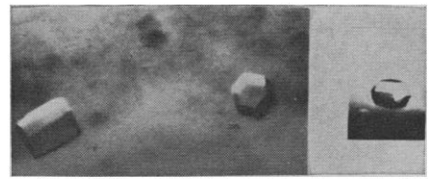


Fig. 3. Crystals of acetylcholinesterase. (Left) Regular hexagonal prisms; (right) possibly pyramidal termination [from Leuzinger *et al.* (*29*)]. The crystals have a length of 150 micrometers and a width of 120 micrometers. According to Dr. B. Low (*67*) the most common form of growth observed on the left is compatible with true hexagonal symmetry; the form on the right may imply, however, a crystal system of lower order. The crystals exhibit low birefringence, so that it is not possible at present to determine whether they are uniaxial or biaxial.

The analysis of protein properties requires considerable amounts of homogeneous and (for x-ray crystallography) crystallized protein. Adequate amounts of homogeneous acetylcholinesterase have been obtained by a large-scale purification of electric tissue with chromatographic methods, and the crystallization of the enzyme has been achieved (*28, 29*). The crystals have the form of hexagonal prisms (Fig. 3). The enzyme is a tetramer with a molecular weight of 260,000; the four subunits are of equal size, but two different polypeptide chains are present (*30*). Methods which greatly improve the yield are being worked out for further studies of the protein properties.

Interdependence between electrical and acetylcholinesterase activity. The localization of the enzyme in various types of excitable membranes does not yet indicate its essential role in electrical activity. Other properties of the enzyme are prerequisites—for example, its high activity with a turnover time of 30 to 40 microseconds or less. Because nerve fibers may conduct 1000 impulses per second, the signal interacting with the receptor must be removed with a speed compatible with the function proposed. The postulated role requires, however, the demonstration that the enzyme and electrical activities are directly associated; potent inhibitors of acetylcholinesterase should affect and eventually block electrical activity. This effect has been demonstrated with reversible as

well as irreversible types of inhibitors (*24, 25*). However, this kind of experiment offers many pitfalls; some of them, such as the existence of structural barriers, were obvious from the beginning. Others became increasingly apparent when information accumulated about the many complex factors which may change the behavior of enzymes in an intact structure. Today it is well recognized that it is frequently impossible to extrapolate from observations in solution to their behavior in intact cells because a variety of factors may modify the reactions (*31*).

A few observations may be mentioned. Electrical activity of the frog sciatic nerve was found to be reversibly blocked by physostigmine, a potent competitive reversible inhibitor of acetylcholinesterase with an inhibition constant K_i of 10^{-7} mole per liter; but the concentration required was 10^{-2} mole per liter, and the time of exposure was 30 to 60 minutes. This preparation is formed by several thousand myelinated fibers surrounded by a sheath poorly permeable to many compounds. When physostigmine was applied to a single fiber of this preparation, in which the excitable membrane of the axon is poorly protected at the Ranvier nodes where myelin is absent, effects on the electrical activity were obtained at 10^{-5} to 10^{-6} mole per liter; within seconds a potentiation was observed followed by a depression and finally a block (*32*). Several other types of complications were encountered with organophosphates. Exposure of various types of nerve fibers to organophosphates blocks electrical activity irreversibly, but in higher concentrations than expected. For example, in the squid giant axon, $5 \times 10^{-3}M$ diisopropylphosphofluoride (DFP) and 30 to 40 minutes exposure are required for producing irreversible block. The actual concentration of DFP inside the axoplasm of the giant axon, at the time when conduction was irreversibly blocked, was small, of the order of 10^{-5} mole per liter (*33*). It was later found that in the giant axon, as in many tissues, a phosphorylphosphatase exists which rapidly inactivates many organophosphates. In some types of axons, rapid and irreversible effects were obtained with relatively low concentrations. Pyridine 2-aldoxime methiodide, the potent and specific reactivator of phosphorylated acetylcholinesterase mentioned above, restored, in some preparations, irreversibly blocked electrical activity, although the compound is a quaternary ammonium derivative and does not readily penetrate the cell (*34*). The successful demonstration that potent inhibitors of acetylcholinesterase rapidly block electrical activity in several types of conducting fibers is strong evidence for the essential role of the enzyme in this process. It would be difficult to reason that the enzyme, although present in excitable membranes, is essential for electrical activity in some, but not in others, simply because the block of conduction is sometimes effected under conditions different from those expected from reactions in vitro (*24, 25*).

When organophosphates became available, in the 1940's, it was thought that this type of compound would permit the determination of the minimum acetylcholinesterase activity still compatible with unimpaired conduction. This value would indicate the excess of enzyme present. In the last few years it has become evident that there is at present no possibility to answer this question. The methods now available do not permit a quantitative evaluation of the enzyme activity in normal tissue. Simple homogenization turned out to be inadequate. Several chemical procedures may increase activities severalfold. After the tissues are exposed to organophosphates, the difficulties are compounded by many complicating factors; some of them became apparent only recently. Thus, for the time being there is no answer to the question of the minimum activity of acetylcholinesterase required for electrical activity, but the claims of a successful dissociation of electrical and enzyme activity after exposure to organophosphates have lost their validity (*24, 25*).

Acetylcholine-Receptor

Monocellular electroplax preparation. The AcCh-receptor has not yet been isolated. A turning point in the studies of this protein was the development of a monocellular electroplax preparation from *Electrophorus* by Schoffeniels (*35*). This preparation is unique for studying the properties of the receptor within the membrane because of (i) the large size of the cell; (ii) the rectangular shape of the excitable membrane, containing both synaptic and conducting parts readily distinguishable by means of electrical parameters; and (iii) the presence of a nonexcitable membrane which facilitates comparison between the two functionally different parts. As described above, the outstanding feature of the cell (that is, the electroplax of *Electrophorus*) is the prevalence of metabolic reactions in the membrane. Although the electroplax responds to externally applied AcCh, curare, and other quaternary nitrogen derivatives at the synaptic junctions only, both AcCh-receptor and acetylcholinesterase are present and functional in the conducting parts of the excitable membrane. During the last decade several refinements have permitted more sensitive analyses of the reactions between the receptor protein and specific ligands by means of electrical parameters comparable with the precision of other methods applied in protein studies (*36*). The preparation permits precise and reproducible titration of the dose-response curves and the evaluation of dissociation constants between ligands and the protein. Acetylcholine and related compounds that affect electrical activity and simultaneously depolarize the membrane by inducing conformational changes are referred to as receptor activators. Other compounds closely related in structure to AcCh act as "antimetabolites"; they prevent the specific signal from interacting with the receptor and are referred to as receptor inhibitors.

Active site. The molecular groups in the active site of the receptor have been analyzed with several series of compounds—for example, derivatives of both aryl- and alkyl-ammonium ions and ambenonium and benzoquinonium compounds—and compared with the reactions of the enzyme in solution (*37*). The functional importance of the anionic group in the active site of both proteins has been demonstrated. Quaternary ammonium derivatives tested on the receptor are a few hundred up to a thousand times more potent than their tertiary analogs. There is no esteratic site in the receptor protomer, as might have been expected from the different function of the two proteins. Small changes, like the substitution of one atom in relatively large molecules, may greatly affect the dissociation constants between either protein and the ligand tested, sometimes in the same, sometimes in the opposite direction for the two proteins. These data support the assumption of the protein nature of the receptor. Additional evidence was obtained with the use of sulfhydryl-blocking and disulfide-reducing agents (*38*). While the active site of receptor and

esterase appear different, the question of whether the two protomers are part of the same macromolecule is still under investigation (*24, 25*).

Oxygen, sulfur, and selenium isologs. Pertinent information about the active site of receptor and esterase resulted from experiments with a large series of S and Se isologs of AcCh and its congeners (*39*). Striking differences in the biological activity of these isologs, tested by the effects on the receptor of the electroplax, and in their reactions with the enzyme in solution have been interpreted in part as being due to differences of electron distribution and in part as being the result of different configurations (*gauche* and *trans*) of the isologs, as determined by x-ray analysis.

Role of receptor in bioelectricity. The essential role of the receptor in bioelectricity has been demonstrated with a group of competitive inhibitors, the so-called "local anesthetics." These substances are closely related in structure to AcCh and act as typical antimetabolites at synaptic and conducting parts of the membrane. The transformation of the molecular structure of AcCh from a receptor activator, which acts on the junctions only, to a receptor inhibitor, which acts on both parts of the membrane, was analyzed by a series of replacements of molecular groups (*40*) (Fig. 4). Benzoylcholine was found to be structurally and functionally the intermediate form; it may act as a receptor activator or inhibitor, depending on the experimental conditions. With the addition of a para-amino group to the phenyl ring, the compound becomes a typical local anesthetic. Small modifications of either the acyl or of the quaternary nitrogen group may greatly increase its potency as a local anesthetic. These compounds block all electrical activity in all excitable membranes; thus, the data support the postulated role of the receptor.

Cooperativity and allosteric sites. Observations of Changeux, Podleski, and their associates (*41*) suggest certain similarities between the behavior of regulatory enzymes and the reactions of the electroplax with ligands acting on the receptor. The dose-response curve of the receptor to AcCh and other activators has a sigmoid shape, thus deviating from the usual Langmuir isotherm. The S-shaped curve is considered a characteristic property of allosteric systems and of cooperative action (*42*). The Hill coefficient (*nH*) of the electroplax response is about 2. After exposure to sulfhydryl-blocking and disulfide-reducing compounds the *nH* becomes about 1 (*43*). In the presence of two different activators, the dose-response curve of the electroplax becomes a hyperbola, with an *nH* of 1; this is considered an indication that the interaction between both classes of ligands may be indirect or allosteric (*41*). At saturating concentrations of activators the maximum response to different activators differs, independent of the ionic environment.

Affinity labeling. Compounds forming a covalent bond with the molecular group in the active site of an enzyme have long been important tools in the analyses of these sites. One type of covalent bonding is referred to as "affinity labeling"; the reagent, because of its steric complementarity to the active site, first combines specifically and reversibly with the site with which it forms a complex; then a small and reactive group reacts with one or more amino acid residues to form irreversible covalent

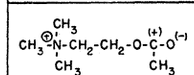
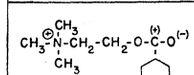
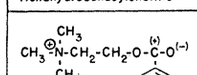
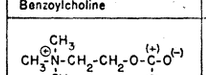
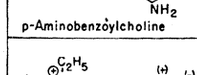
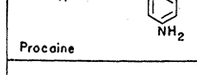
Compound	Synaptic Junctions		Conducting Membrane
	Activator	Inhibitor	
	M concentration		
 Acetylcholine	2.5×10^{-6}	0	0
 Hexahydrobenzoylcholine	5×10^{-4}	0	0
 Benzoylcholine	5×10^{-4}	5×10^{-4}	1×10^{-3}
 p-Aminobenzoylcholine	0	1×10^{-3}	2.5×10^{-3}
 Procaine	0	2.5×10^{-4}	5×10^{-4}
 Tetracaine methiodide	0	2×10^{-5}	1×10^{-5}

Fig. 4. Substitutions of AcCh transforming the molecule from a receptor activator, acting on the synaptic junctions only, into a receptor inhibitor, acting both on junctions and on the conducting membrane (so-called "local anesthetic"). Benzoylcholine is a transitory form both in structure and in biological activity.

bonds (*44*). The first affinity labeling of the AcCh-receptor was described with *p*-(trimethylammonium)benzenediazonium fluoroborate (TDF); the compound blocks irreversibly the electroplax response at a concentration of 10^{-4} mole per liter (*45*), although new observations of Mautner and Bartels (*46*) seem to indicate a more complex reaction mechanism than anticipated. Potent affinity labeling has been achieved with a two-step procedure, when the labeling compounds are applied after reduction of disulfide bridges of the electroplax by dithiothreitol (DTT). *N*-Ethylmaleimide presumably forms a covalent bond with the exposed sulfhydryl groups. Substitution of the ethyl by a phenyltrimethylammonium group, a potent receptor activator, increased the potency by several hundredfold; 4-(*N*-maleimido)phenyltrimethylammonium iodide (MPTA) blocks the receptor at a concentration of 10^{-8} mole per liter. The tertiary analog is not more potent than *N*-ethylmaleimide (*47*). Other potent affinity-labeling compounds that act on the reduced cell were designed by Silman (*48*); one of them is bromoacetylcholine, which forms a covalent bond between the nucleophilic sulfhydryl groups and the carbon of the carbonyl group. In contrast to MPTA, which is a receptor inhibitor, this compound depolarizes the electroplax (*48*). The use of affinity-labeling compounds may permit the isolation of the receptor.

Drastic changes of biological effects may result from the exposure of the electroplax to DTT. Hexamethonium, a bisquaternary reversible inhibitor, becomes a receptor activator after reduction (*47*). The compound TDF, an irreversible inhibitor of the receptor at a concentration of 10^{-4} mole per liter, becomes after reduction a reversible activator at 10^{-6} mole per liter (*49*). Apparently opposite biological actions leading to excitation or inhibition may thus be due to relatively small changes in the state of the receptor and other factors in the membrane, and not—as is widely assumed—to different "excitatory" or "inhibitory" transmitters. An explanation of the basis of such differences requires an analysis of the molecular reactions, as exemplified by the dependence of the action of adenosine triphosphate on the concentration of Ca^{2+} ions in inducing either muscular contraction or relaxation.

Photoregulation of membrane potential by receptor inhibitors. Vision is

based on the *cis-trans* isomerization of retina (*50*). A few quanta of light absorbed by rhodopsin induce the isomerization which leads to nerve excitation in a still unknown manner. The photochromic compound *p*-phenylazophenyl-trimethylammonium chloride inhibits the depolarization of the electroplax produced by carbamylcholine (*51*). The *trans* isomer, which predominates in the light of a photoflood lamp (420 nm), is a stronger inhibitor than the *cis* isomer which predominates under ultraviolet irradiation (320 nm). When the electroplax in the presence of carbamylcholine and this compound is exposed to light of the two different wavelengths, marked changes of the potential difference across the excitable membrane are observed by the shift of the *cis-trans* equilibrium. The system may be considered as a model illustrating how a *cis-trans* isomerization may be linked to a neural impulse.

Organophosphates. The electroplax offers a useful material for studies of the cellular action of organophosphates about which little information is available. For example, the rapid and reversible block of electrical activity, observed in axons by organophosphates, is the result of a direct reaction with the AcCh-receptor (*52*). Observations on the electroplax suggested that the reaction of DFP and other organophosphates with acetylcholinesterase in this cell may be partly reversed within minutes, contrary to the expectations from observations in solution. This was borne out by direct measurements of the enzyme activity (*53*).

Conduction and Transmission

A criterion for the validity of a new concept is its ability to provide more satisfactory explanations for the experimental data than that provided by the preceding concept. In view of the progress achieved in the understanding of chemical reactions in membranes, a reevaluation of the theory of neurohumoral transmission appears imperative. The powerful pharmacological action of AcCh on junctions in contrast to its complete failure to act on axonal conduction has been emphasized as evidence for a mechanism of synaptic transmission basically different from that of axonal conduction. Many drugs act on junctions only, as has been frequently observed since Claude Bernard first demonstrated that curare blocks the transmission from nerve to muscle but does not affect conduction. Curare, a receptor inhibitor with a higher affinity to the receptor than AcCh, prevents the depolarization by the ester. The compound is a quaternary nitrogen derivative and is insoluble in lipids as are AcCh, neostigmine, and other receptor activators or inhibitors. The conducting membranes of axons are surrounded by Schwann cells, which act as structural barriers for this type of compound. Claude Bernard applied curare to the frog sciatic nerve fiber, formed by several thousands of myelinated axons and surrounded by a sheath that is impervious to many chemical compounds. When a single axon of this fiber is exposed to curare, electrical activity at the Ranvier nodes is rapidly and reversibly blocked, just as at junctions where barriers do not exist or are more pervious (*54*). Even in unmyelinated axons the Schwann cells, which contain phospholipids, usually prevent AcCh, curare, and related quaternary structures from reaching the receptor in the excitable membrane, although in some axons with apparently incomplete barriers, for example, those of the walking leg of lobster, a direct action of these compounds on electrical activity has been obtained (*55*). However, chemical treatment may reduce the outside barriers and permit AcCh and its congeners to reach the receptor in the excitable membrane. In the giant axon of the squid the excitable membrane is surrounded by a Schwann cell about 4000 Å thick. When this axon is exposed to AcCh, curare, or neostigmine at high concentrations, no effect is observed. In contrast, physostigmine, a tertiary nitrogen derivative and an inhibitor of acetylcholinesterase equal in potency to neostigmine, blocks electrical activity. The tertiary analog of neostigmine, although a much weaker inhibitor than the quaternary form, has the same effect on conduction. When the axoplasm of the exposed axons are extruded, physostigmine penetrates, whereas the quaternary compounds do not (*56*). After the squid giant axon has been exposed to phospholipase A for a short period of time in low concentrations, electrical activity is blocked by AcCh and curare (*57*); when, under these conditions, the two compounds labeled with radioactive isotopes were used, they penetrated the interior (*58*). Examination by electron microscopy revealed marked structural changes in the Schwann cell, but none in the plasma membrane (*59*). The effect of phospholipase A is fully accounted for by the formation of lysolecithin (*60*). Even synaptic junctions may not react to AcCh and curare, for example, the neuromuscular junction of lobster, although the concentrations of acetylcholinesterase and choline O-acetyltransferase in these junctions is very high. Lipid soluble compounds, such as physostigmine and DFP, affect these junctions. Thus, the system is present and functional but protected against quaternary derivatives.

The second observation considered as evidence for the theory of neurohumoral transmission is the appearance of AcCh in the extracellular perfusion fluid of junctions after stimulation. However, no trace of AcCh appears in the absence of physostigmine even after prolonged stimulation, as was emphatically stressed by Dale *et al.* (*61*). This failure to detect any extracellular AcCh unless acetylcholinesterase, the highly effective inactivation mechanism, is blocked, suggests that the appearance is an artifact attributable to the incomplete hydrolysis. The detection of an efflux of AcCh from the axonal membrane would be prevented by the structural barriers except where they are incomplete, as in the axons of the lobster walking leg. There an efflux was found, provided that the axons were kept in physostigmine; various ions affect this efflux in a way similar to that described for junctions (*62*). Even in the presence of potent enzyme inhibitors, the extracellular amounts found at junctions are far from those necessary for the ester to exercise a transmitter function. Such a sensitive preparation as the electroplax does not respond to $10^{-5}M$ AcCh in the absence of physostigmine; in its presence 10^{-6} mole per liter is required. The amounts released are ten orders of magnitude smaller. This large discrepancy raises a serious difficulty in attributing the postulated intercellular function to AcCh.

An alternative explanation accounts more readily for the data. Acetylcholine-receptor and acetylcholinesterase are both localized in the two membranes of the junction, those of the nerve terminal and of the postsynaptic membrane. Both proteins are functional since AcCh, curare, neostigmine, and related compounds act on both membranes of the junction (*63*). Thus, it seems reasonable to assume that the amplifier process takes place in the membranes of the junctions in a way similar to that of the axons; AcCh released in the terminal membrane acts on the receptor there and triggers the se-

quence of the reactions resulting in the influx of sodium and the efflux of potassium ions. When a strong efflux of potassium ions was found after stimulation at junctions as well as in axons (*64*), Eccles (*65*) attributed the transmitter function to potassium ions. But release of the ions requires the amplification process triggered by AcCh; many millions of potassium ions would cross the gap for each 1000 molecules of AcCh released and effect the release of AcCh in the postsynaptic membrane. Chemical reactions in living cells are chemically and thermodynamically coupled; most of them are structurally organized. It appears more plausible that the specific signal in one of the fastest cellular mechanisms is recognized by the target protein within the membrane where it is released, rather than by a protein in another cell. For many years, the failure to detect flow of current from nerve terminals was considered as a support for chemical transmission. The absence of current flow seemed particularly conspicuous in the giant synapse of squid, in which fractions of the pre- and postsynaptic axons are located side by side and permit monitoring of current flow by the insertion of microelectrodes into both axons. Recently, current flow has been observed from nerve terminals; in the squid synapse current flows in both directions (*66*). The pharmacological action on junctions mimicking nerve stimulation must be reinterpreted, on the basis of the data resulting from the analysis of membrane proteins, as mimicking the signal within the two membranes of the junction and not acting between them. Such a view integrates the observations which seemed to suggest neurohumoral transmission with the biochemical data and with the concept of the fundamental similarity of conduction and transmission (*10*).

The specific chemical forces underlying cellular mechanisms such as motility, energy supply, vision, and genetic control, are remarkably similar throughout the animal kingdom. It has become apparent that this similarity also applies to the specific chemical forces underlying bioelectricity, that is, to the specific proteins controlling the changes of ion permeability in excitable membranes. The great diversity of bioelectric phenomena and the variations of pharmacological effects may be explained by differences of cellular structure, shape, and environment between junctions and axons. These factors are bound to modify the effects of chemical reactions in the membranes and the actions of compounds applied externally. Electrical parameters in axons differ in various types of nerves; conduction velocity, for example, varies from 0.1 to 100 meters per second. These differences are generally attributed to dissimilarities of structure and not to differing basic mechanisms of conduction. Knowledge of the chemical composition and molecular organization of membranes is much too limited to permit speculation about possible differences. The answer to these questions requires much more information on a molecular level.

References and Notes

1. J. F. Danielli and H. Davson, *J. Cell. Comp. Physiol.* **5**, 495 (1935); J. D. Robertson, *Progr. Biophys. Biophys. Chem.* **10**, 343 (1960).
2. F. S. Sjoestrand, *Nature* **199**, 1262 (1963); ——— and L. G. Elfvin, *J. Ultrastruct. Res.* **10**, 263, (1964); E. D. Korn, *Science* **153**, 1491, (1966); D. E. Green and J. F. Perdue, *Proc. Nat. Acad. Sci. U.S.* **55**, 1295 (1966); D. E. Green and D. H. MacLennan, *Bioscience* **19**, 213 (1969).
3. A. A. Benson, *J. Amer. Oil Chem. Soc.* **43**, 265 (1966).
4. E. P. Kennedy, in *The Neurosciences*, G. C. Quarton, T. Melnechuk, F. O. Schmitt, Eds. (Rockefeller Univ. Press, New York, 1967), p. 271; L. Rothfield and A. Finkelstein, *Annu. Rev. Biochem.* **37**, 463 (1968).
5. E. Racker, *Mechanisms in Bioenergetics* (Academic Press, New York, 1965); *Fed. Proc.* **26**, 1335 (1967); *J. Gen. Physiol.* **54**, 38*S* (1969); D. E. Green and J. F. Perdue, *Ann. N. Y. Acad. Sci.* **137**, 667 (1966).
6. New York Heart Association, *Membrane Proteins* (Little, Brown, Boston, 1969).
7. F. S. Sjoestrand and L. Barajas, *J. Ultrastruct. Res.* **5**, 121 (1968).
8. A. L. Hodgkin, *Biol. Rev. (Cambridge)* **26**, 338 (1951); *The Conduction of the Nervous Impulse* (Thomas, Springfield, Ill., 1964).
9. B. C. Abbott, A. V. Hill, J. V. Howarth, *Proc. Roy. Soc.* **B148**, 149 (1968); A. V. Hill. in *Symposium on Molecular Biology*. D. Nachmansohn, Ed. (Academic Press, New York, 1960), p. 153; I. Tasaki, *Nerve Excitation* (Thomas, Springfield, Ill., 1968).
10. J. Erlanger, *J. Neurophysiol.* **2**, 370 (1939); J. F. Fulton, *Physiology of the Nervous System* (Oxford Univ. Press, New York, 1938, 1943); R. Lorente de No, *Amer. J. Physiol.* **121**, 331 (1938).
11. A. Katchalsky, in *Connective Tissue: Intercellular Macromolecules*, New York Heart Assoc., Ed. (Little, Brown, Boston, 1964), p. 9.
12. D. Nachmansohn, *Chemical and Molecular Basis of Nerve Activity* (Academic Press, New York, 1959).
13. ———, in *New Perspectives in Biology*, M. Sela, Ed. (Elsevier, Amsterdam, 1964), p. 176; *Ann. N.Y. Acad. Sci.* **137**, 877 (1966); *Proc. Nat. Acad. Sci. U.S.* **61**, 1034 (1968).
14. ——— and A. L. Machado, *J. Neurophysiol.* **6**, 397 (1943); D. Nachmansohn, in *Handbuch Experiment. Pharmak., Ergw.*, G. B. Koelle, Ed. (Springer, Heidelberg, 1963), vol. 15, p. 40.
15. R. J. Barrnett, *J. Cell Biol.* **12**, 247 (1962); W. W. Schlaepfer and R. M. Torack, *J. Histochem. Cytochem.* **14**, 369 (1966); M. Brzin, V. M. Tennyson, P. E. Duffy, *J. Cell Biol.* **31**, 215 (1966).
16. V. M. Tennyson, unpublished data.
17. S. J. Lundin and B. Hellstroem, *Histochemie* **85**, 264 (1968).
18. M. Brzin, *Proc. Nat. Acad. Sci. U.S.* **56**, 1560 (1966).
19. F. E. Bloom and R. J. Barrnett, *J. Cell Biol.* **29**, 475 (1966).
20. D. Nachmansohn and E. Lederer, *Soc. Chim. Biol. Bull.* **21**, 797 (1939).
21. M. A. Rothenberg and D. Nachmansohn, *J. Biol. Chem.* **168**, 223 (1947).
22. D. Nachmansohn and I. B. Wilson, *Advan. Enzymol.* **12**, 259 (1951).
23. *Handbuch Experiment. Pharmak., Ergw.*, G. B. Koelle, Ed. (Springer, Heidelberg, 1963), vol. 15.
24. D. Nachmansohn, *J. Gen. Physiol.* **54**, 187S (1969).
25. ———, in *Handbook of Sensory Physiology* (Springer, Heidelberg, in press).
26. I. B. Wilson and S. Ginsburg, *Biochim. Biophys. Acta* **18**, 168 (1955); H. Kewitz, I. B. Wilson, D. Nachmansohn, *Arch. Biochem. Biophys.* **64**, 456 (1956).
27. An 8-year-old boy in a nearly comatose condition which had developed within hours was treated by a physician. The illness was recognized as an organophosphate poisoning. The physician treated him with massive doses of atropine and only very much later with pyridine 2-aldoxime methiodide. The boy recovered quickly. After a similar accident 2 weeks later, the source of the poison was discovered to be a pair of jeans worn by the boy just before the two accidents. Organophosphate had been spilled on a package of jeans from a leaky bottle during the shipment [B. Roueché, *The New Yorker* **45**, 123 (1969)].
28. L. T. Kremzner and I. B. Wilson, *J. Biol. Chem.* **238**, 1714 (1963); W. Leuzinger and A. L. Baker, *Proc. Nat. Acad. Sci. U.S.* **57**, 446 (1967).
29. W. Leuzinger, A. L. Baker, E. Cauvin, *Proc. Nat. Acad. Sci. U.S.* **59**, 620 (1968).
30. W. Leuzinger, M. Goldberg, E. Cauvin, *J. Mol. Biol.* **40**, 217 (1969).
31. E. Racker, *Fed. Proc.* **26**, 1335 (1967); L. Goldstein, Y. Levin, E. Katchalski, *Biochemistry* **3**, 1913 (1964); R. Goldman, O. Kedem, H. I. Silman, S. R. Caplan, E. Katchalski, *ibid.* **7**, 486 (1968); I. Silman, *J. Gen. Physiol.* **54**, 50S (1969).
32. W.-D. Dettbarn, *Biochim. Biophys. Acta* **41**, 337 (1960).
33. E. A. Feld, H. Grundfest, D. Nachmansohn, M. A. Rothenberg, *J. Neurophysiol.* **11**, 125 (1948); F. C. G. Hoskin, P. Rosenberg, M. Brzin, *Proc. Nat. Acad. Sci. U.S.* **55**, 1231 (1966).
34. L. P. Hinterbuchner and D. Nachmansohn, *Biochim. Biophys. Acta* (1960); P. Rosenberg and W-D. Dettbarn, in *Animal Toxins*. New York Heart Assoc., Ed. (Pergamon Press, Oxford, New York, 1967), p. 379.
35. E. Schoffeniels and D. Nachmansohn, *Biochim. Biophys. Acta* **26**, 1 (1957); E. Schoffeniels, *ibid.*, p. 585.
36. H. B. Higman and E. Bartels, *ibid.* **57**, 77 (1962); H. B. Higman, T. R. Podleski, E. Bartels, *ibid.* **75**, 187 (1963); *ibid.* **79**, 138 (1964); D. Nachmansohn, in *Current Aspects of Biochemical Energetics*, N. O. Kaplan and E. P. Kennedy, Eds. (Academic Press, New York, 1966), p. 145.
37. T. R. Podleski, *Biochem. Pharmacol.* **18**, 211 (1969); G. D. Webb, *Biochim. Biophys. Acta* **102**, 172 (1965); T. R. Podleski and D. Nachmansohn, *Proc. Nat. Acad. Sci. U.S.* **56**, 1034 (1966); E. Bartels, *Biochem. Pharmacol.* **17**, 945 (1968).
38. A. Karlin, and E. Bartels, *Biochim. Biophys. Acta* **126**, 525 (1966).
39. H. G. Mautner, *Pharmacol. Rev.* **19**, 107 (1967); *Ann. Rep. Medicinal Chem.* **1968**, 230 (1969); P. Rosenberg, H. G. Mautner, D. Nachmansohn, *Proc. Nat. Acad. Sci. U.S.* **55**, 835 (1966).
40. E. Bartels, *Biochim. Biophys. Acta* **109**, 194 (1965); ——— and D. Nachmansohn, *Biochem. Z.* **342**, 359 (1965).
41. J.-P. Changeux and T. R. Podleski, *Proc. Nat. Acad. Sci. U.S.* **59**, 944 (1968); ——— and J.-C. Meunier, *J. Gen. Physiol.* **54**, 225S (1969); J.-P. Changeux, T. R. Podleski, J.-C. Meunier, in *Regulatory Functions of Biological Membranes*, J. Järnefeld, Ed. (Elsevier, New York, 1968).
42. J. Monod, J.-P. Changeux, F. Jacob, *J. Mol. Biol.* **6**, 306 (1963); E. R. Stadtman, *Advan. Enzymol.* **28**, 41 (1966); D. E. Koshland, Jr., and K. E. Neet, *Annu. Rev. Biochem.* **37**, 359 (1968).
43. A. Karlin, *J. Theor. Biol.* **16**, 306 (1967).
44. S. J. Singer, *Advan. Protein Chem.* **22**, 1 (1967).
45. J.-P. Changeux, T. R. Podleski, L. Wofsy, *Proc. Nat. Acad. Sci. U.S.* **58**, 2063 (1967).
46. H. G. Mautner and E. Bartels, in preparation.
47. A. Karlin and M. Winnik, *Proc. Nat. Acad. Sci. U.S.* **60**, 668 (1968); A. Karlin, *J. Gen. Physiol.* **54**, 245S (1969).
48. I. Silman and A. Karlin, *Science* **164**, 1420 (1969); I. Silman, in *Colloquium E: Molecular*

Neurobiology (6th FEBS Meeting, Madrid, 1969), in press.
49. T. R. Podleski, J.-C. Meunier, J.-P. Changeux, *Proc. Nat. Acad. Sci. U.S.* **64**, 1230 (1969).
50. G. Wald, *Science* **162**, 230 (1968).
51. W. J. Deal, B. F. Erlanger, D. Nachmansohn, *Proc. Nat. Acad. Sci. U.S.* **64**, 1230 (1969).
52. E. Bartels and D. Nachmansohn, *Arch. Biochem. Biophys.* **133**, 1 (1969).
53. W.-D. Dettbarn, E. Bartels, F. Welsch, F. C. G. Hoskin, *Biochem. Pharmacol.*, in press.
54. W.-D. Dettbarn, *Nature* **186**, 891 (1960).
55. ——— and F. A. Davis, *Biochim. Biophys. Acta* **66**, 397 (1963); W.-D. Dettbarn, *Life Sci.* **12**, 910 (1963).
56. D. Nachmansohn, T. H. Bullock, M. A. Rothenberg, *J. Neurophysiol.* **9**, 9 (1946); M. A. Rothenberg, D. B. Sprinson, D. Nachmansohn, *ibid.* **11**, 111 (1948).
57. P. Rosenberg, *Toxicon* **3**, 125 (1965).
58. F. C. G. Hoskin and P. Rosenberg, *J. Gen. Physiol.* **47**, 1117 (1964).
59. R. Martin and P. Rosenberg, *J. Cell Biol.* **36**, 341 (1968).
60. E. Condrea and P. Rosenberg, *Biochim. Biophys. Acta* **150**, 271, (1968).
61. H. H. Dale, W. Feldberg, M. Vogt, *J. Physiol.* **86**, 353 (1936).
62. W.-D. Dettbarn and P. Rosenberg, *J. Gen. Physiol.* **50**, 447 (1966).
63. R. L. Masland and R. S. Wigton, *J. Neurophysiol.* **3**, 269 (1940); W. F. Riker, Jr., G. Werner, J. Roberts, A. S. Kuperman, *Ann. N.Y. Acad. Sci.* **81**, 328 (1959); G. Werner and A. S. Kuperman, in *Handbuch Experiment. Pharmak., Ergw*, G. B. Koelle, Ed. (Springer, Heidelberg, 1963), vol. 15, p. 570.
64. S. L. Cowan, *Proc. Roy. Soc. London Ser. B.* **115**, 216 (1934); W. Feldberg, and A. Vartiainen, *J. Physiol.* **83**, 103 (1934).
65. J. C. Eccles, *J. Physiol.* **84**, 50P (1935).
66. P. W. Gage and J. W. Moore, *Science* **166**, 510 (1969).
67. B. Low, personal communication.
68. Supported by PHS grants NB-03304 and NB-07743, by NSF grant NSF-GB-7149, and by the New York Heart Association. I thank V. Tennyson for the use of Fig. 1.

Cybernetics in City Hall

An understanding of the principles of cybernetics can guide fundamental improvements in urban government.

E. S. Savas

The science which is parent to much of modern technology is cybernetics—the science of communiation and control in organized systems. The word itself, introduced and popularized by Norbert Wiener (*1*), is transliterated from the Greek word Κυβερνήτης. That same Greek word has also entered our language in a slightly different transliteration, and translation, as the word "governor." Etymologically, therefore, there is an equivalence between a governor and a cyberneticist, between government and cybernetics.

This equivalence is worth exploring. What happens when a cyberneticist, perhaps naively, assumes that big-city government is "an organized system" and casts his practiced eye on it? What does he see, and what can he tell us about applying the principles of cybernetics to cities?

The cyberneticist brings to his task the view that an organized, adaptive system is a goal-seeking ensemble which can sense its relation to its objective and modify its behavior in order to approach the objective more closely. The simple feedback-control diagram of Fig. 1 is the basic tool of the cyberneticist, and it suffices to illustrate the elements of such a system. The desired condition of the system is selected by some goal-setting process, entered into a comparator, and then tested against the actual condition, which is observed and reported by some process of information feedback. Any discrepancy between the desired and the observed conditions causes the acuator to act upon the system to reduce the discrepancy. The continuing, dynamic nature of this entire process results from the disturbances—that is, causative factors outside the system which upset the system and make it necessary to apply control action to counteract their effects.

The discerning cyberneticist can identify corresponding elements of this feedback control system in city government, even though the latter is far from being a simple system with a single goal. The goal-setting mechanism, which establishes objectives and priorities, is the mayor's decision-making process. A comparison of the desired condition with the observed state of the city results in action to reduce the disparity; municipal administration (that is, the bureaucratic processes of city government) constitutes this action element of the system—a provocative thought indeed! The system being acted upon is the city and its people. It is subject to external upsets that may be classed as social, economic, political, and natural. The output, or observed condition of this living system, is the state of the city. Feedback concerning the condition is transmitted to the mayoral decision center by way of an information system.

What happens when a cyberneticist, impelled by his students and his conscience to seek relevance, examines New York City's government? How would he interpret recent developments there in terms of the five basic attributes and elements of this cybernetic loop: (i) the overall dynamic characteristics of the process, (ii) the information system, (iii) administration, (iv) goal-setting, and (v) disturbances?

Dynamics of Urban Government

The first disturbing realization is that the natural time constants of urban systems are unrelated to the term of elected office. Thus, it is impossible for an official to show visible accomplishments in 4 years on a problem which may require at least a full generation—25 years—to solve. If Moynihan's thesis (*2*) is correct, for instance, then it will be necessary for a black male infant to grow to maturity, with his father as breadwinner and resident head of the house, before his family realizes its potential and acquires a life-style which puts it in harmony with the community.

Similarly, if it takes a year to determine the state of the system (that is, identify a major problem in a way which suggests approaches to its solution), another year to define objectives, to plan, and to allocate resources to attack the problem (in the annual budgeting ritual), and a third year to construct, staff, and test the appropriate administrative structure for implementing the plan, this leaves precious little time,

The author is First Deputy City Administrator, Office of the Mayor, City of New York. This article is based on an address presented at the Annual Symposium of the American Society for Cybernetics, Washington, D.C., in 1968.