BRAIN INFORMATION SERVICE

Society
for
Neuroscience

Fifth Annual Meeting

SOCIETY FOR NEUROSCIENCE

Fifth Annual Meeting

New York, New York
November 2-6, 1975

SUMMARIES OF SYMPOSIA BY:

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Brain Information Service / BRI Publications Office

University of California

Los Angeles

COVER ILLUSTRATION:

From a drawing by Andreas Vesalius showing only nine pairs of cranial nerves, published in 1539.

Editorial Supervision by:

Joyce M. Finzi-Fried

Citation form:

Society for Neuroscience, 5th Annual Meeting. Summaries of Symposia. (BIS Conference Report #43). UCLA, Los Angeles, Brain Information Service/BRI Publications Office, 1976. 151 pp.

The Brain Information Service is part of the NINCDS Neurological Information Network and is supported by contract NO1-NS-3-2306.

TABLE OF CONTENTS

THE CONTRIBUTIONS OF NEUROSCIENCE TO THE UNDERSTANDING AND TREATMENT OF MENTAL ILLNESS

(Grass Foundation Lecture)

Speaker: *Seymour Kety*
(Massachusetts General Hospital, Boston)

Reporter: *Charles Yingling*

Serious mental illnesses (schizophrenia and the affective disorders), though they are not major causes of death like cancer or heart disease, nevertheless rank with these among our most serious national health problems, in terms of the number of people affected, the interruption of their careers, the disruption and anguish of their families, the wastage of human potential, and the public cost. The magnitude of the problem is matched by our ignorance of the causes and prevention of mental illness. There have been many theories which, unfortunately, have tended to become doctrines unconducive to further research, since their adherents feel the answers are already in. However, those who do not know the answers have contributed much basic knowledge and are developing new techniques and approaches which make the search more promising than ever.

Some 30 years ago, one search for a biological substrate for mental illness resulted in the demonstration that chronic schizophrenics did not differ from controls in measurements of cerebral blood flow or oxygen consumption. Obviously, more subtle biochemical processes than the "power supply" to the brain must be involved in schizophrenia; however, only 30 years ago there was no indication of what these subtler processes might be. Many heroic and premature hypotheses were suggested before enough basic data was available; replications of these studies usually failed, leading many to conclude that there was no biological basis for mental illness. Biochemists turned to other more promising lines of research, even those who believed that a biological substrate did exist.

In the absence of a biochemical handle, genetic data appeared to provide evidence for a biological factor in mental illness. It was well known that serious mental disorders ran in families. Also, studies of mono- and dizygotic twins showed a higher incidence of schizophrenia in the monozygotic twin (genetically identical) of a

schizophrenic than in the dizygotic twin (genetically no more similar than other siblings). These studies are compatible with a genetic factor operative in schizophrenia, but are not conclusive. Many things run in families--poverty, wealth, pellagra (once thought for that reason to be genetically transmitted). Obviously, families share their life experience as well as their genetic background, and both influence the outcome. The environmental factor cannot even be considered constant in twin studies, as monozygotic twins look alike, are treated alike by their parents, have the same friends, are rarely separated, and generally develop a great deal of ego identification with one another, in contrast to most dizygotic twins. Therefore, especially in the absence of a clear-cut biochemical marker, although these findings were compatible with genetic transmission, environmental factors could still not be ruled out.

A study of familial patterns of manic-depressive affective disorders yielded the unexpected result that the concordance of these diseases in father-son cases was much less than that for father-daughter, mother-son, or mother-daughter pairs. This would suggest a locus on the X chromosome, which a father transmits to his daughters but not to his sons. Other factors known to be transmitted on the X chromosome (certain types of color blindness, blood group factors) showed linkage with manic-depressive psychosis in some families, again supporting the notion of an X-linkage. Although other studies have not demonstrated this linkage, a critical review of the literature supports the conclusion that a subgroup of manic-depressive disorders is associated with a factor transmitted on the X chromosome.

An approach which has been applied to schizophrenia is the study of adopted children, who get their genetic makeup from one family but share the environment of another. From a population of 5500 adopted persons, 33 were selected who had become clearly schizophrenic according to an agreed set of criteria. These were paired with 33 controls with no history of mental illness, matched for age, sex, and socio-economic status of the adoptive family. Over 500 adoptive and biological relatives were located, and most agreed to participate in extensive psychiatric interviews. These interviews were edited to remove references to adoption or the adopted relative, and were read by three raters who made independent psychiatric diagnoses and were then required to agree on a consensus diagnosis. A significant familial incidence of schizophrenia was found, but only in individuals genetically related to a schizophrenic adoptee. Of course, adopted children still are influenced by the *in utero* environment of the biological mother, and are exposed to at least some early mothering before adoption, so the operation of some perinatal environmental factors was not ruled out. However, the biological paternal half-siblings of adopted schizophrenics (who did not share the same maternal environment) also show a high incidence of schizophrenia which in them could only have been genetically transmitted.

From these studies, one cannot conclude that schizophrenia is a single unitary disorder, or make many inferences about the mode of transmission, since it may be a heterogeneous collection of disorders with different etiologies and different kinds and degrees of genetic and environmental influences. One can conclude, however, that genetic factors do play a role in a substantial part of schizophrenic and manic-depressive disorders. An environmental factor is not ruled out; in fact, twin studies conclusively demonstrate that genetic factors are not all-important, as the concordance for monozygotic twins is not 100%, but closer to 50%, leaving room for substantial environmental input. The environmental influences may be social or psychological, but they may also be biological. Significant interactions between non-genetic and genetic factors have been demonstrated in such diseases as diabetes and myasthenia gravis, the latter of which involves an auto-immune reaction against acetylcholine receptors; two preliminary studies have suggested an association between HL-A antigens and schizophrenia. If genetic factors are important in certain mental illnesses, they can only express themselves through biochemical processes. Recently, some indications of where those processes may be have emerged.

The synapses of the brain, at one time thought to be electrical junctions are now known to be chemical and offer loci where metabolic changes, hormones, and drugs may alter synaptic activity and through that the complex functions of the brain. In the last 15 years, a series of new drugs has been introduced with a high degree of specificity for the symptoms of mental illness: for example, the antipsychotics, antidepressants, and lithium. The impact of these drugs is not only in terms of new and more specific therapeutic measures, but also in terms of what their interaction with the brain can teach us. All of the drugs effective in schizophrenia produce a blockage at dopamine synapses, a conclusion which can now be drawn on the basis of metabolic, biochemical, electrophysiological, and molecular evidence. The mechanism of the antidepressant drugs is not so clearly established, although they do have in common the ability to enhance the activity of noradrenalin, dopamine, or serotonin at synapses; recent evidence is showing that lithium appears to enhance the activity of serotonin at synapses.

Unfortunately, one cannot infer pathology from drug action. For example, anticholinergic drugs have been useful in the treatment of parkinsonism, although the lesion is not in the cholinergic system, but in the dopamine system. Similarly, an effect on dopamine synapses may be effective in schizophrenia by way of an indirect effect on some other system.

Certain polypeptides are becoming increasingly interesting to those working in the field of mental illness. Some, thought originally to be exclusively involved in the release of hypothalamic

trophic hormones, are now known to be widely distributed through the brain. Prolactin release from the anterior pituitary is normally inhibited by dopaminergic activity so that the antipsychotic drugs produce a rise in the blood and cerebrospinal fluid levels of prolactin to a degree that is correlated with their therapeutic efficacy. An indirect effect of these drugs on prolactin or other hormones governed by the dopamine system may play a part in their therapeutic effects.

There are now a myriad of leads, which require much more basic information. More morphological information is needed about the dopamine pathways of the brain, especially the mesolimbic dopamine system, since the better-understood nigrostriatal system is more closely related to parkinsonism than to schizophrenia. The availability of new techniques, using horseradish peroxidase and tritiated amino acid labeling, make possible the mapping of pathways that were inaccessible just a few years ago. New immunochemical techniques allow tracing of various enzymes which regulate the synthesis or inactivation of various transmitters and permit the mapping of their pathways. A technique involving selective uptake of labeled deoxyglucose by active neurons has been developed which makes possible the visualization of functionally active pathways. These advances should greatly enhance the contribution of neuroanatomy and neuropathology to an understanding of the dynamic aspects of the brain.

Similarly, new data are becoming available on the neurophysiological processing of information by the brain, including the precise and elegant studies of sensory systems, motor programming mechanisms, and attentional processes. The neural systems for pleasure and reward, motivation, exploratory behavior, arousal, and sleep are beginning to be defined. All of these are affected in the major mental illnesses.

Powerful new analytical techniques are available in biochemistry, including mass spectroscopy, which is able to characterize with unassailable accuracy minute quantities of various substances. In some instances, this technique has shown that postulated biochemical factors in mental illness were probably artifacts. In one instance, however, the mass spectrograph has led to the identification in cerebrospinal fluid of 5 methoxy-tryptamine at levels 10 to 20 times higher in some patients with major psychoses than in nonpsychotic controls. This is especially interesting since 5 methoxy-tryptamine could be a precursor of an N-dimethylated derivative which is a potent psychotomimetic agent.

New cell culture techniques for tracing genetic markers have already been applied in what may turn out to be the first case of schizophrenia in which a clear genetic lesion has been discovered. A schizophrenic, mentally retarded patient with homocystinurea was found to have a deficiency in N-5, 10-methylenetetrahydrofolate reductase,

confirmed by cell culture studies. On the basis of this finding, large amounts of folic acid were administered and the schizophrenia disappeared, although the mental retardation persisted. The patient left the hospital, discontinued the folic acid treatment, and was later readmitted, again with the symptoms of schizophrenia, which were once again cleared up with folic acid. This is, of course, a rare disorder and hardly accounts for schizophrenia generally, since the vast majority of patients do not have homocystine in their urine. It suggests, however, that the syndrome of schizophrenia may eventually be found to be a heterogeneous group of different disorders with a final common path in behavior and mental state.

It is clear that the answers are not yet in. Instead, for the first time, we have a large background of basic information that is beginning to provide heuristic hypotheses about how the brain works and what may go wrong in mental illness. There is also a generation of competent neuroscientists and psychiatrists who are motivated to test them with the new tools now available. These form the base for a cautious optimism about the possibility of elucidating the biological substrates of the major mental illnesses.

STATE OF THE ART PANEL: NEURAL PROSTHESES

Chairman: *Karl Frank (Fundamental Neurosciences Program, NINCDS, Bethesda, Maryland)*

Participants: *Frederick T. Hambrecht*
J. Thomas Mortimer

Reporter: *Charles Yingling*

Karl Frank *(Fundamental Neurosciences Program, NINCDS, Bethesda, Maryland)* began the symposium by explaining that the term neural prosthesis refers to any device or system of devices by which the activity of the nervous system can be augmented in some desired fashion, usually for some practical objective. There are two general classes of neural prostheses: (1) mechanisms by which information from the nervous system is led outside the body for the purpose of controlling some external device such as an artificial limb (outward information transfer); and (2) mechanisms by which temporospatial patterns of excitation or inhibition are used to modify the state of the nervous system, as in a visual prosthesis which excites an array of electrodes on the visual cortex (inward information transfer). Inward information transfer has reached a far higher state of development than outward information transfer at the present time.

Frederick T. Hambrecht *(Director of the Neural Prostheses Program, NIH, Bethesda, Maryland)* discussed three forms of inward information transfer: electrophrenic respiration (EPR), auditory (cochlear) prostheses, and visual prostheses. EPR is an attempt to stimulate a peripheral nerve (phrenic) to activate the diaphragm for respiration in patients with hypoventilation syndrome of central origin (Ondines' curse) or high cervical spinal cord injuries. Bipolar cuff electrodes are implanted around each phrenic nerve in the neck. Receivers are implanted subcutaneously in the chest, connected to the phrenic electrodes, and coupled to a transmitter placed over the receiver outside the skin. The respiratory duration, the respiratory rate, and the amplitude of the diaphragm excursion can be controlled. This device has been implanted in over 80 patients, and in the longest case has been functional for over seven years. Problems due to atrophy and fatigue of the diaphragm, often encountered in patients who had been dependent on a mechanical respirator for a number of years, can

be overcome by alternate stimulation of one phrenic nerve and then the other. A major area for future improvement will be to incorporate feedback from respiratory or blood gases into the system, which presently operates open-loop with the rate and amplitude externally controlled. The future applications of this device will probably be more limited by the number of patients who can benefit from it than by any biological or technical difficulties.

The auditory (cochlear) prosthesis is being developed for people with a form of sensorineural deafness in which the hair cells are lost but a viable VIIIth nerve remains. The goal for such a prosthesis is to provide adequate hearing for conventional speech communication. An electrode array is placed into the scala tympani, in contact with the basilar membrane and in close proximity to the terminals of the VIIIth nerve. Current devices employ only a single channel, but multiple-channel systems are being developed. Approximately 20 patients have been implanted with the single-channel device to date. These patients report hearing sounds when the electrode is activated, but cannot recognize speech. Electrical stimuli below 100 Hz are typically reported as a "buzzing" sound; frequencies from 100 Hz to 1000 Hz are reported as "bell-like", "clear", or "tonal"; stimulation above 1000 Hz is reported as "tinny" or "noisy". Good pitch discrimination is only obtained below about 500 Hz. The main value of the single channel system has been as an aid to lip reading, by giving information about the rhythm or cadence of speech. There is also a psychological value to hearing sounds, and some information about environmental sounds is obtained. For true speech communication, a multichannel system will be necessary, but there are still many unknowns. Does a place-pitch relationship along the cochlea hold for electrical as well as acoustical stimulation? What is the optimal method for processing acoustical information and converting it into electrical stimuli? Will a multichannel system result in a significant improvement in information to the patient? Can the VIIIth nerve survive a long-term cochlear implant and electrical stimulation? Research into these questions is now under way.

The basis for work on a visual prosthesis is that electrical stimulation of the visual cortex, even in blind people, results in perceived spots of light with a topographical mapping between sites of cortical stimulation and the location of the perceived spots. Many investigators have proposed stimulating an array of such electrodes with appropriately processed output from a television camera as the basis for a visual prosthetic device. Such a device would not give normal vision but rather crude theater-marquee type information as an aid to reading and mobility. Several patients have been implanted with experimental arrays and phosphene maps have been constructed. One of the major problems is that when more than one electrode is stimulated simultaneously or sequentially, complex and unpredictable

phosphene interactions may occur: dropping out of one site, addition of new sites, smearing or streaking between sites, etc. Another problem is the trade-off between decreased latency but increased persistence of the perception as stimulus intensity is increased. These problems create difficulties in obtaining an adequate rate of information transfer into the visual cortex for a practical prosthetic device. Another major problem is the possibility of cortical damage as a result of long-term stimulation. Significant necrosis has been observed in the visual cortex of cats following 35 hours of continuous stimulation at parameters similar to those suggested for human visual prosthesis. On the other hand, one patient has had an array implanted for 7 years with no change in threshold or phosphene characteristics; however, these electrodes have been stimulated only very briefly, rather than continuously.

J. Thomas Mortimer *(Case Western Reserve University, Cleveland, Ohio)* discussed research on stimulation of the neuromuscular system to examine the feasibility of exerting external control over normal and paralyzed muscle for correction of scoliosis or restoration of hand function in patients with high spinal cord injury. There are two basic problems in such a program: (1) controlling the prime mover, *i.e.*, stimulating the desired muscle; and (2) allowing the patient to communicate with the controller. The problems with the prime mover concern the rapid fatigue of electrically-stimulated muscle, and the low force which can be produced by long-paralyzed muscle. The latter problem can be overcome with a program of electrically-stimulated exercise, but the rapid fatigue poses more of a problem. The source of the rapid fatigue is the fast-twitch glycolytic fibers contained in mixed muscles. In normal contraction, the small motor neurons which innervate fatigue-resistant aerobic (red) muscle fibers are recruited first, and the glycolytic (white) fibers, innervated by larger motor neurons, come in only at higher forces of contraction. However, the larger neurons have a lower threshold for electrical stimulation, so that recruitment occurs in reverse order and the easily fatigable white fibers are activated first. Since these fibers develop a higher twitch tension, their contribution to the overall force profile predominates, resulting in rapid fatigue. This is not appropriate since the primary goal for restoration of hand function is to obtain a prolonged, viselike grip for holding utensils, pencils, telephones, etc. It is not feasible with direct electrical stimulation of the motor nerve to alter the order of recruitment; therefore, research has concentrated on the feasibility of altering the properties of the muscle itself. This work is based on the hypothesis that the metabolic and physiological properties of the muscle are governed by the working demands placed on the muscle.

Electrodes were implanted to stimulate the tibialis anterior (mixed) muscle in cats at 10 Hz for periods ranging from 15 min to 24

hrs per day. Measurements were made of twitch tension as well as histochemical determinations of various enzymes related to glycolytic or aerobic metabolism. The oxidative enzymes change rapidly: with 15 minutes of stimulation per day for four weeks there is an increased capacity for oxidative metabolism, and a decrease in fast twitch glycolytic fibers; an increase in slow twitch oxidative fibers is seen with longer periods of stimulation. This is paralleled by an increased fatigue resistance of the chronically stimulated muscle, and a fused contraction at a lower stimulus rate, which helps overcome problems of fatigue at the neuromuscular junction.

For human applications, several percutaneous electrodes are implanted and stimulated out of phase. This results in a fused contraction when integrated at the tendon, but since the electrodes are in different parts of the muscle, problems of junction transmission or transition to anaerobic metabolism are avoided. The electrodes can be left in place for periods of over a year without difficulties.

The current status of the second major aspect of this program, allowing the patient to communicate with the controller, was illustrated with a film of a C-5 quadriplegic with electrodes implanted in the flexor component of the forearm. This patient has no voluntary movement below the elbow, and communicates with the controller by means of shoulder movements. By combining voluntary contraction of the biceps with electrical stimulation of the forearm flexors, the patient is able to obtain both pronation and supination of the forearm, and is capable of pouring water, drinking from a polystyrene cup, etc. The major problem with this system is that the only source of feedback concerning performance is visual, and the patient must concentrate on this in relation to the relative position of shoulder versus sternum in order to control the system. This requires a very high degree of concentration in order to maintain performance and avoid dropping objects, etc. If problems of long-term chronic recording are worked out, it may be possible for information from peripheral sensory receptors to provide feedback to the controller in a closed-loop system, even though this information is not available to the patient's conscious awareness. It may also be possible in the future to employ recordings from more central levels to assist the patient in controlling the system without the requirement for extreme concentration on the control, which can cause the system to become a burden rather than an aid. In summary, the feasibility of exerting external control over the neuromuscular system has been demonstrated; before the system can become a functional unit for people who need it, better means for relieving the patient of some of the direct responsibility for controlling the system must be worked out.

In the concluding discussion, Dr. Frank reiterated that most of the work to date has been on problems of inward information

transfer, and that much room remains for advances in outward transfer of information from the nervous system to external devices. There are many possible sources of information, including recordings of gross or single unit EMG, recordings from peripheral nerves or dorsal or ventral roots, or even cells in the spinal cord or the brain. Recently, monkeys have been trained to exert operant control over single cells in the motor cortex. However, there are problems in recording from single cells for prolonged periods of time.

Currently, electrodes have been able to record spikes distinguishable from noise for periods of 3 to 4 months, a significant improvement over the seconds to minutes of the early days of electrophysiology, but still not sufficient for use in long-term prosthetic devices. Another problem stems from the fact that cells may move with respect to the electrode over time, so that different cells may be sampled by a single electrode at different points in time. This could lead to the necessity of periodic retraining if a patient has learned to control the activity of a single cell which is then replaced, as seen by the recording electrode, by another cell. It will probably be necessary to feed back to the patient information about the firing of cells which are being used to control external devices. Recordings from a single controlled cell can give 3 to 5 bits of information per second to use for control purposes. Independent control of several cells could increase the bandwidth, but we should probably not expect too much along these lines; to get one cell to fire, probably many other cells must be used and it may be that 3 to 4 cells are the absolute limit that can be controlled independently.

It will undoubtedly be many years before prosthetic devices such as the ones discussed by this panel will be widely available. Nevertheless, it is possible to speculate on future developments. Neural prostheses will become more complex and flexible, and the range of things they can do will increase until they will approach the complete return of function of that part of the patient which they are replacing. But this does not pose a necessary absolute limit. There is no reason why prostheses cannot exceed normal functions, and future man-machine combinations may be developed which could be termed "supernormal", for example, a hand prosthesis could be designed to rotate continuously rather than being limited to 180°, with a wide range of speed and torque available.

RECENT DEVELOPMENTS IN THE NEUROBIOLOGY OF MEMORY

Chairman: *James L. McGaugh (University of California, Irvine)*

Reporter: *Charles Yingling*

Participants: *David A. Drachman*
Eric R. Kandel
Franklin B. Krasne
Mark R. Rosenzweig
Larry R. Squire

Eric R. Kandel (*Division of Neurobiology and Behavior, Columbia University, College of Physicians and Surgeons, New York City)* stated that it has recently become possible to apply a variety of cellular biological techniques to the study of behavior and simple forms of learning in a number of higher invertebrates. The nervous system of these animals, such as snails, leeches, and crayfish, contains only about 10^6 cells as compared to the 10^{12} cells of the mammalian brain. Individual ganglia, containing only about 2000 cells, may control a family of behaviors, so the number of cells committed to a single behavioral act may be a few hundred, or even less. In addition, the nervous systems of these animals contain large cells measuring hundreds or, on occasion, even a thousand micron in diameter, making it easy to apply a variety of cellular techniques. Many of these large cells are identifiable so that one can return to the same cell repeatedly in a series of experiments. As a result of these advantages, there are a number of instances in which it has been possible to work out in fairly complete detail the neural circuitry of a specific behavioral act. It then becomes possible to see what happens to the wiring diagram of that behavior when the behavior becomes modified.

Using the mollusk, *Aplysia californica,* Drs. Kandel, Castellucci, Carew, Byrne, and Brunelli have studied the mechanisms of habituation and sensitization as well as the mechanisms between them (Carew and Kandel, 1973; Castellucci and Kandel, 1974; Kandel *et al.*, in press).

The behavior which has been studied is the gill withdrawal reflex of *Aplysia* elicited by weak tactile stimuli to the siphon. This simple behavior exhibits the properties of habituation and sensitization. Habituation is the progressive decrease in the amplitude of the response when the stimulus is presented repeatedly. The