ADVANCES IN NEUROENDOCRINOLOGY

Edited by

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FOREWORD

ACCORDING to notes taken in an endocrinology course in 1939, the word "hypothalamus" was mentioned only twice. Today, some 20 years later, a course in endocrinology not based on an understanding of the hypothalamo-hypophyseal axis would be unthinkable. The participation of the nervous system in the management of endocrine affairs was then restricted to such "exceptions" as induced ovulation, LTH release in rats and mice or milk letdown. Otherwise we were quite content to explain all endocrine events on the basis of hormonal feedback mechanisms which governed the "endocrine orchestra" and told the "master gland" to speed up or to slow down. In fact, even today it is not quite clear why two control systems, the endocrine and the nervous, have evolved in parallel to manage the endocrinology of animals. In perusing the contributions of the various authors who are concerned with the participation of the nervous system in the release of this or that hormone, one is struck by their emphasis, at least under experimental conditions, on the use of stressed animals. The question arises whether the nervous system participates in hormone release only in "stress" situations (in the broad sense of that word), while the hormonal releases involved in the "stressless," day-to-day living, are left to the hormonal feedback mechanisms which lack speed but which are capable of taking care of the daily needs for the production and release of such hormones as somatotropin, TSH or even corticotropins when the latter are not needed to alleviate an immediate and urgent demand. There is no doubt that many such questions remain to be answered. The present volume is intended not as the last word but only as a summary of neuroendocrinology of vertebrates up to December 1961, when this symposium was held.

According to the Chinese philosopher, Meng-Tse (372 to 289 B.C.), a gentleman "when he makes a framework, leaves a loose thread hanging" for he thinks of those who are to continue his task. I think that by this token all participants in the symposium were "gentlemen," for we showed great concern for those who will continue the task and left loose threads dangling in great profusion. It will be interesting to see how many of these are tucked in and secured before the next symposium is held.

In the process of editing the manuscripts, it became apparent that the length of the book had to be reduced as much as possible in order to keep publication costs within the limits of funds available. Accordingly, I took it upon myself to edit out as many seemingly unneeded words as possible and to eliminate from the text most references to names or individual workers. This editorial highhandedness displeased only one or two contributors and I want to apologize to them and to assure the reader that any shortcomings in the style of individual papers should be attributed to me. Similarly, the preferences of some contributors for "hypophysial" *versus* hypophyseal, and for the suffix "trophic" *versus* tropic, etc., had to be ignored in the interests of some degree of uniformity.

The program was jointly organized by Drs. R. Guillemin, R. T. Hill and A. V. Nalbandov with the help and advice of members of the Endocrinology Study Section of the National Institutes of Health, as well as other scientists, to whom the committee is grateful. The following members of the Study Section served as chairmen of the various sessions: Drs. A. Albert (Chairman of the Study Endocrinology Section), I. Geschwind, S. S. Fajans, R. A. Huseby and G. W. Liddle.

Hilda Banks (Mrs. E. M. Banks), through her intelligent and efficient handling of presymposium correspondence and bookkeeping, made the details less tedious. My wife helped by her patient realization that an editor is a "galley slave" ("a criminal condemned to such work; figuratively, a drudge"—Webster).

Finally, I would like to acknowledge the great help received from staff members of the University of Illinois Press who guided me, a complete novice in the field, through the intricacies of preparing a volume of symposium papers for publication.

The Symposium was sponsored by the Institute of Neurological Diseases and Blindness and the Endocrinology Study Section of the National Institutes of Health (Grant No. B2955).

A. V. Nalbandov

December, 1962 University of Illinois

OFFICIAL WELCOME[1]

Richard L. Masland

This important symposium is being supported by a grant from the National Institute of Neurological Diseases and Blindness. In making this reference, however, I believe it is important for all of us to appreciate the fact that although we speak of a grant from the NINDB, we are really referring to money coming from the United States taxpayer and reflecting this country's confidence in the scientific community.

I have often felt that conducting research must be somewhat comparable with traveling through a wilderness. Much of the time is spent in beating through the underbrush to overcome obstacles in the way of some immediate objective. From time to time, the traveler reaches some convenient overlook from which to explore the view. From this point, he can review the path that he has traversed and, hopefully, study the terrain to map out a course for the future.

From the point of view of a National Institute, we might use a different analogy. We are conducting a business in research. We need to take inventory of what has been purchased and what is still lacking from the shelves.

A symposium such as this provides us—and later, through publication, the community at large—an over-all view of the present state of the art and an occasion for taking stock of our present store of knowledge in an important field. Those who attend also find an opportunity for synthesis—to plan further steps to be taken.

I have been asking myself, "What is endocrinology?" In its broadest sense, it is the study of the chemical aspects of the body's regulatory system. But within this definition could be included most of neurophysiology. More specifically, we are concerned with the question, "How does the central nervous system interact with the endocrine system for the control of body function?" A review of the literature and the program of this symposium indicates several broad areas of research comprised within this field.

First, research studies in neuroendocrinology are concerned with the effect of the central nervous system on the glandular system; that is, the nature of the nervous outflow and the liberation of chemicals by the nervous sytem, either centrally in the brain or locally in the effector organ.

Second, studies are concerned with the other end of this mechanism; that is, the process by which the central nervous system is acted upon and through which it is controlled: the role of afferents on the central nervous system, the role of circulating hormones on the central nervous sytsem and the effect of local stimulation by physical or chemical means on the nerve centers themselves.

These phenomena are being investigated by a variety of techniques—by observations and stimulations of portions of the central nervous system, by the effective administration of hormones and tissue extracts and by chemical blockade.

We are studying the basic chemical structure of the enzymes involved in these relationships. By histochemical means, we are studying the distribution of these enzymes and learning about their locus of production,

[1] At the Symposium on Neuroendocrinology, Miami, Florida, December 6, 7, and 8, 1961, sponsored by the National Institute of Neurological Diseases and Blindness and the Endocrinology Study Section of the National Institutes of Health.

liberation and exchange. We are correlating these chemical and anatomic observations with the study of the physiologic changes to which they relate.

Thus, we find that we have defined a broad multidisciplinary approach to a relatively circumscribed area of interest. Just as we are doing in the laboratories, this symposium has assembled people with widely differing backgrounds and techniques, drawn together by a common interest. The mobilization of these multidisciplinary approaches represents one of the most important opportunities and challenges of our day.

There are two ways in which this challenge can be met. One method is to train people with sufficient breadth of background and knowledge so that a given individual can, himself, encompass and master the variety of techniques that he requires. The second approach is more difficult. It involves the organization of teams of people who can work together around a specific problem.

To accomplish either of these objectives, we must look toward a carefully planned and extensive program. It will require the training of individuals in the techniques that we are discussing; it will require the establishment of laboratories within which the varieties of approaches will be available; and it will require the maintenance of teams of individuals and the support of their individual budgets. In looking ahead, we must be prepared to sustain all these activities.

I think we all owe a great debt indeed to the endocrinology study section, and especially to Drs. Guillemin, Hill and Nalbandov, whose work has contributed so much to organizing this symposium. Certainly, it will provide us with a most important view of where we stand and where we are going.

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1

PROLOGUE TO NEUROENDOCRINOLOGY SYMPOSIUM

Robert Towner Hill

This is an occasion of extreme pleasure, to welcome each of you to this symposium, and to present its prologue. The area of neuroendocrinology has long been a favorite subject of mine. It was a pleasure to have received the enthusiastic support from the Endocrinology Study Section for my suggestion of holding this symposium. It was further gratifying to find the willing financial support of the National Institute of Neurological Diseases and Blindness in the form of a research grant award to one of the members (Dr. Nalbandov) of the Endocrinology Study Section for support of the symposium. The organizing committee has performed commendably, but special note is due to the chairman, Dr. Nalbandov, for the diligence that he has exerted in arranging the multitudinous and final details.

It is not the intent of this presentation to cite endless references dealing with the past researches in neuroendocrinology. It is the province of this effort to look backward down a road which is often cloudy with the dust of confusion and to point up a few of the prominences that were encountered by many an intrepid investigator but were rarely, if ever, reduced to their component parts. As this has been true in our past, so it is true at present, and, I fear, will regrettably remain too true in the future.

One of these promontories of the past has had to do with female reproductive physiology of birds. It has long been known that the female of many avian species will lay a clutch of eggs of specific size and then become broody. Regular daily removal of a portion of the clutch will delay onset of broodiness. The addition of eggs to a clutch may summarily stop the laying and induce broodiness. Does anyone suppose the female bird can count, and thereby regulate the size of the clutch? I think not. No one proposes the ovary to be capable of only a predetermined number of ovulations, because this has been proven false. The male of the species certainly seems not to be involved. Food and temperature are not involved. The factors that are involved are limited to the female and an unexplainable awareness of surrounding environment in the form of clutch size. This reaction must involve the nervous system, and thereby becomes a problem in neuroendocrinology. This problem has been with us a long time and is still with us. Here is a wide open area which can be expected to respond to ingenious research. I am sure that the problem can be solved.

While giving consideration to this problem, allow me to point toward an area of research which might lead to a greater understanding of avian ovarian function. When working in the laboratories of Professor Benoit in 1957, I proposed that sacral chordotomy be performed in laying hens. This proposition was made on the assumption that the oviduct of the hen has its secretory mechanisms under the control of the sacral parasympathetic portion of the nervous system. I do not know whether the assumption is correct, but from a morphologic and embryologic viewpoint, it is at least logical. In any event, the procedure was carried out on several laying hens with no gross ill effects except in one, which experienced some diffculty in walking. No more than one egg was laid by any hen after the operation, and then only on the day next following the operation. Laying was resumed on a sporadic basis 2 to 3 months later. Unfortunately no tissue studies were made. The individual who planned to pursue this activity was prevented from so doing because of conditions beyond his control. I am convinced that this idea still remains one of merit as far as the function of the albumen gland and the shell gland of the avian oviduct is concerned. We hasten to add that the avian ovum *per se* has no known dependency on the function of these two glands, but such a possibility has not been ruled out. In any event, the "egg" as commonly known and as an item of commerce would have little present value without normal glandular oviduct activity. I hope there are some among you who will find this approach in reproductive physiology of enough interest to start work on it. I predict interesting results.

Most mammalian ovaries have a cyclic pattern not found in the avian ovary. Recent experiments of mine clearly demonstrate profound changes in the ovary of the adult rat following section of the sacral spinal cord. These changes have to do with the extended life of the corpus luteum. These experiments are a direct follow-up of the well known and 40-year-old findings relative to corpus luteum retention and anovulation following hysterectomy in the 6-day postovulatory guinea pig. We interpret our results as being caused by the inactivation of the uterine endometrium through the separation of its motor secretory nerve supply. My preliminary paper on these studies is now in press, and details of these studies will be presented later in this symposium. In this same vein, we are aware of the experiments of other investigators wherein the spinal cord has been sectioned and an absence of estrous behavior has been noted. We are not aware of any interpretation of these experiments that suggests the involvement of the endometrium. The literature cites instances of traumatic section of the spinal cord in women with attendant menstrual disturbances or cessation. The resulting aberrant sexual cycle is generally ascribed to the over-all debilitating condition caused by the severity of the trauma involved. We know of no tests that may have been made and that might demonstrate a nonfunctional endometrium or a changed ovarian pattern as a result of the loss of motor secretory spinal cord fibers.

I have clearly demonstrated in several mammalian species that the functional nerves to and in the ovary are of vagal origin. Logic and a knowledge of embryology lead me to predict that the functional nerves to and in the testis will be found to be derived from the vagus nerve. We feel certain of this prediction, knowing that the blood vascular bed of the gonad may have a few fibers of sympathetic origin, which, however, serve no direct function relating to the glandular activity of the organ. Several years ago we became interested in the problem of vagotomy in the human male and in its possible resultant effects on his reproductive physiology. Conditions beyond our control prevented pursuing the activity. However, in making inquiries, it was drawn to our attention that some men complain of slight but definite changes in their sexual activity. It is my hope that someone will find interest and time to pursue studies of people in whom complete vagotomy has been done as well as to conduct discrete experiments after vagotomy in laboratory animals.

It has recently been my pleasure to spend some time in the laboratories of Dr. Takewaki of the University of Tokyo. While there, I was shown the results of some experiments of preliminary nature in which the testicular artery and nerve had been sectioned in the rat. In addition, a piece of vagina had been grafted subcutaneously. Some 9 or more months later the normal testicular elements had completely disappeared and the grafted vaginal tissue ex-

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hibited extensive cornification. In each testis (I believe the number of animals used was eight) there was present an obvious body of tissue, probably of a single cell type, which, to me, looked much like adrenal cortical tissue. Dr. Takewaki was unwilling to make a statement concerning the kind of tissue found, its origin or the conditions that allowed it to become so obvious. However, one might deduce that the findings were either the direct or indirect result of loss of normal blood supply or nerves or both. It seems to me that Dr. Takewaki's experiments may serve to open and greatly advance a completely new area of neuroendocrinology. I wish also to make it plain that I mention Dr. Takewaki's work with his full knowledge and consent.

The phenomenon of pseudocyesis is one of neuroendocrinology, and, up to the present, it is just as baffling as it ever was. This condition is very real and into it creep the peculiar idiosyncrasies of the human cerebral cortex. It bears some relationship to psuedopregnancy in other mammals, but the equation will likely remain unbalanced, with the human mind being what it is. Perhaps there will develop a field of psychosomatic endocrinology. If so, there are many possible problems concerning endocrine physiology and mental activity, even capacity.

The hypothalamus is now under vigorous study, and much is being found out about it. It is hard to predict what the future of studies of the hypothalamus will be, except that it is bound to be good. Common mediating pathways in the brain are being studied as they have been for several years. It may well be found that these pathways are not functional as secretory organs but rather as organs of impulse transmission.

Relative to the central nervous system, I should like to bring you back to previous comments involving the vagus nerve. Since sectioning of the vagus nerve affects ovarian function, life span of corpus luteum and adrenal cortical activity, I think it reasonable to suggest that motor nuclei of the vagus may be involved and that they deserve careful study. Studies of cranial nuclei and nerves relative to their participation in the function of the endocrine system will have to be carried out by both physiologic and morphologic means. The studies in this latter area will be aided greatly by the techniques of cytochemistry and by the electron microscope. Much work has been done, and continues to be done, with hypothalamic nuclei and the mammillary bodies, and at this moment it seems certain that good results will continue to be obtained.

Well do I remember some experiments wherein galvanometric deviations were shown to have a direct relationship to ovulation and the number of ova released in the intact rabbit. The same instrument was used in finding correlations between stages of the estrous cycle in the rat and changing electric potentials. Furthermore, I remember a cooperative human female who was destined for elective abdominal surgery, in whom ovulation had been predicted by changing potentials, and confirmed at surgery. It is completely possible that, by a study of electric potentials, certain endocrine phenomena might be more adequately interpreted. It may further be possible that such changes in bioelectric phenomena may be mediated through or by the nervous system.

I find one other case very intriguing. The male katydid appears to be a disinterested party relative to sexual activity until he loses his head. One should add that the female of the species is the direct cause of the male losing his head by the simple method of decapitation. This procedure fulfills the desired purposes, and immediate and sufficient fertilization of the female results. Here is a condition wherein the central nervous system is definitely a deterrent to the propagation of the species. I am not aware of information being available as to the active principle or the explanation of this phenomenon. If you are interested, I am certain that plenty of katydids can be found to work on.

I have mentioned here many things in the area of neuroendocrinology that I hope will be of interest to you and other workers in endocrinology. Many additional items might have been mentioned. They are problems that remain unsolved and need ingenious activity. I have ventured a few predictions. It is to be hoped that as this symposium progresses, each of you will exercise the privilege, and may I say duty, to present your material and then to project your ideas a bit into the future. Mayhap your projections will be down a straight path—maybe it will be a devious path, even to the point of backtracking a bit. This symposium should, most importantly, be a "think" session. I hope it is. We look forward to the final résumé to see how well we have done.

2

CENTRAL NERVOUS ORGANIZATION AND THE ENDOCRINE MOTOR SYSTEM

Walle J. H. Nauta

THE existence of a functional connection between the central nervous system and the endocrine apparatus is not surprising if it is realized that endocrine functions play important, if largely sustaining, roles in animal behavior. The anatomic link between the two systems, however, is a highly complex one. Whereas most other effector organs are controlled by the central nervous system, first and foremost by the medium of a more or less direct peripheral innervation, there is now evidence that the central nervous control of endocrine tissues, with the notable exception of the adrenal medulla, is largely independent of the peripheral nervous system. Instead, the path of centrifugal transmission to endocrine organs appears to be organized in the form of a complicated chain in which secretory effectors alternate with vascular links, a chain that begins in the central nervous system and leads over the pars distalis of the hypophysis to the endocrine target organs.

For those interested in neural mechanisms it is logical to ask if, in this pathway of transmission, a neuronal element exists that could be compared with the motor neuron—Sherrington's "final common path" of the somatic motor organization. It appears that the last neuron in the neuroendocrine system is located in the medial region of the hypothalamus, but it is difficult to equate it with the somatic motor neuron, because its axon does not leave the central nervous system and hence does not terminate within the target organ. One is confronted here with the remarkable likelihood that certain hypothalamic neurons innervate "nothing," *i.e.*, neither other nerve cells nor any effector tissue. As this matter will no doubt be discussed more competently elsewhere in this symposium, it will suffice here to point out that the hypothalamic neurons in question combine characteristics of nerve cells and secretory cells and are thought to elaborate humoral principles, some of which are hormones, or their precursors, in their own right, whereas others serve as transmittor substances affecting the secretory mechanisms of the anterior pituitary. Whatever their glandular characteristics, these cells must nevertheless be regarded as the last neuronal link in the major endocrine motor organization and hence as an unusual sort of "final common path."

In this anatomic contribution I shall attempt to define the position of the hypothalamic endocrine motor neurons within the over-all organization of the central nervous system. The available data are incomplete because at this time it is not even possible to identify the cells in question with certainty. Even if it were justified to consider, for example, the entire medial hypothalamic region as the "hypothalamo-hypophyseal motor zone," there would still be considerable uncertaintly as to the afferent connections of the region, for the hypothalamus has so far been relatively refractory to studies by such decisive histologic techniques as the Golgi method for axons. Despite all this, it will be possible at least to give an account of some of the major neural organizations related to the hypothalamus and, by implication, to the hypothalamo-hypophyseal motor system. The amplitude of the problems confronting the student of neuroendocrine relationships can, perhaps, best be appreciated if the subject of hypothalamic connections is approached by way of a more general consideration of central nervous organization. The reader familiar with the writings of C. Judson Herrick (16) will find that much of what follows is based upon the fundamental notions developed by that pioneer of neurobiology.

From a neurologic point of view it seems reasonable to think that the phylogenetic increase in the response repertoire of organisms is determined by two major factors, which are mutually related but by no means evolving in parallel. The first of these is the degree of differentiation achieved by the motor apparatus, *i.e.*, the effector tissues together with the innervating system of motor neurons. The second factor is the differentiation of the sensory receptor mechanism and, closely correlated with the latter, the volume and organization of what could be called "the great internuncial net," *i.e.*, the neuronal apparatus interposed between the primary sensory receptor neurons on the one hand and the motor neurons on the other. In phylogenetic development the first, or "motor" factor, although by no means inconspicuous in its effects, appears to be outrun considerably by the second, the "sensory-internuncial." This unequal developmental emphasis may explain the remarkable phenomenon that the phylogeny of animal behavior is characterized to a larger extent by a general increase in the facility to analyze the environment and to respond differentially to a variety of environmental stimuli than by an increasing arsenal of motor mechanisms designed to cope with the environment. This appears true particularly in regard to visceral and endocrine functions.

It must be emphasized that the central nervous system of vertebrates contains only two classes of neurons: motor neurons and the cells of the great internuncial net. The latter has its humble beginning in the seemingly diffuse neuronal net of low invertebrate forms. It shows a phenomenal development in the phylogenetic series, a development which far exceeds that of the motoneuronal apparatus. The internuncial neuronal net is the recipient of nearly the entire sensory influx—in mammals it is bypassed only by the monosynaptic components of the kinesthetic reflex arc—and it is clear that it must undergo considerable differentiation if it is to subserve increasingly differentiated modes of animal behavior. Whatever its degree of development, to be functionally useful it must combine, as Herrick has pointed out, the fundamentally different properties of *analysis* and *integration*. The net, in other words, must contain neural organizations capable of analysis of incoming sensory information, as well as mechanisms that can integrate the neural codes of several such analyses into communal and more "condensed" codes of neural signals capable of eliciting meaningful patterns of motoneuronal activation and inhibition. It appears likely that the two properties of analysis and integration are to various extents and in various ratios represented throughout the neural net, and that patterns of sensory information are analyzed and integrated by all of the central nervous cell groups traversed. There is, furthermore, strong evidence to suggest that components, *i.e.*, different modalities, of one and the same volume of sensory information are more or less simultaneously processed by a number of different, although interconnected, analyzor-integrator systems, some of which can "distinguish" only relatively crude characteristics such as volume and frequency, whereas others are equipped to deal with more intricate spatial and temporal parameters of the sensory pattern.

Anatomic delineation of analyzor systems in the internuncial neural net, however vague, is an early development in phylogeny, evident in the nervous systems of all but the lowest invertebrates. It appears that such anatomically recognizable subdivision resulted first and foremost from a process in which progressively differentiating peripheral sensory systems came to employ certain parts of the neuronal net more than other parts. By this mechanism such cell assemblies as the socondary sensory cell groups, *e.g.*, the cochlear and sensory trigeminal nuclei of the brain stem, became progressively more clearly identifiable as the main receiving stations for sensory nerve fibers related to peripheral receptor organs. It is noteworthy that many details in this process of monopolization of entrance portals by individual sensory nerves evolve slowly; even in vertebrate forms as highly developed as the tailed amphibians, according to Herrick's monumental Golgi studies, "all exteroceptive peripheral fibers of the V to X cranial nerves discharge into a common sensory pool or neuropil, which seems to be approximately, although not completely, equipotential in all parts" (17).

The phenomenon of progressively more pronounced "crystallization" of secondary sensory neuronal groups from the originally diffuse net exemplifies a process leading to the distinction of "specific" from "less or nonspecific" regions of the great internuncial net. It must be emphasized that this terminology, as currently used, appears to refer to the *afferent* characteristics of cell organizations in the net, and much less to regional functional specificities, which are determined also by the efferent connections of the regions in question. If the adjective "specific" is used in this sense, one is forced to conclude that, in all forms below the mammals, the sensory analyzor systems, insofar as they can be delineated at all, show a pronounced absence of specificity. Although in such submammalian forms the secondary sensory cell groups may be to a certain extent specifically related to certain sensory modalities, the lemniscus systems, *i.e.*, the fiber bundles originating and ascending from these cell groups, show a great deal of mingling and overlap considerably in their distribution to higher levels of the nervous system. Such primordial lemniscus systems presumably represent general exteroceptive, proprioceptive and visceroceptive sensory modalities largely comparable to the so-called protopathic modalities of mammalian forms. They terminate widely in the brain stem reticular formation and in the mesencephalic tectum; a few, of both spinal and bulbar origin, extend as far forward as the thalamus (17). There is no doubt that all of these terminal areas of the primordial lemnisci can relay lemniscal impulses to the primordial cerebral mantle, but there are within these rostral levels of the submammalian nervous system only few indications of subdivision subserving individual sensory functions. The olfactory and visual systems form exceptions to this rule and will be mentioned again below.

It is only in mammals that more highly specific analyzor mechanisms become conspicuous. It must be emphasized that such more specific organizations do not replace the primordial mechanisms, but are added to the latter. These analyzor systems, representing the progressively developing more refined sensory modalities (the so-called epicritic modalities) generally consist of well defined secondary sensory nuclei giving rise to lemniscus systems that typically bypass the reticular formation and mesencephalic tectum and terminate in specific thalamic cell groups, which in turn are connected with circumscript neocortical fields. Throughout their extent, these phylogenetically new analyzors maintain a high degree of specificity for corresponding sensory modalities; *i.e.*, there is no or minimal "sharing" of neural elements among individual sensory modalities.

The difference between the primordial and phylogenetically more recent analyzor systems is striking and fundamental, but it is important to avoid the notion of mutually independent mechanisms working in isolated parallel with each other. Actually, there is anatomic as well as physiologic evidence to suggest that the two categories of analyzors communicate with each other, and, from certain points of view, they can even be regarded as to some extent linked in series with each other. To clarify this statement I propose to classify the analyzor mechanisms mentioned above into three categories. It goes without saying that this, like any other systematization of mechanisms as complex as the central nervous system, can have only relative validity and usefulness, and that much more detailed classifications may prove necessary when the nervous system is considered from other points of view. As most or all of the neural organizations to be mentioned below have integrative as well as analytical functions, they will be listed as analyzor-integrator systems.

ANALYZOR-INTEGRATOR SYSTEMS OF THE FIRST ORDER: THE BRAIN STEM RETICULAR FORMATION

As stated in the foregoing account, the reticular formation receives a massive influx of fibers from the primordial lemniscus systems, conveying mostly "protopathic" exteroceptive and general proprioceptive and visceroceptive impulses. Beside such more fundamental sensory pathways, it receives numerous afferents from the higher order analyzors to be mentioned below (see Figs. 2-1 and 2-4), and there is good reason to believe that the reticular analysis is in the intact animal amalgamated, *i.e.*, integrated, with neural codes emanating from such higher levels of the central nervous system.

It is extremely difficult to define the extent of the reticular formation.[1] The term is used here to encompass not only the reticular cell groups of the medullary, pontine and mesencephalic tegmentum and the central gray substance, but also structures that could collectively be called the "forebrain reticular formation": the paleothalamic cell groups (intralaminar nuclei and the habenula), the subthalamus and the entire complex formed by the hypothalamus, preoptic area and septal regions with some associated regions such as the substantia innominata. This is undoubtedly arbitrary, but it is done partly because there are neither clear anatomic boundaries nor great differences in general structure between these reticular forebrain regions and the mesencephalic reticular formation, and partly also because of the apparent conti-

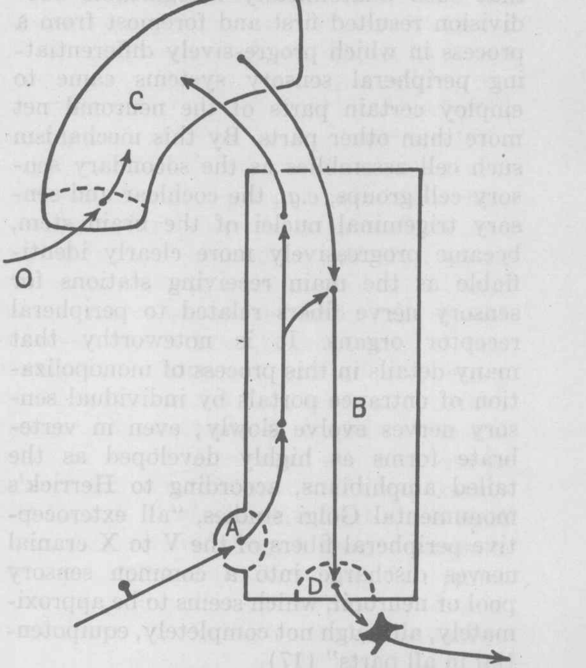

FIG. 2-1. Diagram illustrating the general interrelationships between sensory nuclei (*A*), the first order analyzor-integrator mechanisms of the brain stem reticular formation (*B*) and "second order analyzor-integrator systems:" the limbic forebrain and corpus striatum (*C*). According to this schematic view, the limbic and striatal forebrain are "linked in series" with the reticular formation: with the exception of part of the olfactory influx (*O*), all afferent pathways to the limbic and striatal forebrain structures are relayed through the reticular formation. Conversely, these second order analyzor-integrator mechanisms can affect the motoneuronal apparatus only via reticulo-motoneuronal pathways, probably in turn interrupted by a pool of internuncial cells (*D*).

[1] According to one point of view (2), the reticular formation encompasses those nerve cells of the brain stem that are neither motor neurons nor components of second or third order sensory cell groups. If this criterion is accepted, one must conclude that such "leftover cells" compose virtually all brain stem structures beside the known sensory and motor nuclei. Bishop (4) proposes the term *reticular system* to indicate a nonspecific neuronal apparatus pervading the entire length of the nervous system including the cerebral cortex. The term, reticular formation, as used in the present account refers to cell groups of the brain stem that (*a*) do not show any systematic arrangement of cells and fibers comparable, for example, to the organization of cortical formations, (*b*) exhibit polymorphic cytology and (*c*) have heterogeneous afferent connections. The applicability of all three of these criteria has, of course, not been established with certainty for all cell groups currently included in the reticular formation.

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