Edited by
HAROLD E. HIMWICH

BRAIN METABOLISM AND CEREBRAL DISORDERS

SECOND EDITION

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Galesburg, Illinois

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For Harold Himwich:

A Foreword and an Appreciation

It is flattering and delightful to be invited to write a preface to a book concerned not only with a subject of longstanding interest to me, but with long-standing and cherished friends. The subject of brain chemistry, or neurochemistry, was drawn to my unsuspecting and uncomprehending attention in 1928 when, for no apparent reason, I was invited to form a chemical division in the Deutsche Forschungs Anstalt für Psychiatrie in Munich, Germany, with none other than the great chemist, Richard Willstatter, as my advisor. My contributions to brain chemistry were minor, consisting of establishing a laboratory and initiating work on chemical transmitters. It soon became apparent that it was prudent to leave Germany because of the increasing threat of Nazism. Unfortunately, only one person in the United States had ever heard of neurochemistry. That person was my instructor in Cornell Medical School, Harold Himwich, who made up for the dearth of scientists interested in the subject.

On returning to this country to work under Donald Van Slyke, I bade farewell to the discipline of brain chemistry by writing a book on the subject which promptly became a "publisher's remainder." Some years later, I returned to the field tangentially through our work on serotonin, which, to our amazement, we found in the brain, exemplified in the "serotonergic" neurons. Most of this is trivia except for the hope that, in a small measure, it may have nudged Himwich ever-so-slightly into becoming the doyen of brain chemistry, crowned by his formation, in 1951, of the Psychiatric Research Laboratory at Galesburg, Illinois, felicitously named by him "Thudichum" laboratory in honor of the long forgotten J. L. W. Thudichum, who died in 1903. Himwich carved a remarkable career for himself.

Himwich himself has written, in the proper preface, a resumé of the contents of the present volume and thereby saved me an enormous task for which I am scarcely fitted. The result is I could read the manuscript for pleasure. However the reader will read it, I am sure he will agree it is up to the Himwich standard, which says all that needs saying on this score.

I cannot avoid comparing the body of knowledge encompassed by this book with that when Harold and I were very young. The only living persons who might be aware of the enormous development, so far as I know, would be Judah Quastel and K.A.C. Elliott. The understanding of the brain's palpable functions has been vastly extended. The past 45 years have been used by younger scientists to demonstrate their mettle in furthering the work, and they have not failed.

But in the area of the transcendental function of the brain, success has been elusive. The argument continues as to whether thought is merely an integral part of an ever-increasing complexity of chemical functions or is a function not understandable by current methods of thinking. This is not a trivial question with an obvious solution, as many overconfident researchers would lead us to believe. Anyone reading the brilliant and highly controversial monograph of John Eccles, "Facing Reality" (Springer, N. Y. 1970), must realize this truth. It is a topic I remember with pleasure, because it was the subject of discussion with my old associate, Homer Smith, of renal physiology fame, and with Harold Himwich, under the mutual influence of a martini with a twist!

The contents of the book are not easily identified as belonging to strict vocational classification. Himwich himself takes the broad philosophical functional approaches of Jackson, Moruzzi and Magoun, Jasper and the Vogts, and then proceeds to a more searching analysis of cerebral metabolic functions with important additions by Sachs. Meyer and Barbeau exemplify the clinical-chemical aspects of disordered cerebral metabolism, while the more strictly physiological aspects are treated by Baptista, Oldendorf and Ingvar, and Lassen.

The current way of writing a book, more likely than not, consists of the editor asking his friends to write chapters for which they are competent. True editing is, therefore, seldom tolerated with any grace by the contributors. The result, all too often, is an expensive series of mini-monographs to which the editor has contributed the time of his secretary and postage. For example, I am in receipt of a two volume work with three editors, only one of whom added two small articles. Not so in the case of this book, in which Himwich has provided six of the twelve chapters. Clearly, Himwich belonged to the old school that believed that, when you wrote a book and took credit for it, you wrote at least an important part of the work.

It is one of the prerogatives of older age to look back and tiresomely remind the next generation that there was a generation before it which fought battles just as difficult as those it faces. For that reason, I want to emphasize how much Harold Himwich, along with Williamina, have done to make the past a rich contribution to the future. Harold's life was a fine one; he leaves a great heritage and challenge. The present generation must learn from what he wrought so they may go and do likewise. The past must not be screened off from the young, for if it is, they will live to regret it. People can no more successfully ignore their intellectual heritage than their genes. It is a privilege to ally myself with the contributors to this volume in an ever-so-small way.

Irvine H. Page, M.D.

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CHAPTER 1

Introduction

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Outstanding in its influence on the author is the theory of Hughlings Jackson (1884) on the phyletic organization of the central nervous system. For purposes of clarity and also because of its import in the composition of this book and in the interpretation of experimental results, the theory of Hughlings Jackson is rehearsed as follows:

The brain of man as we see it today looks like a static structure which has existed unchanged for eons. But when it is examined more closely in the light of the phyletic conception, we see that it has come to its present construction as a result of a long series of accretions, beginning with the spinal cord and medulla oblongata and spreading in a cephalad direction, layer upon layer, until the cerebral hemispheres form the greatest mass of the brain. It is not to be supposed that each level is independent of its predecessors, but rather that it exists with specific relationships, both anatomically and physiologically, to the phyletically older portions (Tilney and Riley, 1928). Owing to these relationships, the central nervous system may function as a unit, but a unity which is brought to a higher plane of integration with each successive step. The human brain is undoubtedly the latest arrangement of the central nervous system, but not necessarily the final one. Hughlings Jackson wrote of three levels: the lowest, consisting of the spinal cord, medulla, and cerebellum; an intermediate one, including the motor cortex and striatum; and the highest, formed partly of the prefrontal cortex. In this volume we are concerned with Hughlings Jackson's conception of levels of function rather than his specific anatomical delimitation of these levels.

Probably the earliest aquatic vertebrate, as far as organization of the central nervous system is concerned, was chiefly a bulbospinal animal, and irrespective of the subsequent development of the brain, the bulb always remains an important center especially for viscerosomatic integration. In the course of evolution, each additional part of the brain did not accrue in a haphazard fashion but took root directly in front of a preexisting part, and always toward the oral end of the animal. Sir Charles Sherrington (1933) has expressed this conception.

> That leading end, the head, has receiving stations signalling from things at a distance, things which the animal in its forward movement will next meet. A shell of its immediate future surrounds the animal's head. The nerve-nets in the head are therefore busy with signals from a shell of the outside world which the animal is about to enter and experience. The brain has thus arisen where signalling is busiest and is fraught most with the germ of futurity. Small wonder then that the brain plays a great role in the motor management of the muscle. Nerve management of muscle resolves itself largely into management of nerve by nerve, especially by brain, more and more so as evolution proceeds. With no greater equipment of muscle the superimposed amount of nerve becomes greater and greater; each new nerve-growth seems to entail further nerve-growth. Fresh organization roofs over prior organization. Brain is an example. "So on our heels a fresh perfection treads." But were it a government office we might be suspicious. This brain of ours is a perfect excrescence although our endowment of muscle remains but moderate.

To climb the phyletic ladder from our remotest ancestors through the fish, amphibia, reptiles, and mammals would entail a tremendous volume of description, which is not the point of this treatise. The general trend of this process of cephalization, or concentration of neural functions in the oral end of the animal, may be described briefly: As far back as the fish the brain is divided into five portions as it is in man, but in the fish and amphibia the chief site of integration for sensory and motor impulses lies in the midbrain. In these species the highest portion of the brain consists chiefly of the olfactory bulb, and the cerebral cortex, which becomes all important in man, is represented only by a thin layer of cells. On further ascending the phyletic scale to reptiles and birds, as well as mammals, the subcortical structures immediately anterior to the midbrain become more prominent as the organism achieves greater coordinating control. Last, the cerebral cortex, though getting off to a late start, gradually attains more complexity of structure and diversity of function until in the lower mammals it surpasses all other regions, and in the primates, especially in man, forms the largest and most complex part of the cerebral tissue. The proportion of neocortex is lowest in rodents, increases in carnivores, and is highest in primates (Harman, 1957). The ratio of neocortex to brain in prosimians, monkeys, apes, and man is 50.5, 66.8, 74.4, and 80.4%, respectively.

Similar phyletic relationships are seen within the segments themselves as well as in the brain as a whole. Close examination of the most recent layer of the brain shows that it is divided into two portions—the phyletically newer cerebral hemispheres and the more primitive subcortical basal ganglia. These motor ganglia, in turn, are made up of the neostriatum and paleostriatum. Such a division is also found in the thalamus, the midline nuclei being comparatively ancient sensory centers, while the other nuclei developed along with the cerebral hemispheres and serve as way stations for sensory impulses relayed on to the cortex. The cerebellum may likewise be divided into parts of different phyletic origin (Dow, 1942). The paleocerebellum makes connections with the cord and the vestibular nuclei of the medulla, while the neocerebellum was developed simultaneously with the motor and sensory areas of the cerebral cortex.

Though each part of the brain is capable of subserving special functions, the brain acts as an integrated unit because of the anatomical and functional relationships existing among its constituent parts. It would seem that once a section is formed, it is never scrapped, but is retained and combined with the succeeding phyletic layer, continuing to play its part under the guidance of this newer layer. Stephan and Andy (1969) have suggested that the great increase in neocortex within the primate order indicates a process of "neocorticalization." It is possible either that the functions in nonmammalian vertebrates subserved by older cortical areas or subcortical structures are subserved by neocortex in primates and other mammals or that there is a greater dependence of functions on the neocortex as it increases in size (Stephan et al., 1970). Passingham and Ettlinger (1974) have referred to this as "progressive neocorticalization." This striking increase in size of the brain and neocortex within the primates may be correlated with ability. An involvement of the association areas and a relationship between their size and learning have been demonstrated by lesions of the brain.

Evidence for such a conception is found not only anatomically but also physiologically. Each portion of the central nervous system, even the lowest—the spinal cord—retains within it the centers for functional integration. The spinal animal (Sherrington, 1911), a decapitated preparation kept alive by artificial respiration, still responds to stimulation with an approprate muscular action. Though these primitive reflexes are preserved even in the highest animals, they are nevertheless modified by the newer layers. The motor expression of their activities can take place only "with the permission" of the higher centers. In a word, the recent levels preside over and dictate to the older and less specialized ones, holding them in check. It is necessary to have such an hierarchy of organization because the newer parts bring to the central nervous system a more delicate sensory discrimination and a finer execution of motion. In this connection, not only are tactile sensation and perception of pain more accurately appreciated and localized when the cerebral hemispheres are active, but motor responses are better adapted to stimuli. For the organism, however, to take advantage of these improved capacities, the behavior of the lower portions must be subjected to the control and regulation and the inhibition and reinforcement of the higher planes. Examples of inhibition and reinforcement are legion and many are presented in the present text, but a most convincing experimental proof for inhibition comes from the work of Hines (1937), who demonstrated that stimulation of a strip on the anterior border of the motor cortex (4s) in the monkey suppresses current activity, in this instance tonic extension of an extremity, and that ablation of that strip results in spasticity due to removal of inhibitory influences.

Charles Darwin's work (1896) established the theory of evolution of species. Hughlings Jackson's conception is a special application of Darwin's theory to the central nervous system. The importance of this interpretation appears not only in the analysis of normal physiology as indicated by the fact that the caudad sections of the brain function only under the guidance of the more cephalad ones, but it is also of practical value in explaining the origin of pathological phenomena. An abnormal clinical manifestation may arise either from stimulation of some part of the brain or constitute a release phenomenon as a superior part of the brain gives way, permitting the unrestricted activity of a lower and more primitive area. This segregation of the regions in the brain and their interactivity is of extreme consequence in seeking a diagnosis and treatment for cerebral disease. Because complexity of organization is accompanied by susceptibility to deprivation of cerebral energy, the changes observed in anoxia, hypoglycemia, and anesthesia, for example, are a mixture resulting from failure of the newer parts of the brain and hyperactivity in the older portions.

As indicated in the frontispiece, Jackson (1884) observed changes of two types with injury of the brain. The functions of the parts that have been destroyed disappear—the phenomenon of "dissolution." On the other hand, entirely new "mental symptoms" appear in their place, signs of release from higher control. Thus, Jackson came to his conclusion by clinical studies of his patients. Approximately 90 years later, Eugene Roberts (1972) independently developed the same conception of the organization of the central nervous system. Roberts' ideas of the inhibition of the lower regions of the central nervous system by the higher ones in hierarchical arrangements and the loss of inhibition emanating from the highest levels and release of the lower ones fit in with Jackson's interpretation of the phenomenon of dissolution. Roberts had, however, the advantage of the intervening years of advances in the neurophysiological sciences and could, therefore, suggest a probable mechanism of action.

According to Roberts, the central nervous system consists largely of genetically programmed circuits that can be released for activity by the inhibition of pace-setter or command neurons at the top of the neuronal hierarchies. In behavioral sequences he finds that genetically preprogrammed circuits are released to function by inhibition of neurons that are tonically holding the command neurons in check. The activity of such circuits would be regulated by neurons exerting tonic, inhibitory effects on the command neurons. If a behavioral sequence involved the voluntary movement of a limb muscle, the command neuron might be held in complete check by the tonic action of inhibitor neurons. The presumption, therefore, is that sensory input could act by disinhibiting the spinal neurons

A second conception of the functional organization of the central nervous system found root in the observations of Moruzzi and Magoun (1949), as well as Jasper (1949) and Bremer (1954). If the conception of Hughlings Jackson may be considered that of a horizontal organization, the more recent one might be characterized as vertical. As emphasized by Livingston et al. (1954), the central nervous system may be regarded as divided into three vertical columns extending throughout the entire length of the central nervous system. The first includes ascending spinal pathways carrying sensory impulses that are relayed by the thalamus to specific sensory areas of the cortex. The second column consists of the descending motor pathways of the corticospinal tracts. Between these two columns is a third composed of indirect connections: association areas of the cerebral cortex, the reticular formation of the brain stem, and the extrapyramidal motor tracts descending to the anterior horn cells of the spinal cord. The third column also possesses ascending functions in the two parts of the activities of the mesodiencephalic activating system combining the reticular formation (Rinaldi and Himwich, 1955a,b) with functions which are continued in a rostral direction by the diffusely projecting thalamocortical unspecific projections. The vertical conception presents another analysis of the functional organization of the central nervous system. This point of view, like the horizontal one, yields a matrix within which some of the functions of the central nervous system can be explained, but is of less general application as its use is hindered by the very gross differentiations of the central nervous system, thus making it impossible to pinpoint what has happened in a particular nucleus. It is more difficult to use as a heuristic hypothesis than the horizontal conception because it is not as accessible to anatomical dissection. However, in a location where vertical dissection is relatively simple, such as in studies of the visual tract, including retina, geniculate body, superior collculi, and visual cortex, this concept may be used advantageously.

A third viewpoint is that of the Vogts' (1925, 1935), whose studies revealed that injurious substances may affect the various cerebral areas in such selective manner as to indicate that some are especially susceptible to a given toxic substance. They suggested a physiocochemical basis to explain the greater sensitivity exhibited by some brain structures in comparison with others. Later histochemical researches revealed additional evidence for the third type of stratification of cerebral functions, for example, anesthesia with barbiturates and convulsions due to picrotoxin produce selective injuries in the cerebral neurons of dogs (Swank and Cammermeyer, 1949; Cammermeyer and Swank, 1951).

Another hypothesis of the functional organization of the brain has been called "systemogenesis" by its chief proponent, Anokhin (1964). Anokhin postulated that development follows a pattern which allows maximum adaptation for the survival of the neonate. Two examples are presented to illustrate Anokhin's idea. Among the earliest reflexes to develop in the human baby and in the newborn of some infrahuman primates are sucking and grasping. The neurons controlling sucking mature earlier than other neurons of the facial nucleus, and the innervation of M. flexor digitorum is the first of that group of nerves to become mature. During this stage the nerve of the flexor muscle is differentiated while others, for example, the intercostal nerves, have not yet achieved as mature a degree of differentiation. Again, as previously seen in the concept of Livingston et al. (1954), its application in terms of biochemical development has not been widely used, and the difficulty lies in the dissection of the material for biochemical study.

In considering the relationships between the sequence of events in neurogenesis and the emergence and refinement of behavior, Coghill (1929) from his work on the salamander (*Amblystoma*) hypothesized a dominant organic unity in the development of behavior and saw the emergence of local reflexes as a special feature within a more diffuse but dominant action of the whole organism. He concluded that the local action of an appendage is not a primary but a secondary behavior pattern derived from the total pattern by a process of "individuation."

However, Hamburger (1968) questioned the applicability of generalizations from studies on the salamander and emphasized that early movements in the chick embryo are not integrated, but are aimless and random (Hamburger, 1971). Hamburger's finding implies regional, unintegrated neural development as opposed to Coghill's concept of organized neurogenesis.

It is possible that the theories of Coghill and Hamburger and of others, for example, Anokhin's theory of systemogenesis, are not inconsistent, but that the emergence and the interaction of inhibitory and excitatory influences may vary in different species at different ages, whereas the basic patterns in the development of neurogenetic and physiological events may be generally the same.

It must be kept in mind, however, that none of these theories is absolute. Each may be called upon when its use will yield the most productive interpretation of the results. Much of the work in this book bears an intimate relationship to the theme on neurophylogenesis, the oldest but not the only theory of the maturation of the brain still entirely viable, and much of our evidence not only supports this hypothesis, but extends its usefulness into biochemical, morphological, and clinical fields.

Probably the earliest data on the functions of the central nervous system were acquired through clinical observations of the diverse effects of accidental injuries and of different forms of cerebral disease on the brain. Later a second source of information became available when experimental investigation came into use, for the functions of component parts of the brain could be explored by noting the effects of their mechanical, electrical, or chemical stimulation. Conversely, the effects of the extirpation of the same structures on behavior and adaptive responses could be examined. The chemical analysis of cerebral constituents took its place among the advances in methodology concomitant to the development of the fundamental sciences. Electroneurophysiological studies of spontaneous or induced modifications in the electrical potentials of cell groups or of single units yielded information of significant value.

Biochemical analysis of the brain involves, among other techniques, the analysis of the oxygen and carbon dioxide exchanges in the brain, commonly referred to as *respiratory metabolism*. Cerebral tissues freshly excised from the living organism are similarly studied with the aid of appropriate apparatus. It is also possible to examine the brain with all its anatomical connections and physiological relationships intact by analyzing cerebral blood samples for their gaseous and chemical exchanges. In animals the usual procedure is to trephine the skull (Himwich and

Nahum, 1932) so that venous blood may be collected from the longitudinal sinus. Comparison of the oxygen content of this blood with that of the arterial blood entering the brain yields the A–V oxygen difference/100 ml blood. A second necessary datum in the calculation of the oxygen consumption of the brain is the quantitative measurement of cerebral blood flow; that factor can be supplied by measuring the cerebral blood flow directly, as was done, for example, by Ingvar and Söderberg (1956). Multiplying the A–V oxygen difference by the cerebral blood flow yields the metabolic rate or the oxygen consumption of the brain for a given time. Myerson developed the technique whereby cerebral blood can be withdrawn from the brain of human beings (Myerson et al., 1927). By tapping the internal jugular vein, Myerson and colleagues were able to collect samples of blood returning, almost entirely, from the brain, and by measuring the oxygen content of this venous blood and comparing it with that of the arterial blood going to the brain, to obtain the A–V oxygen difference for that organ. It is difficult, if not impossible, to make direct examinations of human cerebral blood flow. Kety and Schmidt (1945, 1948a) subsequently achieved an indirect method whereby they determined cerebral blood flow quantitatively by measuring the mean transit time through brain tissues of a metabolically inert freely diffusible indicator as it was absorbed by that organ from the arterial blood and released into the venous blood. Kety and Schmidt used nitrous oxide. The data provided by their methods greatly enhanced the significance of results made available by Myerson's previous discovery. Thus, it became possible to make quantitative analyses of the oxygen consumption of the brain. Many of the techniques for determining global cerebral blood flow that were developed later also employed the principles of Kety and Schmidt, and thus may be considered modifications of their method. This volume contains many of the results obtained by Kety and his co-workers on human cerebral blood flow and cerebral metabolic rate in health and disease as well as the later observations on regional cerebral blood flow by Ingvar and Lassen in Chapter 8. If the indicator employed is a nondiffusible radioactive gamma-emitting radionucleotide and is given via the carotid artery, its uptake in the brain as well as its elimination from that organ, i.e., main transit time, can be recorded by the reading of multiple detectors over the brain, for example, continuous recording of gamma cameras. They show quantitative variations in blood volume and achieve measurements of regional cerebral blood flow.

The material of the text falls into two distinct divisions. The first part, "Energetics," describes the methods by which energy is elaborated, as well as distributed, to support nervous activity. The second part, "Patterns of Nervous Activity," explains energetics in terms of behavior.