Meetings

Brain Research

One activity of the International Brain Research Organization (IBRO, UNESCO) is the organization and support of workshops, or visiting seminars, in various countries. Seminars are requested by local scientists wishing to become acquainted with disciplines of brain science that are not well represented in their countries, or to further their knowledge in areas in which they are particularly interested. Scientists who request the seminar plan the program; visiting scientists give lectures and laboratory demonstrations pertaining to the subjects selected. The audience (up to 50) is elected by the local committee and usually consists of young laboratory workers. Participants may come from the geographical region as well as from the host country. Visiting scientists are supported financially by the PHS and by IBRO.

At the second seminar (New Delhi, October 1964), 20 modern techniques encompassing the fields of neurophysiology, neuropharmacology, and neurochemistry were demonstrated. Two lectures each morning were followed by informal discussion.

A. Lajtha (New York State Research Institute for Neurochemistry and Drug Addiction) discussed the transport mechanism controlling the uptake and release of amino acid by the brain. The process is highly specific; there are separate carriers for the various classes of amino acids, regional differences, and differences during development. The brain barrier system (a collection of membranes) emerges as a specific metabolic control mechanism capable of transporting single substrates in or out of the brain or to or from specific areas when such need arises. Alterations of this control mechanism may cause specific pathological changes and should be considered in studies of the mechanism of action of several drugs.

Lajtha also discussed protein metabolism in brain. Most if not all the proteins present in brain are continually turning over at quite variable rates; some have a half-life of a few hours or less, others, of a few days or even months. There are significant differences among various brain areas, and during development protein turnover gradually slows. Protein turnover, which changes during excitation and inhibition, was also discussed by Lajtha with relation to the problem of axoplasmic flow. Present evidence regarding the breakdown of brain proteins was summarized, with emphasis on the important role of cathepsin and proteinase.

G. P. Talwar (All-India Institute of Medical Sciences) reported on his recent contributions on RNA metabolism in brain tissues. His report evoked a lively discussion of the relation between RNA metabolism and the storage of information in brain. J. J. Gosh (University College of Science and Technology, Calcutta) presented results on the effects of drugs on ribonucleoproteins in nerve tissues.

J. V. Passonneau (Washington University Medical School) discussed methods for assaying substrates and cofactors of the Embden-Meyerhof pathway in small samples of brain tissue. The concentration of these substrates changes when the glycolytic rate is increased many times by sudden ischemia (decapitation). Onset of this increased rate is characterized by decreases in glucose, glucose 6-phosphate, and fructose 6-phosphate, and by increases of all substrates from fructose diphosphate to lactate. The increased rate of phosphorylation of glucose and fructose 6-phosphate is a determining factor in the increase of the glycolytic rates; facilitation of the phosphofructokinase step is attributed to increases in inorganic orthophosphate or adenosine 5′-phosphate, adenosine diphosphate, and NH_4^+, which are capable of overcoming inhibition of this enzyme by adenosine triphosphate. Passonneau also demonstrated tools and techniques used for these microchemical analyses.

The importance of micromethods for discriminating between different components of nerve tissue (nerve cells, glial cells, blood vessels, and so on) was emphasized by E. Giacobini (Karolinska Institute, Stockholm). After discussing the sensitivity range necessary for such a microanalysis, Giacobini presented three different groups of techniques: (i) an ultramicroadaptation of the cartesian diver technique described by Linderström-Lang; (ii) the fluorometric cycling technique of Lowry; and (iii) the microanalytic technique for RNA and DNA described by Edström. These powerful analytical tools may be used to study energy requirements connected with excitability of nerve cells and ion pumps essential to maintain nerve function. Giacobini then reported his biochemical and electrophysiological studies of the properties of excitable membranes, for which he used the stretch receptor cell of the crayfish. The difficulty of analyzing and interpreting results of such microchemical studies was emphasized.

G. D. Pappas (Columbia University) used electron-microscope evidence in discussing the function of the endoplasmic reticulum in reference to the Nissl substance and the fine structure of exodendritic and axosomatic synapses. The structural specialization of the synapses was contrasted with the morphology of the electrotonic junctions. Pappas also presented electron-microscope data on the ontogenesis of cat neocortex, as contrasted with that of cerebellum and hippocampus. The development of the neuropile and changes occurring during formation of the blood-brain barrier were also considered.

L. W. Chacko (All-India Institute of Medical Sciences) presented a study of the lateral geniculate body carried out with the aid of classic neuroanatomical methods. R. P. Chaiurvedi (Medical College of Jaipur, India) spoke on the distribution of Purkinje cells in snakes and lizards.

Visualization of a transmitter within the neuron is a basic requirement for studies on neurotransmission; this was made possible by a histochemical method recently developed by Falck and Hillarp. The chemical background of the reaction involved and the application of this method to various tissues from vertebrates and invertebrates were described by C. Owman (University of Lund, Sweden). So far, only epine-

phrine, norepinephrine, dopamine, and serotonin have been found to occur in tissues; either other phenylethylamines and indole derivatives do not form highly fluorescent derivatives, or their concentrations are not detectable. The method has proved useful for studies of uptake, storage, and metabolism of biogenic monoamines; it has also made it possible to map out monoaminergic systems in hypothalamus, cerebral cortex, and brain stem, as well as in the spinal cord. Owman submitted that this evidence strongly supports the view that these monoamines may serve as neurotransmitters in different parts of the nervous system.

D. Purpura (Columbia University) discussed the manner in which intracellular recording from cortical and thalamic neurons was employed to study the origin and nature of evoked potentials and the mechanism of thalamocortical synchronization and desynchronization. He then drew attention to the usefulness of microphysiological techniques in analyzing different varieties of synaptic organizations. The changing properties in immature cerebral and cerebellar cortex were presented as a method for investigating this neuronal organization. Purpura showed that during maturation of cortical neurons the excitability properties of neurons undergo various changes that are indicated by characteristics of intracellularly recorded activities at various stages of development. Emphasis was placed on ontogenetic studies that have revealed the existence of powerful inhibitory effects in immature cerebral cortex; x-irradiation also was used in attempts to modify normal maturational patterns in cellular cortex.

Rhythmic movements of the peripheral respiratory organs, whether lungs or gills, are a common feature of all vertebrates and of most invertebrates. R. von Baumgarten (University of Göttingen) began his lecture on the correlation of patterns of neuronal discharges in the respiratory system by showing that the appropriate innervation of the peripheral machinery of respiratory muscles requires a brain apparatus able to integrate incoming impulses into a rhythmic stream of outgoing discharges traveling down toward the periphery. The respiratory muscles are usually divided into inspiratory and expiratory muscles. Physiological studies show that the respiratory center is very often correspondingly divided into antagonistic groups of neurons, even if, as is usually the case, the inspiratory phase of respiration is the only active phase, expiration being merely passive. In addition to originating a rhythmic form of breathing, the respiratory centers are known to perform what we call regulation of respiration with the help of intracentral and peripheral chemoreceptors. The respiratory center is not formed by a single pool of neurons as was assumed by Flourens; it is a complex of different neuronal pools connected by a self-inhibiting control system that regulates the activity of the different neurons. These neurons continue to discharge, even when all respiratory movements are blocked by curare-like substances; in this experimental condition, with all feedback impulses abolished, intracentral self-inhibiting mechanisms, similar to the Renshaw mechanisms, have been described. Von Baumgarten described other neuronal interactions whereby the respiratory center transforms a constant stream of incoming impulses into a rhythmic stream of outgoing impulses.

M. Mancia (University of Milan) discussed the neurophysiological mechanism during different stages of physiological sleep. A point was made in favor of the importance of measuring patterned activity. Sleep, which appears as inhibition of function, represents a pattern of interneuronal integration in which different structures actively function at different times; for instance, spinal post-tetanic potentiation, as well as mono- and polysynaptic spinal reflexes, is abolished during paradoxical sleep but not during physiological sleep. Mancia speculated that the spinal inhibition of paradoxical sleep may be presynaptic because it is not reversed by strychnine. However, paradoxical sleep is not characterized by a diffused inhibition because cortical responses to stimulation of the lateral geniculate body are enormously increased during paradoxical sleep. The study of interaction between a conditioning transcolossal stimulus and a test geniculate impulse revealed that during paradoxical sleep the facilitation is increased and its time-course is shortened. During light sleep, the testing response undergoes a long-lasting inhibition that is never observed in either wakefulness or paradoxical sleep.

A clear-cut example of integration between glucose concentrations in blood and patterns of neuronal discharge rates was presented by B. K. Anand (All-India Institute of Medical Sciences) in discussing integration patterns of the central nervous system with

reference to the functional importance of the limbic system. Anand opened a discussion on the relation between discharge rates of hypothalamic units and changes of some homeostatic conditions with a series of experiments, thus attempting to classify nervous regulation of food intake in the same category as the control mechanisms that regulate various other visceral activities which maintain the constancy of the *milieu intérieur*. G. S. Chhina (All-India Institute of Medical Sciences) dealt with the control of sexual behavior in monkeys by the central nervous system.

P. B. Dews (Harvard Medical School) stressed the importance of studying the regularities of the patterns of activity of the central nervous system which are revealed by measures of the behavioral output. He defined conditioned behavior and characterized it by examples in contrast with reflex behavior. Development of the scope of conditioning was outlined from the limited situation of Pavlov, which could deal only with behavioral responses induced by stimuli presented to the test object, to that of operant conditioning in which any response the animal makes can be followed by reinforcing stimuli and usually conditioned. Dews also described the process of shaping; with this term, he described the possibility of evoking in an animal unusual responses that can be conditioned with appropriate techniques. The concept of neighboring stimuli as a way to effect responses, even when the responses occur some time before the reinforcing stimuli, was also introduced; its value in making possible the conditioning of indefinitely long sequences of behavior was emphasized. The effects of conditioning were summarized as dynamic modulations of on-going behavior. Dews then described some actual patterns of conditioned behavior and related them to specific schedules of reinforcement. The differential effect of drugs on these behavioral patterns was finally discussed.

Lecturing on fluorometry and spectrofluorometry, W. Hammer (U.S. National Heart Institute) presented the theoretical background of the fluorescence phenomenon and also led a discussion of the theories and technical problems connected with the assay of biogenic amines in brain tissue.

Basic problems of drug metabolism, of interest in therapy, were discussed by J. R. Fouts (University of Iowa). Inhibition and stimulation of drug metabolism were presented to the audience

in their biochemical and clinical implications; stimulation of drug metabolism was shown by Fouts to depend on the synthesis of new enzymes in liver.

Malhotra (Lady Hardinge Medical College, New Delhi) introduced a discussion of the mechanism of drug action by describing original experiments on the role of cholinergic mechanisms in brain function as revealed by the action of various depressants of the central nervous system. This discussion was continued by E. Costa (National Heart Institute) who presented a provisional model of the integrated biophysical unit, which, in nerve endings, controls synthesis, storage, release, and metabolism of norepinephrine. Costa emphasized that synthesis, storage, release, and metabolism of norepinephrine are not unrelated phenomena and must be considered together in interpreting drug action. The action of various drugs that act on sympathetic tone was discussed in relation to the neurochemical transducer. The validity of this model was also investigated in adrenergic mechanisms present in the olfactory bulb of rabbits; data obtained in this structure were not at variance with the model prepared to explain the function of peripheral sympathetic nerve endings. In discussing the mechanism of action of reserpine, Costa pointed out that the effect of the alkaloid on brain concentrations of amine indicates that a new dynamic equilibrium has been obtained as a result of the drug action; therefore the rate of serotonin biosynthesis, higher than that of norepinephrine, becomes of paramount importance in explaining reserpine action. The fast turnover of serotonin, when only a portion of the storage process is blocked, assures that enough serotonin occupies receptors to produce a sedative response.

Both the liveliness of the discussions and Indian hospitality were admirable.

E. COSTA
Laboratory of Chemical Pharmacology, National Heart Institute, Bethesda, Maryland

Forthcoming Events

May

12–13. Control of **Water Quality**, natl. forum, American Soc. for Testing and Materials, Philadelphia, Pa. (ASTM, Committee D-19 on Industrial Water, 1916 Race St., Philadelphia 19103)

12–24. **Power Instrumentation**, 8th