NEUROLOGICAL STUDY UNIT

October 13, 1959

Hemiballismus, Rigidity, and the Basal Ganglia.* By J. Purdon-Martin, National Hospital, Queen Square, London.

Renewed interest in the clinical-pathological approach to basal ganglia disease has been occasioned by the extension of surgical procedures to this area. Anatomically, the internal capsule separates the globus pallidus and striatum laterally from the more medial subthalamic nucleus (corpus Luysii) and substantia nigra. Fiber connections show these ganglia to be grouped with the globus pallidus at the center, receiving fibers from the striatum and substantia nigra and having a two-way connection with the corpus Luysii. Two longer afferent pathways leave the globus pallidus via the ansa lenticularis and fasciculus lenticularis to end in the ventral thalamus. Afferent fibers come to these structures from other parts of the brain, those of cerebellar origin being the most important.

Evidence from clinical-pathological observation and from animal experiments indicates that tissue destruction limited to the corpus Luysii gives rise to a marked hemichorea, or hemiballismus, but with little reduction in muscle tone. Within limits, the underlying capacity for voluntary movement (such as touching index finger to nose) remains intact. Hemiballismus can be abolished by a surgical lesion placed either in the globus pallidus or in the ventral thalamus (pallido-fugal block). Again, in cases of idiopathic Parkinson's disease or postencephalitic parkinsonism in which muscular rigidity was a sole or major involvement, the cells of the substantia nigra are damaged or completely destroyed, and surgical evidence is accumulating that operative lesions in the globus pallidus abolish rigidity in these cases.

A destructive lesion cannot give rise to "positive" symptoms; the irregular impulses which enter the motor system must arise from and be transmitted along fibers that remain intact. Any pathological disturbance in the basal ganglia, therefore, must be considered in relation to the group as a whole. Hemiballismus and the muscular rigidity of parkinsonism interfere with voluntary movement by maintaining a continuous and excessive muscular activity. The anatomical arrangement of the basal ganglia suggests that the group acts through the globus pallidus. A lesion here or among its afferent fibers in the fascicularis lenticularis abolishes the positive symptoms and it seems that the responsible impulses must emanate from the globus pallidus. The corpus Luysii seems to act as a moderator of impulses from the globus pallidus. Destruction of the substantia nigra, with the corpus Luysii intact, leads to excessive muscular tone and rigidity; thus the substantia nigra would seem to exert under normal circumstances a direct or indirect inhibition upon the activity of the globus pallidus. The striatum as well seems to exert an inhibitory control.

The physiological conditions under which the mechanism for muscular activity contained in these structures is called into play are unknown. When

* See Purdon-Martin, J.: The functions of the basal ganglia. Lancet, 1959, 1, 999.
its action is blocked, no defect in normal function is apparent. It is suggested that the dynamic control of such a mechanism would hold it ready to be brought into operation in special circumstances.

D. M. B.

October 14, 1959

Neuro-ophthalmology. By David Cogan, Boston, Mass.

Dr. Cogan presented brief case histories of a number of patients suffering from brain lesions. In these patients visual difficulties were accompanied by other neurological symptoms. For lesions in the parietal and temporal lobes the signs and symptoms produced could be placed in three general categories:

1. Signs and symptoms associated with lesions of either side.
   (a) Optokinetic response (deviation to the side of the lesion)
   (b) Deviation of eyes with closure of lids (deviation to the side opposite the lesion)
   (c) Astereognosia and metamorphopsia
   (d) Confusion and inability to fix
   (e) Photopsia, hallucinations and illusions
   (f) Convulsive episodes
   (g) Brain stem compression and herniation.

   It is worth noting that the optokinetic response is independent of hemianopsia. In normal people the response is always symmetrical, although the absolute response varies from person to person.

2. Signs and symptoms associated with the dominant hemisphere.
   (a) Alexia
   (b) Aphasia
   (c) Acalculia
   (d) Finger agnosia (body agnosia in general)
   (e) Right-left confusion.

3. Signs and symptoms involving the nondominant hemisphere.
   (a) Topographic agnosia
   (b) Constructional apraxia
   (c) Dressing apraxia
   (d) Neglect of left side
   (e) Auto accidents (?).

   Dr. Cogan was not certain that 3(e) above should be put in definitive form, but in his experience patients in category 3 had shown a distinct tendency to have automobile accidents.

An additional category was concerned with lesions in the occipital region. Some of the characteristics of such lesions could be described by the following list:

   (a) Hemianopsia
   (b) Photopsia and hallucinations
(c) Pain in homolateral eye (?) 
(d) Denial of blindness 
(e) Loss of visual imagery 
(f) Convulsive deviation of eyes 
(g) Brain stem signs 
(h) Absence of other neurological signs.

Of these symptoms (h) was regarded as most characteristic, although exceptions could always be found.

S. J. F.

ZOOLOGICAL JOURNAL CLUB

October 14, 1959

Distribution of the Bathypelagic Fishes of the Genus *Melamphaes* in the Eastern Pacific Ocean. By Alfred W. Ebeling, Scripps Institute of Oceanography, La Jolla, California.

Early concepts of the zoogeography of the bathypelagic organisms, those found below 200-300 meters in the ocean, were based on the theory of widespread distribution, due to the uniformity of environmental conditions and the lack of large physical barriers in this realm. Recent studies, however, demonstrate that many bathypelagic species display a localization in specific geographical areas.

The distribution of individual species of the genus *Melamphaes*, consisting of 19 presently described species, generally conforms to the geographical location of distinct water masses in the Pacific Ocean. Water masses are usually delimitied by distinctive temperature and salinity characteristics.

Data for one species, *M. aconthomus*, as well as inferences from other studies, suggest that young and larval stages are more closely confined to their respective water masses than are the adults, which may wander beyond the limits of the breeding population. Adult fish are also commonly capable of diurnal migrations of several hundred meters, whereas the young ontogenetic stages are thought to be restricted to a narrower range of depths nearer the surface. Although physico-chemical features of water masses may be important in directly limiting the distribution of young stages, the biological patterns associated with water masses are believed more important as isolating mechanisms between species. Species of larger size, four to six inches, are associated with regions or water masses of relatively high photosynthetic activity, while dwarf species are generally found in the less productive areas. It is suggested that low food supply or different types of food in the less productive regions may have favored natural selection for these morphological differences. Further evidence for this theory comes from a single species found in two separate areas of different productivities; again the larger individuals are associated with the area of higher productivity.

W. Pearcy
ANATOMY SEMINAR
October 20, 1959

PROBLEMS OF BIOASSAY OF HUMAN URINARY PITUITARY GONADOTROPHIN. By R. Borth, University Clinic of Gynecology and Obstetrics, Geneva, Switzerland.

There are four essential problems which must be considered in the design of an effective hormone assay method: one, technique; two, reliability, which includes specificity, accuracy, precision, and sensitivity (in bioassay, specificity often has meaning only in terms of the end point used, since many biologically active compounds, e.g., the luteinizing hormone, have not been chemically identified); three, practicability, under which are subsumed speed, expenditure, and skill; four, sources of error.

To achieve a good bioassay, it is essential to secure a dosage-response curve for both the unknown and a standard. The standard must be chosen with care so that it is similar to the unknown extract. If the dosage-response curve of the unknown is not parallel to that of the standard, the two preparations are dissimilar, and the assay cannot be evaluated. Even with parallel dose-response curves, two preparations may be biologically dissimilar as evidenced by a variation in their relative potency when different end-points are used. By the latter criterion, some degree of dissimilarity has been demonstrated between gonadotrophin preparations obtained by various authors from human nonpregnancy urine.

There may be several reasons why two preparations are biologically dissimilar. Two or more active factors may be present in unequal ratios, and the two end-points used may be differently sensitive to such mixtures. A difference in inactive material affecting absorption, inactivation and transport may manifest itself differently, with regard to the time-concentration curve in the target organ, in two assay methods. Differences in toxicity may affect two end-points differently. Two responses may be differently sensitive to interfering substances such as synergists, antagonists, toxin.

In view of these possibilities, it would be unwise to interpret evidence of dissimilarity of gonadotrophin preparations too rashly only in terms of FSH/LH ratios.

R. BORTH

ZOOLOGICAL JOURNAL CLUB
October 28, 1959

A COMBINED BIOCHEMICAL, HISTOCHEMICAL AND ELECTRON MICROSCOPIC STUDY OF OXIDATIVE ENZYMES. By Russell J. Barnett, Yale University.

Recent studies on the localization of oxidative enzymes throw new light on the problem of relating function and structure in biological systems. The succinic dehydrogenase system of mammalian heart muscle has been localized by using potassium talurite as an electron acceptor. Following the reaction (as the substrate is oxidized and the reagent reduced by an enzymatic transfer of electrons), crystalline and particulate precipitates can
be detected with the electron microscope and are found to occur predominantly in mitochondria, the crystals being closely associated with, and oriented parallel to the cristae. Similar studies using tetrazolium salts as electron acceptors (as nitro- and iodonitro- BT), and high resolution electron microscopy, reveal that the final products of the reaction (formazans) are deposited on cristae in various parts of mitochondria.

Evidence of another type comes from electron microscopy of an isolated and purified preparation containing cytochromes, succinic dehydrogenase, and DPNH-oxidase isolated from heart muscle. The preparation was obtained by homogenization and repeated extraction with distilled water, coupled with centrifugation and precipitation with salt solutions. Enzyme systems that would still oxidize succinate or DPNH were associated with membranous structures in such preparations. Treatment with deoxycholate resulted in the removal of cytochrome c from the system; other absorption curves were for the most part unaffected. Electron micrographs of the remaining enzyme-containing system revealed paired membranous structures.

Thus, evidence favors the hypothesis that terminal oxidative enzymes not only are found in mitochondria, but also are intimately related to membranous structures therein.

PHYSIOLOGY SEMINAR

November 4, 1959

ANALYSIS OF CEREBRAL PERFUSATE FOLLOWING STIMULATION OF THE CENTRAL NERVOUS SYSTEM. By Loring F. Chapman, Assistant Professor of Physiology, Cornell Medical College, New York City.

The presence of a polypeptide responsible for local vasomotor control has been demonstrated by past investigations, notably those of Keele et al., who showed that a polypeptide was present in blister fluid, in fluid collected from painful joints, and in inflammatory pleural fluid. Ostfeld et al. demonstrated that a similar substance is present in tissue fluid removed from regions of local scalp tenderness during vascular headaches of migraine type. Hilton and Lewis described a proteolytic enzyme present in saliva and in saline perfusate of salivary gland; this enzyme formed vasodilator polypeptides when incubated with plasma proteins. These authors observed increased amounts of enzyme during heightened metabolic activity of the gland and concluded that the enzyme and polypeptides are responsible for local vasomotor control in the salivary gland. The properties of the polypeptides corresponded to those of "bradykinin," the name given by Roche e Silva, Beraldo, and Rosenfeld to substances produced on incubation of certain snake venoms or trypsin with serum, plasma, or plasma globulin. These authors reported that when such incubated mixtures were applied to smooth muscle (isolated rat uterus or guinea pig ileum), delayed, slow, and sustained contractions occurred.

These observations led to the study of the biochemical aspects of cerebrospinal fluid in clinical cases, from which it was concluded that increased amounts of "protease" and vasodilator polypeptides in cerebrospinal fluid are associated with (1) active inflammatory or degenerative disease of the
central nervous system, (2) vascular headache of migraine type, associated with sustained vasodilation, (3) prolonged noxious stimulation or pain (sustained excitation within the central nervous system), and (4) chronic schizophrenia. It is suggested that the protease-polypeptide system is implicated in local vasomotor control within the central nervous system, and when in excess the components of the system may be related to disease.

In animal studies carried out with Ramos and Corrado in Brazil and with Symmes at Yale University, a system was employed in which a polyethylene cannula is inserted into the lateral ventricle of cats and another into the cisterna magna or into the sub-arachnoid space. Solution can thus be flushed in and out with ease. In cats anaesthetized with Nembutal and so cannulated, the sciatic nerve was stimulated. In other experiments the cats were curarized and maintained on artificial respiration. Samples of cerebrospinal fluid were collected at 10-minute intervals and assayed. The samples exhibiting the greatest “protease” activity appeared approximately 15 minutes after sciatic stimulation. After 30 minutes the cerebrospinal fluid again exhibited the normal absence of protease activity. At the end of the experiment the cannula was perfused with dye in order to make a more detailed inspection of the area studied. In other experiments chronic cannulae were implanted in the lateral ventricle and in the sub-arachnoid space overlying the cortex.

This perfusion technique offers promise in future work, since it gives one the opportunity to study secondary biochemical and pharmacological effects of drugs administered peripherally. It allows the administration of drugs directly into the cerebrospinal fluid over a long time interval. In chronic preparations, the effects of sleep deprivation, for example, could easily be studied. The technique offers a useful research tool in the investigation of drug penetration into brain tissue, the short and long term effects of drugs on brain metabolism and function, and of metabolites released into the cerebrospinal fluid during stress.

G. VIRGINIA UPTON

JOHN PUNNETT PETERS MEMORIAL LECTURE

November 17, 1959

THE CLIMATE FOR THE CULTIVATION OF CLINICAL RESEARCH. By Maurice B. Strauss, Boston University and Tufts University Schools of Medicine, Boston, Massachusetts.

John Punnett Peters believed that the special province of the clinical investigator was the study of disturbances created by nature in man. Fully aware that such research was more difficult than animal or test-tube investigation, he did not shrink from it and his work was never far removed from the patient. Two trends, both alien to Dr. Peters’ creed, are now visible on the contemporary horizon—one, the divorce of the medical scientist from the bedside, and the other, a preoccupation with mathematical, biochemical, and biophysical techniques. Neither is new. The 17th century, during which medical thought was oriented to the exact sciences, saw the rise of iatromathematical, iatrochemical, and iatrophysical schools (translate biomathematical, biochemical, etc.). Significant discoveries were made but the pre-
occupations of the discoverers was with hypotheses: each school believed that all disease could ultimately be explained in terms of a single unified system—mathematical, chemical, or physical. The study of the patient was neglected, and medicine suffered while physicians indulged in violent polemics. The inevitable reaction was accompanied by disinterest and hostility to the really important discoveries that had been made. It required Claude Bernard in the mid-19th century to reorient medicine in the direction of science. He made it abundantly clear that although there was but one order of nature, there were many techniques with which it might be studied. Each had its own problem and its own point of view, and confusing these could only lead scientific investigation astray. The complexity of the biological sciences, necessitating the help of all the other sciences, often caused increased confusion.

This confusion, in part, stems from a metaphysical assumption widely accepted in the 17th century and still prevalent today among biological scientists although long since rejected by physicists—the assumption that the properties of a whole system can be fully deduced from information about the behavior of its isolated parts. This assumption neglects the fact of organization, well recognized by the physicist who knows that an electron is only an aspect of a total situation, the major part of which is the rest of the apparatus, and that the quantum theory has clearly demonstrated that situations must be encountered as wholes. Isolation of parts produces artefacts not present in nature.

Until the biological scientist rejects this ancient but false assumption he will not be aware of the fact that the terms “more basic,” “more fundamental,” and the like have no meaning when applied to one or another division of science and that there is no “higher” and no “lower” among the disciplines employed in medical research.

Clinical investigation is arduous. It is not for those who suffer from the spiritual distemper of our time—the desire to make a “fast buck.” It may not reward its disciples with a succession of papers turned out with clock-work regularity. It may not speedily win them research grants or academic promotion. However, it cannot be denigrated on the basis that it is concerned with a different level of organization than biochemical or biophysical research. The clinical investigator can repeat with Dr. Peters one of his favorite quotations: “The proper study of mankind is man.”

M. R. STRAUSS