Physiological Foundations of Neurology & Psychiatry

ERNST GELLHORN, M.D., PH.D.

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Das schönste Glück des denkenden Menschen ist das Erforschliche erforscht zu haben, und das Unerforschliche ruhig zu verehren. – "The greatest happiness of thinking man is to have investigated what can be investigated, and quietly to revere what cannot be."
– Goethe

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OF NEUROLOGY AND PSYCHIATRY

BY

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TO

The Office of Naval Research

AND IN MEMORY OF

Irene Florence Gellhorn

(1930–1952)

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Preface

THE material for a discussion of the physiological foundations of neurology and psychiatry is based on physiological, clinical, and psychological research. The mass of data which are available and demand coordination is enormous. On the physiological level it comprises investigations which start with the peripheral nerve and the nature of the nerve impulse, pass through the spinal and supraspinal activities of the central nervous system, and end up in the complexities of cybernetics. Physiological and psychological investigations overlap in areas such as sensory functions, conditioning, the basis of emotion, and the psychophysiological mechanism of neurosis. Finally, clinical observations and experimental studies on neurological and psychiatric cases have added to our knowledge of the physiology of the central nervous system, particularly of the higher functions of the brain (e.g., language, aphasia) which cannot be subjected to animal experimentation.

To collect and discuss critically this material would require several volumes and is probably beyond the intellectual capacity of a single man. The aim of the present book is more modest. By no means all, but only some, physiological foundations of neuropsychiatry are treated, those with which the writer is familiar through his own experimental work. In spite of omissions, which might be reduced should future editions of this book become necessary, it is hoped that significant topics have been selected, of interest to physiologists, endocrinologists, internists, neurologists and neurosurgeons, psychiatrists and students of human behavior.

The book is based on the assumption that the elucidation of the mechanisms underlying the behavior of the neurons at various levels of complexity will ultimately be of great importance to neurologists, neurosurgeons, and psychiatrists. Diagnosis will be aided by such

knowledge, and therapeutic procedures will be based on it. This trend is exemplified in the last chapter, in which some recent unpublished work of the author is reported. It is hoped that the facts and ideas elaborated in this chapter will be studied with great care by those primarily interested in the prevention and therapy of functional psychoses and psychoneuroses.

Although the experimental work performed in the writer's laboratory is the backbone of this book, he is keenly aware of the fact that progress in science depends on many minds. An attempt has therefore been made to integrate with this work the data of the experimental and clinical literature, as indicated by the extensive list of references. If the material and the ideas presented in this book should inspire any young men and women to dedicate their lives to the furtherance of the neurological sciences, the writer would consider his labors to have been not in vain. Approaching the evening of his life, he realizes, more than ever before, that not personal achievement or success, and still less, power, is an aim worthy of the scholar, but only untiring devotion to the science of his own choosing.

The writer is deeply grateful to Drs. J. Hyde, H. Klüver, W. P. Koella, G. N. Loofbourrow, J. P. Murphy, and J. S. Tucker, who read the manuscript in part or entire and greatly aided him by their criticism; to Dr. W. P. Koella for several diagrams designed for the book; to Mr. H. M. Ballin for photographic work; to the entire staff of the University of Minnesota Press, and especially to Dr. Doris Franklin, whose competence and spirit of collaboration made the tedious job of checking, arranging, and correcting a pleasure; and to Mr. J. Kingsley, Mrs. V. Clausen, and the staff of the Bio-Medical Library for their unfailing cooperation. Last but not least he is greatly indebted to his collaborators.*

Without the support, both moral and financial, of the Office of Naval Research, especially Captain C. W. Shilling, Dr. Ora Reynolds, and Dr. F. H. Quimby, this book would not have been written. The writer wishes likewise to acknowledge several research grants from the Graduate School of the University of Minnesota and to express to Dean Blegen his appreciation for prompt and courteous action.

E. G.

* Drs. Arnett, Beckett, Bernhaut, Bosma, Conley, Cortell, Darrow, Dick, Feldman, Gay, Glickman, Greenberg, Hyde, Kessler, Kiely, Kraines, Loofbourrow, Murphy, Redgate, Safford, Teschan, L. Thompson, M. B. Thompson, Ury, and Yesinick (indexed in the Bibliographical Index of Authors at the end of the book), and Drs. Allen, Ballin, Carlson, Frank, French, Hailman, Hamilton, Heymans, Ingraham, Janus, Johnson, Joslyn, Kaplan, Lambert, Levin, Mehlman, Minatoya, Moldavsky, Northup, Packer, Pollack, Riggle, Spiesman, Storm, and Weil (appearing in the Bibliographical Index under Gellhorn *et al.*).

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Part V. Integrations

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Physiological Foundations of Neurology and Psychiatry

One of the differences between a good and a bad scholar is that one specializes in topics which complement each other, and together light up most of the general area of his interest, while the other works on peripheral and unrelated provinces, like the frontier administrator who tries without success to understand the central problems of an empire.

– Gilbert Highet, *The Classical Tradition* (1949)

Es ist das Vorrecht des Wissenschaftlers, für seine Arbeit zu leiden, und wer nicht hin und wieder bei seiner Arbeit der Verzweiflung nahe war, hat nicht erfahren, was wahres Forschen ist. – "It is the privilege of the scientist to suffer for his work, and the man that has not now and then in the course of his labors been near to despair has not experienced what true research is."

– Otto Riesser, in *Archiv für experimentelle Pathologie und Pharmakologie* (1949)

Introduction

EXPOUNDING the physiological foundations of neurology and psychiatry is perhaps more difficult than the application of physiology to any other branch of clinical medicine. In no other area of study are the phylogenetic differences between man and the readily available laboratory animals so profound. The very limited use of anthropoid apes has been confined almost exclusively to explorations of the motor cortex and to behavioral studies. Although the monkey has served for experimental work more extensively, particularly in the last decade, there are still many physiological problems which have thus far been attacked only in the cat, dog, or even lower forms like the rat. These reasons, as well as the great difficulties inherent in the investigation of complex neurological relations account for the fact that the gap between experimental data and clinical observations is closing more slowly in this field than in other branches of medicine. The need for a careful survey and evaluation of the links which can be established is therefore all the greater.

Since the differences in brain functions between various species are greatest in the neocortex, the danger of false extrapolation from the animal to the human brain is considerable in this area, but much less in the phylogenetically older autonomic nervous system. Therefore extensive use has been made of clinical observations amenable to physiological analysis and of direct experiments on man. But even in those not infrequent cases in which no counterpart of the observations made on animals is available in human pathology, the physiological experiment is worthy of study not only for its intrinsic value in its own realm of knowledge but also as a guidepost for future research in human neurology.

Although the emphasis in this book, as in the writer's *Autonomic*

Regulations, lies on integrative processes within the central nervous system, consideration is given to some of the principal working mechanisms of the neuron, which, in spite of various attempts to dislodge it from its key position, still represents the elementary unit of the central nervous processes. No attempt is made to review the basic physiology of the spinal cord, from which so much of our knowledge about the fundamental properties of the neuron is derived, and the reader is referred to the comprehensive works of Sherrington and for the newer aspects of these problems to Lloyd. However, the principles by which nervous activity is gradated is discussed for motor and sensory functions of the somatic and also for the autonomic nervous system (Chapter 1). Aside from the important data leading to the formulation of the Adrian-Bronk law, which is a cornerstone of modern neurophysiology, the presentation of this work gives an opportunity to acquaint the reader with some aspects of electrophysiology that will be utilized in their practical application for electromyography (in Chapter 6).

The changes in neuronal activity induced by alterations in the internal environment are dealt with in Chapter 2 because it is felt that information gained by such studies is of considerable medical interest at present and of even greater potential value. Further questions applicable to the neuron in general are discussed in Chapter 11, in which a survey of the action of neurohumors is given. It is presented at that place in conjunction with some aspects of autonomic physiology.

Of the many problems pertaining to the special physiology of the central nervous system, that concerning the factors determining voluntary movements occupies a central position in somatic physiology. Consequently the organization of the motor cortex is discussed (Chapter 3) largely on the basis of the work of the author and his collaborators, and proper emphasis is placed on the interaction of spinal cord and cerebrum. That a sharp separation of motor from sensory processes is impossible is stressed in studies on the modification of motor activity through proprioceptive and nociceptive impulses. This work is utilized for the physiological analysis of willed movements and is expanded by observations on movements with deafferented extremities and by related experimental and clinical studies. Sensorimotor integration appears to be the foundation of voluntary movement (Chapter 4). In "The Restitution of Movements after Cortical Lesions" (Chapter 5) an attempt is made to contribute to an understanding of one of the most complex questions of cortical physiology and to eliminate, on the foundation of the basic work of Weiss and Sperry, the mystic concept of the plasticity of neuronal

function which has invaded physiological and clinical literature to a considerable degree. Moreover the principles developed in the studies on the motor cortex are applied in order to arrive at a rational therapy of motor lesions of the central nervous system.

In Chapter 6 electromyography is briefly discussed because of its value clinically and as a physiological method which allows one to record muscular activity under strictly physiological conditions and to gain thereby some insight into various types of innervation patterns. The section dealing with the motor system is concluded with Chapter 7, on "Experimental Convulsions." Similarities and differences between normal and convulsive activity are described on the basis of studies concerning the action of acetylcholine and anoxia on the cerebral cortex. But the problem of convulsions cannot be fully understood by an analysis of the individual neuron or groups of homogeneous neurons. As in many other neurophysiological questions, the hierarchical structure of the nervous system in general and the motor system in particular must be taken into account. Convulsions of cortical and subcortical origin behave quite differently under similar experimental conditions. This is illustrated by the effect on convulsive discharges of anoxia and asphyxia. The clinical significance of these and related studies for the mechanism involved in the precipitation of convulsions is pointed out.

Through clinical observations on coma in lesions of the brain stem, the discovery of the EEG by Berger, and the experimental studies on the relation of the hypothalamus to the waking state inaugurated by Ranson, the problem of consciousness has been removed from the realm of philosophical speculation and has become in recent years the proper object of physiological research. The investigation of the influence of sleep on brain potentials, the mechanism of the arousal reaction, together with the ingenious studies of Magoun and his collaborators on the influence of the reticular systems in pons and medulla on cortical activity, have elucidated the physiological dynamics underlying awareness, sleep, and coma. Chapters 8, 9, and 10 of this book are devoted to the problem of consciousness. The differences between sleep and experimental coma are discussed, and the fundamental importance of the hypothalamic-cortical system for the state of wakefulness is emphasized. The applicability of the general concepts thus obtained for specific problems of neurology is shown in the discussion of the basic physiology of the phantom limb.

Some aspects of autonomic physiology are treated in Chapters 11 and 12, although care has been taken in these as in all other parts of this book to choose functional considerations and not anatomical

boundaries as the basis for discussion. The concept of neurohumors, although clearly established originally for the autonomic nervous system, has apparently a wider application than was thought at first. The role of acetylcholine in nervous conduction and in the transmission through somatic synapses is still under dispute. Some newer aspects of these problems are discussed: they include the action of synaptic blocking agents such as tetraethylammonium chloride (TEA) and the nature of sympathin and secreted adrenalin, with emphasis on the role of nor-adrenalin.

Space does not permit the writer, nor was it ever his intention, to discuss fully the function of the autonomic nervous system. To exemplify the principles governing its activity in a single organ is therefore desirable. Although the basic principles of life can be demonstrated in an individual cell, the function of the nervous system is one of integration, and at least an organ is necessary to illustrate its fundamental characteristics. To what extent the eye reveals autonomic organization will be shown in Chapter 12.

Integrative functions of the nervous system are presented in Chapters 13 through 17. The intimate relations of the autonomic nervous system to the endocrines, and particularly the influence of the hypothalamus on the anterior and posterior pituitary, are evaluated in Chapter 13. The implications for neuropsychiatry are outlined.

The fundamental changes which accompany emotion illustrate further nervous-endocrine integration (Chapter 14). However, the nervous component is not confined to the autonomic division but involves the somatic nervous system as well. It is shown that the hypothalamus is responsible not only for the coordination of somatic and autonomic discharges, which account for the symptomatology of emotion, but also for subjective changes which are thought to be due to hypothalamic-cortical discharges.

Autonomic-somatic integration also underlies the conditioning process, which represents an important element of behavior (Chapter 15). The striking changes in conditioning reactions which result from insulin coma and electroshock appear to be related to alterations in hypothalamic excitation and its influence on the cerebral cortex.

Homeostasis (Chapter 16) is shown to involve an integration of somatic, autonomic, and endocrine functions. The organism cannot operate properly without a relative constancy of the internal environment (Bernard, Cannon, Barcroft). Similarly orientation in the external environment, which is the basis of directed action, is unthinkable without adjustment reactions which tend to keep the individual in a constant external environment. This counterpart of the regulation of

the internal milieu is shown to be due to cortical reactions (Chapter 17).

The next two chapters (18 and 19) deal with the physiological foundation of the so-called shock therapy of mental diseases and the more recently introduced carbon dioxide therapy of psychoneurosis. Obviously the experimental work discussed in this section neither supports nor contradicts the clinical findings concerning the therapeutic values of these procedures. However, it is believed that a physiological analysis of the effects actually produced in the central nervous system under these conditions may be of help in establishing a rational basis for the therapy of functional psychoses.

The final chapter (20) attempts to show that relatively simple autonomic tests, recently introduced by Funkenstein *et al.*, give an indication of hypothalamic sympathetic excitability. On the basis of these findings the principles of a physiologically oriented therapy of psychoneuroses and functional psychoses are outlined.

The central position of the hypothalamic-cortical system is emphasized throughout the whole book. Such diversified problems as the propagation of experimental convulsions, the physiological basis of consciousness and emotion, the action of carbon dioxide on the brain, and the restoration of previously inhibited conditioned reactions are shown to be related to its activity. Repetition is therefore unavoidable, though kept to a minimum by the use of cross references. This situation is the expression of the important fact that motor and sensory processes are strictly separable only in thought, not in nature, and that physiological and pathological processes utilize the same basic integrative mechanisms.

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PART I

Intrinsic and Extrinsic Factors Regulating Neuronal Activity

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The Unit Analysis of Nervous Activity

PHYSIOLOGICAL investigations in general are based on two procedures, analysis and synthesis. In the former an attempt is made to determine the activity of the individual cell or even parts of the cell in various physiological processes, whereas the object of research in the latter is to understand the interaction of the cells in a particular organ and, still more important, the integration of the functions of the various organs. Applied to the nervous system, the goal of analysis is the knowledge of the intimate function of the neurons, while synthesis is more concerned with complex patterns of activity, the interrelations of the nervous system with other organ systems such as the endocrines, and the behavior of the organism as a whole in a variety of circumstances.

The most successful method for the cellular analysis of nervous activity was developed by Adrian (5) and Bronk (12, 13) and consists of the recording of the action potentials of single neurons. No attempt was made to record the activity of a single neuron in the dense cellular network of the gray matter of the brain and spinal cord; instead, microelectrodes were inserted into the muscles or brought in contact with individual nerve fibers. In order to record from the latter, the nerves were cut until only one or two active fibers remained. These procedures have been applied to the somatic and autonomic efferent as well as to the somatic afferent systems and have given insight into the principles of the quantitative gradation of nervous activity which are commonly referred to as the Adrian-Bronk law. This law states that the intensity of excitation is directly related to the frequency of the discharge of the individual neuron and to the number of active neurons.

Unit Activity in Reflexes

Adrian and Bronk (13) studied with these methods the nervous discharges in ipsilateral flexor and contralateral extensor reflexes as well as in the state of decerebrate rigidity. If the skin was pinched and the potentials were recorded from the motor nerve supplying an ipsilateral flexor muscle, it was found that single neurons discharged with increasing frequency in response to increasing intensities of stimulation, the maximal frequency being 30 per second for the peroneus longus and 45 per second for the tibialis anticus. It appeared that this increase in frequency was the principal factor in the gradation of the motor response. The low frequency of the discharges in a system capable of responding to 1,000 stimuli per second is remarkable.

In a study of crossed extensor reflexes elicited in the decerebrate cat through mechanical stimulation or by means of labyrinthine reflexes it was found that the frequency of motor neuron discharge increased up to 90 per second and that in addition more units became active (recruitment) as the stimulus increased in intensity. Apparently the low-threshold neurons respond first and other neurons are brought into action with stronger stimuli. Decerebrate rigidity is maintained with discharges of 5 to 25 impulses per second.

It is true that in flexor reflexes elicited by electrical stimulation of afferent nerve fibers, the frequency of the discharge follows the stimulus frequency within wide limits (277) and may therefore be much higher than indicated above. But this form of stimulation leading to a synchronous discharge is the result of simultaneous (electrical) stimulation of many afferent nerve fibers and is hardly comparable to a reflex response elicited by strictly physiological means, which would involve asynchronous excitation of afferent neurons. It should be emphasized, however, that even in those experiments in which the flexor reflexes were elicited by pinching of the skin, they were, for the sake of analysis, studied in an unphysiological isolation, since the motor nerve was separated from the muscle. In the intact organism a nociceptive stimulus leads to a reflex contraction, and this process will in turn excite proprioceptive end-organs whose impulses return to the spinal cord and will intensify the reflex through increase in the frequency of the discharge of previously activated neurons and the recruitment of additional neurons. Consequently the motor discharge in a nociceptive reflex is determined by the interaction of nociceptive and proprioceptive impulses on the anterior horn cells of the spinal cord.

Motor Discharges from the Respiratory Center

The physiological activity of the respiratory center is due to spontaneous discharges of the medullary center and rhythmic inhibition from the vagi and the pneumotaxic center in the pons.* Its activity can be greatly altered by reflexes mediated by the pulmonary endings of the vagi, the tension receptors in the respiratory muscles, and the chemoreceptors of the sino-aortic area. Direct stimulation of the respiratory center by carbon dioxide or electrical stimulation may also be used. Under these conditions the motor discharges of single units have been determined by recording the action potentials from single nerve fibers and motor units of the respiratory muscles.

Studying unit discharges in single nerve fibers of the phrenic nerve in the rabbit, Adrian and Bronk (12) noted a frequency of 20 to 30 per second in normal respiration, but higher rates of 50 to 80 per second in forcible respiration induced by increasing degrees of asphyxia, the maximal rate recorded being 112 per second. Potentials from different nerve fibers were not synchronous in normal respiration, but under conditions of relatively high frequency discharge a definite tendency to synchronization was noted. Since even at the low rates of 20 to 30 per second the contraction of the diaphragm was smooth, although a higher rate was required to produce a complete tetanus by stimulation of the peripheral nerve, it may be concluded that the asynchrony in the discharge of many units accounts for this result.

However, the increase in the frequency of the discharge of single neurons is not the only mechanism by which the strength of the contraction of the respiratory muscles is controlled. Unit recordings from the external intercostal muscles during inspiration show that with increasing intensity of respiration induced by rebreathing, three changes occur: increase in the frequency of single neurons, already mentioned; recruitment of additional neurons; and increased duration of the discharge in each neuron (143) (Fig. 1). In such experiments it is seen that not all the units start to discharge with the onset of inspiration but that some begin their activity later than others. With increasing intensity of breathing these units appear earlier so that the duration of their discharge increases. In the dog the range of frequencies recorded from intercostal muscles is apparently much smaller than found in the phrenic nerve of the rabbit;† consequently intensity

* See the textbooks of physiology.

† It is permissible to use the frequency of the action potentials of the muscle as an indicator of the rate of discharge of nerve impulses since, within the limits set by the latent periods of muscle and nerve, a one-to-one ratio exists between the potentials in the neuronal and muscular portions of a motor unit.

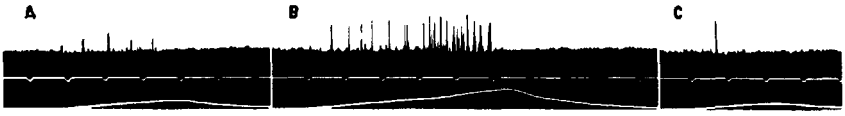

FIGURE 1. The discharge of motor impulses in a nerve twig to an external intercostal muscle in three successive inspirations of varying depth: *A*, moderate; *B*, deep; *C*, shallow. Time marker: 1/5 second. The lower line is a pneumogram, the upward movement indicating inspiration. (Bronk and Ferguson, 143.)

of breathing does not run parallel to the frequency of the discharge in individual units but to the total number of potentials recorded in each inspiration. The chief factor by which muscle strength is graded appears to be the number of activated units and the duration of their discharge (Gesell *et al.*, 46, 533, 534).

This mechanism of increasing the respiratory effort is likewise valid for the phrenic neurons. The recruitment of additional units is particularly marked in the vagotomized animal when respiration is increased by the inhalation of carbon dioxide. The removal of inhibition through vagotomy acts similarly to reflex excitation, since this operation leads likewise to an increase in the frequency of the discharge of the individual units in the phrenic nerve and to additional recruitment (1017). The vagotomized decerebrate cat in which the pontine pneumotaxic center is removed is in a state of inspiratory cramp with maximal discharges over the phrenic neurons. Vagal stimulation produces rhythmicity of respiration, and the inhibitory action on the medullary respiratory center involves a diminution in the frequency of the discharge of single units and a decrease in the number of active units (decruitment).

The exact delimitation of the medullary center and the separation of the inspiratory from the expiratory center (1020) made it possible to study the effect of their stimulation on the discharge of single units in the phrenic nerve. Here again the same principle was found to be valid. Thus, increasing the excitation of the inspiratory center increases the frequency and duration of the discharge of individual phrenic neurons and leads to additional recruitment. These effects are induced to an increasing degree by either increasing the voltage or by increasing the frequency of the stimulation without a change in voltage.* On the other hand, stimulation of the expiratory centers

* It was also shown that with decreasing oxygenation of the blood the effectiveness of stimulation of the inspiratory center is enhanced, as indicated by the augmentation of the rate of discharge and its duration in single neurons and by recruitment (1016).

inhibits the inspiratory center and the phrenic neurons which reflect its state of activity, and here again increased stimulation produces increasing degrees of inhibition through a decrease in the frequency of the phrenic potentials and decruitment (1016) until inspiratory contractions stop.

Discharges from the Motor Cortex

The validity of the Adrian-Bronk law was recently tested for the motor cortex of the monkey. If the motor cortex is stimulated with increasing intensity or frequency, the amplitude of the EMG * and the tension of the activated muscle increase. Analysis shows that the number of discharging motor units is augmented (862). The insertion of microelectrodes into the muscles makes it possible to correlate these gross changes with alterations in the activity of single units. The records show that both procedures of increasing the stimulation of the cortex lead to an increase in the frequency of the potentials in individual neurons, to recruitment, and to an increase in the duration of the discharge. The change in the frequency is relatively slight and seems to play only a minor role in the intensification of the contraction, whereas slight increases in either the frequency or intensity of the stimulation lead to marked recruitment (Table 1) (723). Since the summation time † decreases in both forms of increased stimulation, the discharges appear with a decreasing latency, and this factor in conjunction with the recruitment of more neurons accounts largely for the increased tension of the muscles. Apparently the gradation of muscle strength is achieved in the same manner in such divergent processes as the contraction of the respiratory muscles under the influence of hypercapnia, asphyxia, or stimulation of the medullary inspiratory center, and the activation of the skeletal muscles through electrical stimulation of the motor cortex.

Since relatively large areas in the motor cortex of the monkey send impulses to a muscle such as the biceps or triceps, it is possible to study the processes of summation. Simultaneous stimulation of two foci in the motor cortex may induce a distinct contraction, although when they are activated singly, the effect may be minimal or nil. Unit analysis shows that here again the total number of potentials, which is closely related to the duration of the discharge and the number of activated neurons, is of greater importance than the maximal fre-

* Electromyogram, obtained through large surface electrodes which record the activity of numerous motor units (gross response).

† The time interval between the onset of stimulation and the beginning of response.

TABLE 1. The Influence of Increasing the Intensity and Frequency of Stimulation on the Number of the Responding Motor Units and Their Frequency of Discharge* (Gellhorn and Riggle, 512)

Volts	Frequency per Second				
	11.4	33	53	83	102
Number of Units Responding					
2.1	..	..	0	0	0
2.6	..	2	..	5	..
3.0	0	2	3	4	5
3.5	..	5	..	6	7
4.2	0	5	5	5	7
4.9	2	6	4	..	8
5.7	3	..	..	..	8
Maximal Frequency of Any Unit, in Cycles per Second					
2.1	..	..	0	0	0
2.6	..	30	..	28	..
3.0	0	32	48	28	36
3.5	..	33	..	44	51
4.2	0	32	53	35	51
4.9	12	34	53	..	51
5.7	28	..	..	..	54
Gross Response, in Millimeters					
2.1	..	..	3	0	0
2.6	..	7	..	17	..
3.0	4	8	8	11	9
3.5	..	10	..	18	10
4.2	5	9	10	25	10
4.9	7	12	12	..	11
5.7	8	..	..	..	13

* The experiment was performed on a macaque in "Dial" anesthesia. A biceps point of area 4 was stimulated with condenser discharges of 7.7 ms. duration.

quency of discharge (Fig. 2) (512). If during the cortically induced contraction of the biceps, a triceps focus is stimulated, or vice versa, inhibition results. Unit records show that this is accomplished by decruitment and decrease in the rate of discharge (Fig. 3).

Adrian and Moruzzi (17) studied unit potentials from the pyramidal tracts at the level of the medulla oblongata and in an important paper reported the relation of these potentials to the activity of the motor cortex. They found a good correspondence between cortical potentials and pyramidal discharges in various forms of anesthesia, with wide variations in the frequency of the cortical potentials. Records of activity in single axons of the pyramidal tract indicate that individual cortical neurons discharge single impulses or trains of two or three

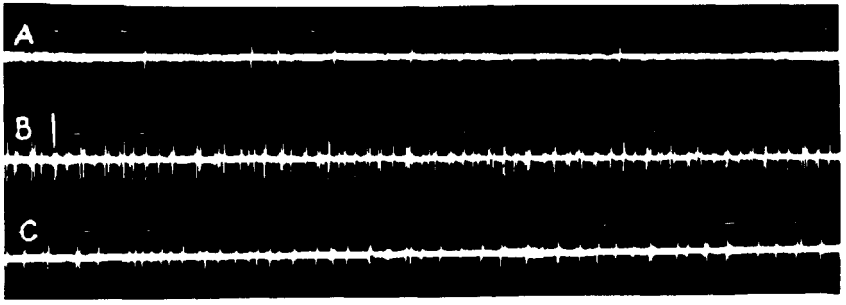

FIGURE 2. The effects of summation on single motor unit responses through the stimulation of two cortical sites in the macaque. Monopolar stimulation. Calibration: 300 microvolts. Timing marks: 0.1 second apart. Muscle: right triceps. *Record A:* electrode 3 mm. anterior to the central sulcus and 7 mm. lateral to the midline; stimulus intensity, 3.5 volts; frequency, 53 per second. *Record C:* electrode 1 mm. anterior and 7 mm. lateral; stimulus intensity, 3.8 volts; frequency, 82 per second. *Record B:* the effect of the A and the C stimulus together. (Gellhorn and Riggle, 512.)

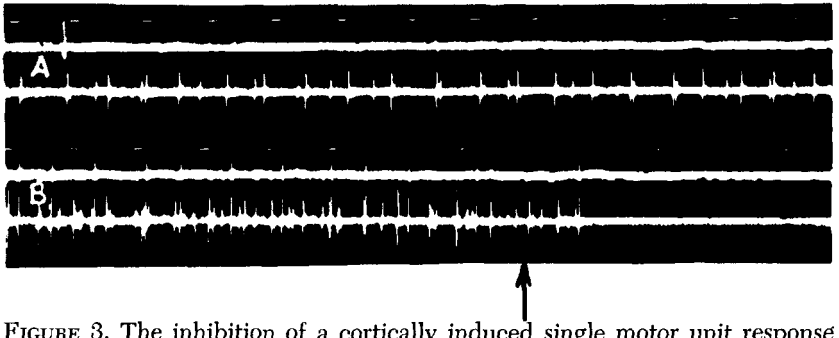

FIGURE 3. The inhibition of a cortically induced single motor unit response through the stimulation of a second cortical site in the macaque. Monopolar stimulation. Calibration: 300 microvolts. Timing marks: 0.1 second apart. Muscle: right triceps. *Record A:* electrode 1 mm. anterior to the central sulcus and 8 mm. lateral to the midline; stimulus intensity, 4.2 volts; frequency, 83 per second. *Record B:* same as record A up to the arrow; to this first stimulus is added at the arrow the inhibitory stimulus, 3 volts in intensity, at 82 per second, with the electrode 1 mm. anterior and 19 mm. lateral. (Gellhorn and Riggle, 512.)

impulses which appear in rapid succession. They occur in the anesthetized animal without movement or change in muscle tone. A single shock applied to the motor cortex produces in barbiturate anesthesia a group of impulses, at 7 to 10 per second, which are similar to the groups which occur spontaneously in this form of narcosis. Like the spontaneous potentials they are not followed by movements. How-

ever, repetitive stimulation (i.e., a series of stimuli) elicits movements which are accounted for by an increasing number of discharging neurons and multiple discharges in the pyramidal tracts which correspond to the frequency of stimulation. As the intensity of the stimulus is increased, the number of impulses occurring with each stimulus may increase from one to four. A similar increase is noted as the result of temporal facilitation; i.e., at the beginning of a series of stimuli a unit may discharge only in response to every third stimulus, a few seconds later a single potential appears at the stimulus frequency, and still later bursts of two or three impulses are noted with each stimulus. Obviously the frequency and number of the discharging units in the pyramidal tracts constitute the factors which produce sufficient summation to excite spinal neurons and determine the strength of the muscular contraction.

The Regulation of Voluntary Activity

Systematic investigations of the motor unit responses in man at different degrees of muscular effort have shown that complete relaxation is not accompanied by action potentials and that with increasing effort potentials appear which show increasing rates of discharge and, more importantly, evidence of recruitment. The frequency in Lindsley's experiments (845) did not exceed 50 per second with maximal effort; however, in paretic muscles frequencies up to 80 or 90 per second have been observed (Seyffarth, 1106). With contractions of lesser intensity the frequency varies between 5 and 30 per second, and the smoothness of the movement with these subtetanic frequencies appears to be due to the asynchrony of the discharge of the active units, as in the animal experiments in which movements had been induced reflexly or by electrical stimulation of central structures. Figure 4 shows that more units are called into action with increasing effort. The greatest recorded frequency is similar in different units, but increases only slightly as the tension is increased. Seyffarth, performing an experiment in which the tension was increased at first and then diminished gradually, noted that the units which as effort is increased are called in last are the first to drop out as the tension diminishes. If a movement is performed in which highly paretic muscles and their normal synergists are activated at the same time, it was found that the frequency of the units in these muscles is similar, although the contribution of the paretic muscle to the tension may be minimal. This similarity seems to indicate that the frequency of the discharge is primarily related to the central (cortical) excitatory

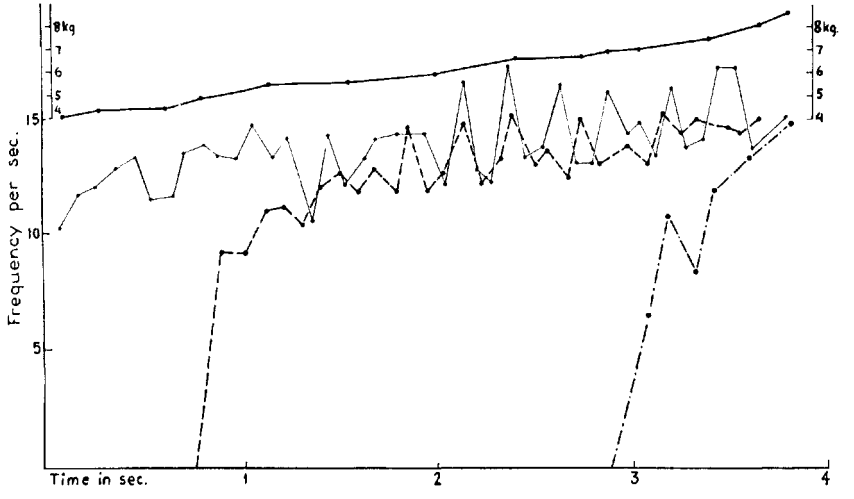

FIGURE 4. The behavior of three motor units in healthy m. tibialis anticus during an increase in tension due to isometric ankle flexion. The new units rapidly attain the frequency of the first. (Seyffarth, 1106.)

processes or, as Seyffarth expresses it, "all the muscles in the synergy are under a common governing force."

It is of interest to mention that a very brief, weak voluntary twitch may be induced by a single potential in one unit (547, 1162). A somewhat stronger twitch seems to be based on the nearly simultaneous discharges of several units, each discharging only once.

If the tension of a group of muscles is maintained long enough to induce fatigue, the frequency of the discharge of the individual units declines and the number of the active motor units diminishes progressively. The units which appeared with the least effort are again the last to disappear. The frequency of the discharge in fatigue seems to be similar to that in nonfatigued conditions when the same tension is produced (Seyffarth, 1106).

Another form of "fatigue" appears when voluntary contractions are performed with the arm under conditions of ischemia. They are likewise characterized by a progressive diminution of the number of active units and a decline in the frequency of the discharge. This phenomenon occurs if only an occasional movement is carried out in ischemia. Seyffarth suggests that it is due to afferent impulses originating in the muscles, which exert an inhibitory action on the central nervous system. This interpretation is supported by recent work showing that proprioceptive impulses from the Golgi organs are responsible

for the low frequencies of motor neuron discharges during voluntary and reflex activity (567). The intensity of these inhibitory effects must be great, since the frequency of afferent proprioceptive impulses is much higher in ischemic than in normal muscles (909). The well-known increased fatigability of ischemic muscles seems to be based on this mechanism. The rapid decline in frequency and the decruitment of the motor units account for the progressive reduction in the contractions.

The Nature of the Central Excitatory Process

From the observations described in the preceding sections it may be concluded that motor activity is graded on the basis of the simple principle expressed in the Adrian-Bronk law. No matter whether movements are induced at the cortical, medullary, or spinal level, and regardless of the nature of the stimuli which initiate the movement — volition, electrical stimuli applied to motor cortex or medulla oblongata, or reflex stimulation (involving mechanical or chemical stimulation of various receptors) — its intensity is graded through the number of activated neurons and the rate and duration of the discharge of each neuron. This remarkable uniformity in the mechanism of the gradation of the motor response (and, as will be seen, also of the sensory response) suggests that the activation of the motor neurons is accomplished in the same manner in these different conditions. Now it is known from studies on the peripheral nerve (Erlanger and Gasser, 323) and also from Kuffler's work (807) on the myoneuronal junction that as the result of an excitation induced by a brief shock, a slow potential develops which is a measure of the local excitatory state. With increasing stimulation this potential increases in amplitude and as soon as a critical value is reached it leads to a propagated disturbance, the action potential. Similar conditions prevail in the central nervous system. The local, slow (electrotonic) potential indicates the central excitatory state and is the basis for the development of the fast potentials which appear in the transsynaptic neuron (Fig. 5).

Barron and Matthews (76) have studied the relation between the slow electrotonic potentials and the fast spikes in the motor root after different degrees of reflex stimulation. They found that pinching the toes with a gradually increasing pressure sets up in the motor neurons a central excitatory state of increasing magnitude, indicated by a rising slow potential which is recordable from the motor root in close proximity to the spinal cord. On this potential is superimposed a series of spike discharges of increasing frequency which are propagated to the muscle. However, if the same stimulus is applied sud-

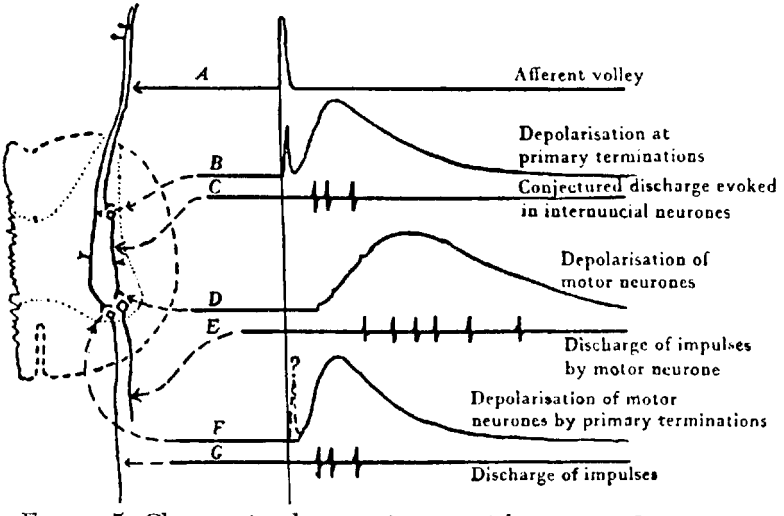

FIGURE 5. Changes in electrotonic potentials associated with a spinal reflex. (Barron and Matthews, 76.)

denly and then released, the slow potential is steep and declines slowly, with the higher frequency of the spikes confined to the beginning of the electrotonic potential. Similar records are obtained from the posterior root as the result of afferent impulses. As the diagram in Figure 5 suggests, the internuncial neuron is depolarized and a slow local potential develops in its cell body which gives rise to propagated spike potentials. As these potentials reach the synapses with the motor neurons, the slow and spike potentials recordable from the anterior roots are produced.

Further support for this interpretation comes from Gesell's work (536) on the relation between spinal potentials and phrenic discharges at different degrees of respiratory activity. The technique was similar to that of Barron and Matthews, and the potentials were recorded from the phrenic roots close to the spinal cord.

It was noted that during inspiration a slowly rising potential appears on which fast spikes are superimposed. The latter are the propagated action potentials which may also be recorded from the phrenic nerve and the diaphragm. The slow potential is an electrotonic potential such as results from the application of a constant current to a nerve. In both instances the slow potential declines very rapidly with increasing distance from its source. This electrotonic potential seems to originate in the motor horn cells and is related to their activity inasmuch as forcible breathing gives rise to a larger and steeper electrotonic potential than is noted during normal breathing. Apparently the rate

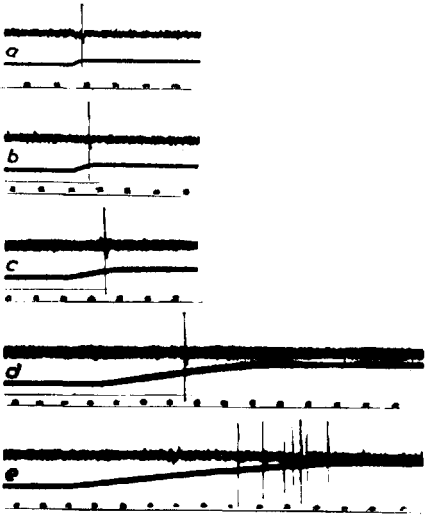

FIGURE 6. The effect on the latent period and frequency of action potentials of stimulating the sciatic nerve with currents of different strengths and gradients. Leads on filaments of the motor roots. For each record the rising time, the final strength of the current, the duration of the latent period, and the strength of the current at the end of the latent period are as follows:

a	6 ms.	28 μamp.	5 ms.	24 μamp.
b	15 ms.	40 μamp.	12 ms.	32 μamp.
c	35 ms.	52 μamp.	27 ms.	40 μamp.
d	120 ms.	120 μamp.	60 ms.	60 μamp.
e	200 ms.	170 μamp.	120 ms.	102 μamp.

The less the gradient, the higher is the threshold. (Kugelberg and Skoglund, 812.)

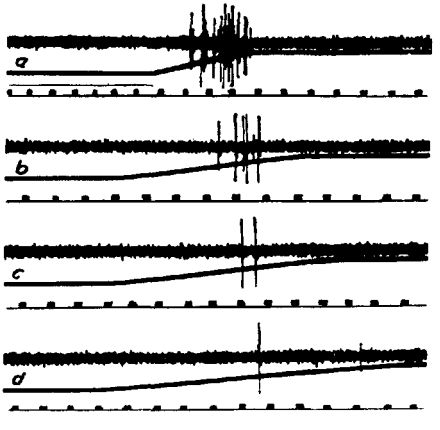

FIGURE 7. The effect of stimulating the sciatic nerve with successively slower gradients rising to the same final value. Timing marks: 20 milliseconds. The rising time, the final strength of the current, the duration of the latent period, and the strength of the current at the end of the latent period are as follows:

a	80 ms.	120 μamp.	35 ms.	53 μamp.
b	120 ms.	120 μamp.	65 ms.	65 μamp.
c	170 ms.	120 μamp.	100 ms.	70 μamp.
d	200 ms.	120 μamp.	115 ms.	70 μamp.

(Skoglund, 1118.)

of development of this potential as well as its magnitude determines the number of active neurons and the frequency of the rate of discharge. The experiments of Skoglund (1118) on the effect of linearly increasing currents on the peripheral nerve may be used as a physiological model for the understanding of the action of these electrotonic currents. If a current reaching a given intensity is applied to a peripheral nerve, the frequency of the discharge and the number of discharging units increase as the gradient is increased or, if the gradient is kept constant, as the intensity is increased (Skoglund, Figs. 6 and 7). The interested reader may consult Gesell's papers (532) on the genesis of these electrotonic potentials; for our purposes it may be

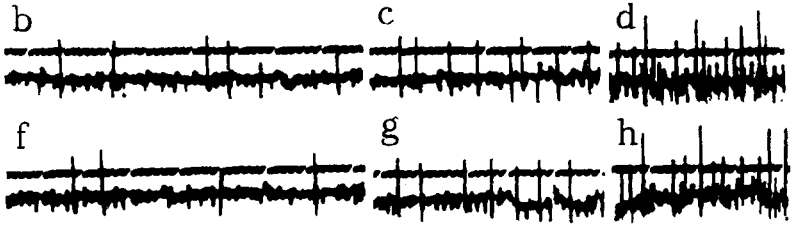

FIGURE 8. Action potentials from the first interosseus muscle during increasing degrees of voluntary contraction (b to d) and of electrical stimulation (f to g). (Kugelberg and Skoglund, 812.)

sufficient to point out that as the result of voluntary and reflex excitation nonpropagated electronic potentials, which determine the number and frequency of the propagated action potentials discharged by the motor neurons, appear at the motor horn cells.

These procedures of activating several units of a motor nerve with gradually rising currents have been applied to man (Kugelberg and Skoglund, 812), and the action potentials thus obtained were compared with those recorded through the same electrodes while a contraction was slowly increased through voluntary effort. As Figure 8 shows, the records are very similar under both conditions. At the first stage (Fig. 8, b, f) only very small and infrequent potentials appear, while with greater effort and stimulation this unit discharges at a greater frequency and a second unit, characterized by larger spikes, discharges a few times at irregular intervals. With further degrees of electrical and voluntary activation these units increase their rate of discharge (c, g) and finally cause the appearance of a third unit of a still larger amplitude (d, h). Apparently the same neurons react first to voluntary activation and electrical stimulation.

The striking similarity of the records under the two conditions makes it highly probable that the fundamental mechanism by which the neurons are excited is similar. An electrotonic potential of varying degrees of steepness and amplitude seems to underlie the central excitatory state of Sherrington (1110, 1111) and to produce graded movements at all levels of the central nervous system.

The Functions of the Sense Organs and the Adrian-Bronk Law

The preceding discussion has shown that movements originating at various levels of the central nervous system, from the simple reflex to the complex mechanisms underlying a voluntary act, are graded in intensity by processes involving the same principle. This result raises the question of the validity of this principle for the transmission of impulses via sensory nerves and the relation of the electrical activity recorded in these nerves to the gradation of the intensity of sensations. In the experiments designed to answer this question the procedure was similar to that mentioned earlier and aimed at the isolation of one or at the most a few sense organs or nerve fibers conducting the excitatory process to the central nervous system. The relation to the end effect is more complex than it is with movements, since in these animal experiments only the relation between the intensity of the stimulation of a sense organ and the action potentials recorded in the sensory nerve can be determined; but the resulting intensity of the sensation cannot be measured. As will be shown later, however, such a relation can be established, at least in certain cases, by indirect means.

STRETCH RECEPTORS AND THE EXCITATION OF SENSORY NERVES

Because of their importance for the activity of striated muscles, the discussion of the mechanism by which graded excitation can be transmitted to the central nervous system may be started with the stretch receptors in the muscle. Matthews' investigations (909) have shown that the striated muscle contains four different kinds of receptors which are located in the muscles themselves and in the fascia (Table 2). The former react to tension, the latter to movements of the muscle. Some are excited by muscle tension no matter whether it results from passive stretch or active contraction; others react only to passive tension and cease firing on contraction of the muscle. Although the excitation of proprioceptive receptors remains to a large extent below the level of consciousness and expresses itself in the coordination and reinforcement of cortically or reflexly induced

movements, their impulses reach the sensorimotor cortex (416). This accounts for our ability to reproduce voluntarily a movement leading to the development of a certain tension under mechanically different conditions and after the elimination of cutaneous receptors through anesthesia (von Frey, 389, 390).

Matthews studied the effect of stretch and contraction of the muscles on single nerve endings and found that with an increase in

TABLE 2. Some Physiological Characteristics of the Proprioceptive Sense Organs (after Matthews, 908)

Threshold	Excited by	Structure
A1 ..... Low	Stretch	Flower-spray endings of muscle spindle
A2 ..... Medium	Stretch and contraction	Annulo-spiral endings
B ..... High	Stretch and contraction	Ruffini's corpuscles in tendons
C	Movement	End-organs in the fascia

the load the rate of discharge increases, the maximal rate being nearly 200 per second. The frequency, however, increases not only with the load but also with the rate of loading. Matthews' records show that some receptors react to passive stretch and cease firing during contraction of the muscle whereas others react only to high tension and are called into action during contraction. The former produce small action potentials and show a low threshold, while the latter set up larger potentials and have a higher threshold. The difference in magnitude between the action potentials indicates clearly that different units are activated.

Finally it should be mentioned that the effects of stimulation of the motor cortex on a certain muscle may be greatly intensified by proprioceptive impulses induced by the fixation of a joint in such a position that the muscle is stretched slightly. The increased tension is paralleled by an augmentation in the amplitude of the EMG.* The unit analysis shows that an increase in the frequency of the discharge of individual neurons and recruitment are involved (512) (see Table 3).† The latter is in part due to the fact that, as Matthews noted,

* See p. 64 for further details.

† Bearing in mind the fact that impulses from the Golgi receptors restrain the frequency of motor discharge (see pp. 19, 37), it may be said that proprioceptive reinforcement is due to increasing rates of discharge and recruitment which occur within the limits set by the activity of the Golgi organs.

TABLE 3. The Influence of Proprioception on Single-Unit Response to Cortical Stimulation of Varying Frequencies* (Gellhorn and Riggle, 512)

Intensity, in Volts	Frequency, in Cycles per Second	Ankle†	Total No. of Units Responding	Maximal Unit Frequency, in Cycles per Second	Total No. of Spikes in 1 Second ‡
3.0	27	70	2	28	17
3.0	27	140	4	28	42
3.0	53	70	2	56	27
3.0	53	140	4	58	57
3.0	102	70	4	51	63
3.0	102	140	6	72	83

* Stimulation of a hind-leg focus of area 4 in a "Dial" monkey. Recording from the tibialis anticus.

† The numbers indicate the angle at which the ankle has been fixated.

‡ Selected from the period of optimal response.

different groups of receptors have different thresholds (see Table 2). This "peripheral" recruitment results in central summation, with activation of more motor neurons.

Stretch receptors are also found in respiratory muscles. During tracheal occlusion the tension is greatly increased in the inspiratory muscles. Proprioceptive reflexes are set up which reinforce respiration (365). Unit electromyograms of the external intercostal muscles show an increase in the frequency of those units which discharge under resting conditions, and the recruitment of new units (Worzniak and Gesell, 1250). Since these effects also occur in the vagotomized animal, they are independent of the reflex action of the vagal stretch receptors.

Another group of stretch receptors which influence circulation and, to a lesser degree, respiration are located in the carotid sinus and the arch of the aorta. They are called into action when the pressure in the sino-aortic area is increased and lower the tone of the medullary sympathetic centers and thereby diminish the blood pressure and heart rate.* They depress the respiratory minute volume through reflex action on the respiratory center. By recording action potentials from the carotid sinus nerve after its reduction to only one or a few active fibers, Bronk and Stella (145, 146) found that the rate of the discharge of each unit increases linearly with increases in the pressure and that more and more units are recruited under these conditions. When the pressure is low the discharge may be confined to the systole; at higher pressures it also occurs during the diastole. Apparently the

* Concerning the simultaneous reciprocal effects on the vagus, see Gellhorn, *Autonomic Regulations* (446), pp. 208ff.

carotid sinus, just like the striated muscle, contains stretch receptors with widely different thresholds.

Finally, stretch receptors send their impulses via the vagus to the respiratory center (Adrian, 6). They are activated progressively with increasing inflation of the lungs. This is indicated by the mounting rate of discharge recorded in single-unit preparations of the vagus and by recruitment if the preparation consists of several nerve fibers. The various units show again widely different thresholds, while the range of frequencies varies between 0 and 50 per second. At a certain value these impulses become strong enough to inhibit inspiration. The lungs begin to deflate and the discharge from the stretch receptors falls rapidly. If the respiratory center is in a state of heightened activity during carbon dioxide inhalation, a greater degree of inflation is necessary to inhibit respiration through the excitation of vagal stretch receptors, and the frequency of the vagal impulses is augmented. The loss of this inhibitory afferent control of respiration results in an increased depth and duration of inspiration, as demonstrated by the effect of bilateral vagotomy. Under these conditions the unit analysis of respiratory muscles reveals that the increased inspiration is due to recruitment and an increased rate of discharge from the inspiratory center.

Further studies (787) indicate, on the basis of threshold determination, rate of adaptation, and physiological function, that three different stretch receptors are present in the endings of the vagus in the lungs. The first two are brought into action by inflation of the lungs. Those of low threshold are activated by moderate degrees of expansion of the lungs, inhibit respiration, and adapt slowly, whereas high-threshold receptors discharge briefly (i.e., adapt rapidly) and intensify inspiration. There is in addition still another respiratory reflex produced by vagal stimulation, but it occurs not on inflation of the lungs but on deflation provided that the latter goes beyond the level attained in normal breathing (819, 1250).

VESTIBULAR AND ACOUSTIC RECEPTORS

Impulses recorded from single vestibular nerve fibers have likewise shown the validity of the Adrian-Bronk law for the receptors located in the ampullae of the semicircular canals and also for those in utriculus and sacculus which are stimulated by changes in the position of the otoliths (9). If the potentials of a single fiber of the right vestibular nerve are recorded, it is found that during rest there is a slight tonic discharge which is greatly increased on clockwise rotation but is diminished on anticlockwise rotation. Recordings from the whole

nerve show recruitment and decruitment respectively under these conditions (875, 876). Similar preparations in which the activity from small branches supplying sacculus and utriculus was studied showed in these nerves a tonic discharge and increases or decreases in the frequency of these potentials depending on the position in space. The frequency range is between 0 and approximately 70 per second (874).

Different neurons of the cochlear nucleus respond to different frequencies of auditory stimulation. As the intensity of the sound is increased, the frequency of the rate of discharge increases, the maximum being about 400 per second (407). Some neurons show, as do also those of the vestibular nerve, a spontaneous low frequency discharge which can be inhibited by a tone of a frequency slightly different from that to which the neuron is specifically attuned (261).

THE ACTION OF CHEMORECEPTORS

Action potentials in the carotid sinus nerve are due to impulses originating in the pressoreceptors and chemoreceptors at the bifurcation of the carotid artery. The former are larger in amplitude, are said to be mediated by nerve fibers of larger diameters, and show a higher conduction rate than the latter. This interpretation of the action potentials which are recorded from the carotid sinus nerve is based on the fact that surgical removal of the pressoreceptors only reduces or eliminates the large potentials.

The chemoreceptors are activated by the increased carbon dioxide tension and the lowered oxygen tension of the arterial blood, as indicated by the observation that the small potentials disappear on the inhalation of pure oxygen and hyperventilation. If the pressoreceptors have been removed previously, these procedures lead to the elimination of all potentials. Apparently the normal carbon dioxide tension in the blood is adequate to induce impulses in the carotid sinus nerve, since potentials persist even after complete saturation of the blood with oxygen. An increase in the carbon dioxide tension as well as a decrease in the saturation of the blood with oxygen increases the frequency of the potentials. The records suggest that with an increase in the intensity of the chemical stimulation the number of reactive nerve fibers is augmented (recruitment). It may be added that these actions of hypercapnia and anoxia on the chemoreceptors are abolished by the injection of ammonia. Apparently a lack of oxygen as well as an increase in the carbon dioxide tension acts on the sensory receptors through increased cellular acidity (von Euler, Liljestrand, and Zotterman, 330).

Single fiber preparations of the chorda tympani and the glossopharyngeal nerve give evidence of three specific taste receptors which respond to acid, sodium chloride, and quinine in various combinations (Pfaffman, 1007). The discharge rate increases as the concentration of the chemical stimulants is increased.

OPTICAL RECEPTORS

The investigations of Hartline (606–608) give valuable information on the relation between optical stimulation of the retina and action potentials in the optic nerve. In the invertebrate retina (limulus) each nerve fiber responds only to the excitation of a single retinal cell, and the discharge rate increases with increases in the intensity of illumination. In the vertebrate eye functionally different groups can be distinguished in the optic nerve. Twenty per cent of the nerves react to illumination with a high frequency discharge, followed by a steady discharge at a lower rate while the optical stimulation persists; 50 per cent react to both the onset and the cessation of light; and 30 per cent give only an "off" effect. But even under these complex conditions it is obvious that the frequency of the discharge and its duration increase with the intensity of illumination.

Studies on the discharge in single fiber preparations of the optic nerve are of importance because they furnish some indirect evidence of the relation of these nerve discharges to the intensity of sensation. It is known that the subjective brightness shows for the dark-adapted eye a maximum in the green part of the spectrum and falls off rather symmetrically for light of lesser or greater wave length. If light of different wave lengths is used on the eye of limulus and the intensity is determined which causes the appearance of a constant number of nerve impulses, it is found that a similar curve is obtained which indicates greater responsiveness to light in the green (565). The absorption of light by the visual purple, the subjective brightness, and the susceptibility of the retina to light, as measured by the intensity necessary to produce a specified number of nerve impulses, run parallel.

The relation between neuron discharge, as measured by the number of action potentials in a single afferent nerve fiber, and the intensity of sensation can also be explored by determining the subjective and objective criteria for the visual threshold. The following consideration is pertinent. It is well established that within certain limits the threshold of a light sensation is determined by the equation $I \times t = c$. That is, with a decrease in the intensity (I) of light, the time of exposure (t) increases in proportion. Similarly it is found that if the time of exposure is increased 10, 100, and 1,000 times as

the intensity of the illumination decreases to $\frac{1}{10}$, $\frac{1}{100}$, and $\frac{1}{1000}$, the effect on the action potentials in the optic nerve remains unchanged (Hartline, 606). The fundamental work of Hartline seems to show not only that with the intensity of the stimulation the frequency of the action potentials in an individual fiber and the total number of the discharges increase, but also that the intensity of the sensation is directly related to these discharges.*

CUTANEOUS RECEPTORS

Studies on the relation of cutaneous sense organs to sensory nerve discharges show a rather curious result. Whereas the stimulation of touch receptors results in large, frequently grouped potentials, the excitation of pain receptors through needle prick induces very small impulses which are apparently related to small, slowly conducting nerve fibers (Adrian, 15; Zotterman, 1259). This work was confirmed by the study of action potentials in sensory nerve fibers after the stimulation of teeth. The application of pressure gives rise to large impulses which may discharge as often as 1,000 times per second, whereas high and low temperature stimuli, which presumably cause pain sensations, cause only small potentials, mediated by slowly conducting nerve fibers (1005, 1006).

The work of Adrian and his group seems to support von Frey's concept that pain and pressure sensations are mediated by different neurons. There is, however, some interesting evidence for the assumption that proprioceptive neurons may under certain conditions conduct nociceptive impulses. It is well known that voluntary contractions of the ischemic muscle become exceedingly painful (Lewis, 839). Matthews (909) showed that occlusion of the circulation, particularly when combined with stimulation of the motor nerve, leads to spontaneous discharges from stretch receptors, up to 400 to 500 impulses per second, which are far in excess of those seen in response to maximal stretch in the normally oxygenated preparation. There is a remarkable parallelism between the spontaneous high-frequency discharges of the occluded muscle and the appearance of pain in Lewis's observations. It is possible that the rapid discharges in proprioceptive neurons are interpreted as pain or that contractions of the ischemic muscle cause high frequency discharges from proprioceptive end-organs and in addition stimulate through an unknown chemical principle (Lewis factor "P"?) the pain endings in the muscle. A decision between these two mechanisms is at present impossible, but it

* On the modifying action of the cerebral cortex on the perception of visual intensity, see p. 424.

should be emphasized that high frequency of discharge per se does not elicit pain, as experiments involving cutaneous stimulation indicate (Adrian, Cattell, and Hoagland, 15). On the other hand, Matthews mentions that stimulation of a muscle nerve through the skin at 500 per second becomes very painful, and observations to be discussed later* indicate rather close relations between proprioceptive and nociceptive impulses with respect to cortical excitation.

THE CONDUCTION OF EXCITATION FROM THE SENSE ORGANS TO THE AFFERENT NERVE

Thus far the relation between the stimulation of a sense organ and the discharge in an afferent nerve has been considered, but not the important intermediary processes by which the mechanical, chemical, thermic, or other stimuli are converted into an excitation of the sense organ which is transmitted to the nerve. A recent study of Katz (757) gives some valuable information on this problem, and although confined to the proprioceptors of the muscles, it permits some generalization.

If the potential difference between the muscle and the afferent nerve fiber is recorded very close to the muscle spindle of the extensor digitorum longus IV, it is possible to relate rate and intensity of stimulation to certain local electric changes of the sense organ and to the propagated disturbance of the nerve. Only a minimal stretch is necessary to cause a depolarization of the muscle spindle, which appears in the form of a negative potential. Its amplitude increases with the rate as well as with the magnitude of stretching, and these two factors, as was mentioned earlier, determine the frequency of the firing in the afferent nerve. The local potential and the propagated disturbances can be separated by procaine, which eliminates the propagated impulse but does not alter the local potential. This work confirms and expands the principles established by Gasser and Erlanger (323) regarding the electrical excitability of nerves. The stimulation of a nerve with subthreshold currents produces a local electrotonic potential, and only with further increase in the intensity of the stimulus does a propagated disturbance (action potential) appear. The principle involved in the production of nervous impulses is the same regardless of the means by which excitation is evoked. The adequate stimulation of proprioceptive end-organs through stretch induces a local depolarization of the end-organ which determines the degree of sensory excitation and consequently the frequency of the neuronal discharge. Similar changes result from the

* See pp. 197ff.

application of an electrical stimulus to the nerve. This fundamental agreement in these two sets of observations is perhaps not surprising, since the sense organs in the skin and muscles are part of the sensory neurons, as attested by experiments on peripheral nerve regeneration; but it provides another indication of the electrical nature of the excitatory process and of the nerve impulse.

From the work of Barron and Matthews (76) and Gesell (536) it may be inferred that electrotonic potentials are responsible for the transmission of impulses through the spinal cord and the gradation of motor discharges at the spinal and medullary levels. The similarity between the voluntary discharge and that induced by slowly rising currents applied to motor nerves in the human being suggests that both processes are initiated in a similar manner, i.e., by a local depolarization, since this is the effect of applying a linear current to the nerve. Apparently there is a uniform electrical basis for local and propagated excitation, independent of whether the latter involves conduction from sense organ to spinal cord or in addition transmission through one or more synapses.* The peripheral and the central excitatory state are characterized by the degree and the rate of depolarization of receptors and sensory, motor, and internuncial neurons.

The Gradation of Autonomic Activity

An application of the methods previously described to the autonomic nerves made possible a study of the rules by which the activity of these neurons is quantitatively regulated. In the earlier work (Adrian, Bronk, and Phillips, 14) an analysis in terms of single autonomic units was not yet possible, but recordings from different sympathetic nerves showed that action potentials appeared in groups related to cardiac and respiratory activity. These groups increased in frequency during inspiration and disappeared gradually during expiration. They indicate temporal variations in the degree of the excitation of sympathetic centers, since the elimination of important afferent impulses through vagotomy and curarization were without significant effect. Moreover it was found that the sympathetic discharges increased when the blood pressure had been lowered by histamine or amyl nitrite, while the converse change in sympathetic activity accompanied the pressor action of adrenalin. These changes in the frequency of grouped action potentials in the sympathetic nerves were practically abolished by sino-aortic denervation. Apparently the reflex changes initiated by the stretch receptors of this area

* The chemical aspect of the problem of synaptic transmission is treated in Chapter 11.

are responsible for the alterations in the frequency of the sympathetic discharge.

HYPOTHALAMIC STIMULATION AND SYMPATHETIC ACTIVITY

An excitation of the sympathetic centers leads to quantitative changes in the peripheral neurons in agreement with the Adrian-Bronk law. If potentials are recorded from a single nerve fiber of the superior cervical nerve, the rate of discharge increases as the intensity of the hypothalamic stimulation is increased (Pitts, Larrabee, and Bronk, 1019). If more than one active fiber is present, more fibers are called into action as the central excitatory state is augmented. Obviously recruitment and the rate of discharge are the mechanisms by which the motor effect is graded in the autonomic nervous system. As in the somatic nervous system, the threshold varies considerably for different effector neurons.

Simultaneous recordings of the blood pressure and of the discharge in the inferior cardiac nerve show clearly the functional significance of the changes in sympathetic potentials. If the hypothalamus is stimulated with increasing intensity, the neurons discharge in increasing numbers and with increasing frequency, while the pressor action on the blood pressure is augmented (Fig. 9).

It was mentioned earlier that the degree of excitation of the motor cortex and of the respiratory center could be varied by either increasing the intensity or the frequency of stimulation. Bronk *et al.* (144) showed that this rule applies to the autonomic system and results in increasing rates of discharge. It should be noted that in either case the rate of discharge is low; in sympathetic nerve fibers it is mostly below 20 per second even with stimuli of considerable intensity or frequency.

The fact that stimulation of the ipsilateral and contralateral hypothalamus alters the activity of a single neuron of the cervical sympathetic makes it possible to study summation phenomena. The experiments of Pitts and Bronk (1018) show that the total effect corresponds rather closely to the algebraic sum of the action of the two stimulations. Apparently there is little central overlap in the neurons mediating these sympathetic effects, in contradistinction to the conditions prevailing in somatic reflexes, in which with strong stimuli occlusion* occurs.

* That is, the total effect expressed in reflex tension is less than the sum of the action of the two stimuli. Occlusion is considered a measure of central overlap (244).

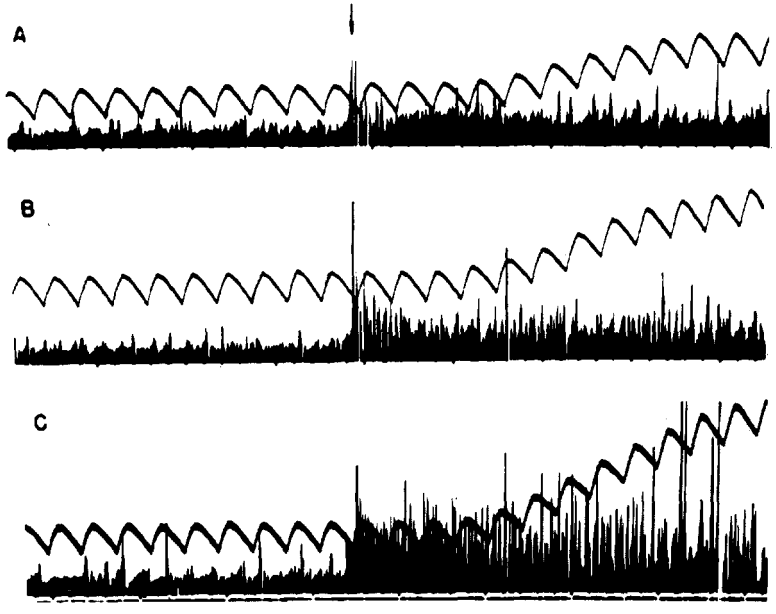

FIGURE 9. The increased discharge of sympathetic impulses in the inferior cardiac nerve and the rise in the blood pressure produced by stimulating the hypothalamus with a frequency of 150 per second. The beginning of stimulation is indicated by the arrow. Relative strengths of the stimuli: *A*, 1; *B*, 2; *C*, 3. Time: $\frac{1}{5}$ second. (Bronk, Pitts, and Larrabee, 144.)

It is known that sympathetic discharges are inhibited through the carotid sinus. This inhibition of sympathetic discharges is controlled in the same manner as the inhibition of somatic neurons, i.e., by a decrease in the rate of the discharge of individual neurons and by decruitment. But inhibition of the sympathetic discharge can also be accomplished by appropriate stimulation of the sympathetic centers. Hare and Geohagan (591) have shown that stimulation of the hypothalamus with low frequencies tends to lower the blood pressure, while high frequencies produce a pressor response. Since these effects persist after vagotomy, it appears probable that excitation and inhibition of the peripheral sympathetic can be controlled by varying the frequency of the stimulation in the hypothalamus. Action potential studies confirm this interpretation and show that with higher frequencies (20 per second) the total discharge in the cardiac nerve increases, whereas on stimulation with a rate of 2 per second the discharge is abolished at first and then its rate is reduced below that of the spontaneous discharge recorded before the stimulation. The change in

the sympathetic discharge is reflected in corresponding changes in the blood pressure (94).

Since the chief efferent factor in sympathetic regulation of the blood pressure lies in the splanchnic nerve, an investigation of its activity according to the principles established by Adrian and Bronk is of particular interest. It was to be expected that procedures which lead to an increase in the blood pressure would be accompanied by an increase in the number of impulses in the splanchnics whereas those causing a depressor action would result in a reduction of the electrical activity of this nerve. The work of Gernandt, Liljestrand, and Zotterman (530) illustrates the dependence of efferent splanchnic impulses on sino-aortic reflexes. A lack of oxygen increases and the inhalation of pure oxygen decreases the number of splanchnic potentials through chemoreflexes of sino-aortic origin, since after denervation of this area variations in the oxygen tension no longer have an effect on them. The inhalation of carbon dioxide increases activity in the splanchnic nerve, but in contradistinction to the mechanism involved in anoxia, this action of hypercapnia is not solely of sino-aortic origin, since it persists, although to a lesser degree, after elimination of the chemoreceptors. These experiments agree with previous studies (Gellhorn and Lambert, 502) in which it was shown that the pressor action of anoxia on the blood pressure is abolished by sino-aortic denervation whereas that of hypercapnia persists, a fact indicating that the latter exerts a hypertensive effect through the direct stimulation of sympathetic centers as well as through reflex action on chemoreceptors.

Variations in the carotid sinus depressor reflexes induced by changes in intrasinusal pressures likewise alter the potentials of the splanchnic nerves. A lowering of the blood pressure by acetylcholine or bleeding increases, and a rise in the pressure due to the injection of adrenalin decreases, the sympathetic potentials. These effects are abolished by sino-aortic denervation. The tonic activity of these reflexes is demonstrated by the fact that sino-aortic denervation increases the splanchnic discharge which parallels the increased blood pressure.

NEURONAL EXCITABILITY AND THE RATE OF SYMPATHETIC DISCHARGE

The preceding discussion has shown that in spite of the bewildering complexity in the structure of the nervous system, the neuron – somatic and autonomic, afferent as well as efferent – accomplishes the gradation of activity by the simple means of altering the rate and duration of the discharge and varying the number of discharging units. There are considerable differences between different neurons in the range of

the rates of discharge and in adaptation. Even the same neuron shows wide variations in this respect depending on its state of excitability. This is well illustrated by Pitts and Bronk's investigations (1018) on the sympathetic system. They found that stimulation of the hypothalamus with a certain intensity or frequency results in a steady discharge rate maintained unchanged over a number of seconds. If during this stimulation (A) the contralateral side of the hypothalamus is briefly stimulated (B), it is noted not only that the discharge rate during the simultaneous stimulation of both sides of the hypothalamus is increased – this is the phenomenon of summation previously mentioned – but also that the reactivity of the sympathetic neuron to A is altered as the result of the preceding stimulation by A and B. Instead of firing after the cessation of B at the same rate at which it discharged prior to the application of this stimulus, it shows a decline in the rate or a cessation of firing at first and then gradually increases its rate until the control level is reached. This diminished rate of discharge and its duration may be taken as an indicator of the diminished excitability of a sympathetic neuron, and the degree of change is directly related to the intensity, frequency, and duration of the B stimulus.

This surprising simplicity in the behavior of a sympathetic neuron may serve as an illustration of the important fact that the responsiveness of a neuron or a group of neurons to a series of stimuli is determined not only by gross changes in the internal environment, explored so assiduously by physiologists since the time of Claude Bernard, but also by the impulses which reach a particular neuron from various levels of the central nervous system before the test stimulus or simultaneously with it. With these internal factors kept constant, increased excitation appears in the activation of a growing number of neurons (recruitment), discharging at increasing rates, whereas inhibition leads to decruitment and a decreased rate of discharge if not to a complete cessation of activity.

Concluding Remarks

This survey has shown that the centrifugal transmission of motor discharges and the centripetal transport of afferent impulses are related in a simple manner to the excitatory processes set up in motor neurons and sense organs respectively. The frequency of discharge varies within wide limits but remains in almost all instances far below its physiological limit, which is determined by the absolute refractory period of the nerve. The chief difference between the various sense organs as far as the transmission of impulses is concerned lies in the rate of the adaptive process which is a characteristic of the peripheral

receptor organ. If a constant stimulus is applied (a given light intensity or a given pull on a muscle, etc.) the excitation produced in the receptor organ declines very little and slowly or very much and rapidly (5). In the first case adaptation is slow, as in almost all stretch receptors, or rapid, as in cutaneous receptors. Optic and acoustic receptors show an intermediate degree of adaptation. The slow adaptation of stretch receptors in the carotid sinus and in striated muscles accounts for the continuous presence of the important vascular carotid sinus reflexes and the persistent reflex reinforcement of muscular contraction under load. The rapid adaptation of cutaneous sense organs initiating the sensation of touch and pressure makes it possible to perceive in quick succession many impulses from different parts of the skin and thereby facilitates the tactile recognition of objects. The objective indicator of slow and rapid adaptation is the degree of the decline in the discharge rates and the degree of decruitment in sensory nerves while a constant stimulus is applied to a receptive area. This change is considerable in nerves activated by rapidly adapting cutaneous sense organs, but minimal in those stimulated by carotid sinus pressure receptors.

In spite of the similarity in the mechanisms by which the gradation of excitation is achieved in motor and sensory neurons, a striking difference between them should be pointed out. Whereas the frequency range of discharge is very wide and rates of more than 1,000 per second have been observed in sensory neurons, the rate is low in skeletal muscles even under conditions of maximal effort. The gradation of muscular activity in voluntary movements and on stimulation of the motor cortex seems to involve primarily changes in the number of activated neurons. Some authors claim that the rate is independent of the intensity of effort (584). The significant difference between motor and sensory neurons implies that inhibitory processes keep the rate of discharge low in the motor neurons. This form of "autogenetic inhibition" probably originates, as already mentioned, in the Golgi organs of the muscle tendons. "The low firing frequencies of ventral horn cells suggest that they always work with the inhibitory brakes applied" (Granit, 567).

~ 2 ~

The Internal Environment and Central Nervous Activity

THE changes produced in sensory and motor neurons by physiological stimuli have been analyzed in the preceding chapter on the basis of action potentials which indicate that the gradation of activity is achieved in the same manner in the somatic and in the visceral nervous system. This work must be supplemented by the study of neurons under the influence of chemical factors. Any nervous function at spinal or supraspinal levels can be investigated for this purpose; but the great responsiveness of the cortex to such changes, related to its high metabolic rate, and the importance of this structure for problems of physiology and neuropsychiatry make it a very suitable test object for the evaluation of neuronal activity under these conditions. Although it is possible to obtain unit action potentials from the gray matter, the bulk of the literature is derived from experiments in which the activity of numerous neurons has been recorded either directly, from the surface of the brain (as electrocorticogram, ECG), or indirectly, from the skull (as electroencephalogram, EEG). It is of particular value not only that a comprehensive material on the reactivity of the cerebral neurons of man and animals has been secured through these methods but also that some insight has been gained into the group behavior of neurons, especially concerning variations in the degree of synchrony. For this reason the effect of changes in the internal environment on the EEG or ECG, occasionally supplemented by studies on other nervous structures, will be reported.

Cortical Activity and the Oxygen Supply

The great sensitivity of the cerebral cortex to a reduction in the oxygen supply is well established. It is evident from the diminution

of sensory acuity (435, 514, 515) and from the lengthening of the duration of simple mental operations (496, 501). These subjective changes are paralleled by changes in the cortical potentials (99). In the early stages of hypoxia the frequency of the cortical potentials declines in man (544) and animals (772); then large, slow delta waves appear;* and finally the amplitude decreases and approaches zero. Even under these conditions normal potentials can be restored by the readmission of air. The reduction in frequency and the appearance of delta potentials seem to be an expression of increased synchrony,† while the diminution in the amplitude which occurs at a later state is accounted for by gradual decruitment of the actively discharging neurons. However, occasionally signs of excitation in the form of brief periods of increased frequency appear in the EEG which probably indicate increased discharges from subcortical structures, temporarily released from the inhibitory action of the cortex.‡ In spite of the sensitivity of the cortex to anoxia, EEG studies reveal a large factor of safety, since the slowing of cortical potentials does not take place in man until the oxygen saturation of the venous blood in the brain has been reduced from 60 to 30 per cent (544). With a further reduction of the venous blood to 28 per cent, consciousness is lost. Variations in respiratory activity may be reflected in the EEG in certain conditions. Thus an acceleration in the frequency of cortical potentials is observed in patients with Cheyne-Stokes breathing during the hyperpneic phase (319).

The ligation of one carotid artery in man may or may not lead to a slowing of the ipsilateral cortical potentials, depending on the degree of collateral compensation (623). By occlusion of almost all the blood vessels in the neck through a pressure cuff, it has been found that cessation of the cerebral blood flow causes the appearance of delta potentials in the EEG together with loss of consciousness within a few seconds (1070). The capacity for circulatory adjustment under condi-

* The observation that sodium cyanide on intravenous injection in man (1073) increases the cortical frequency when excitability is high and decreases it when excitability is low (in narcolepsy and catatonic stupor) needs confirmation.

† There is a tendency for groups of neurons to discharge in synchrony in the absence of stimuli. This accounts for the alpha potentials seen in the EEG when the eyes are closed. The synchronizing effect is probably due to action potentials of some discharging neurons which influence adjacent neurons. Arvanitaki (42) showed in invertebrates that isolated neurons beating independently assume the same rhythm when they are brought close together. Moreover a resting neuron may pick up the rhythm of a proximate active neuron. Further investigations showed the validity of this concept for the vertebrate brain. Electrical effects due to normal or convulsant potentials influence adjacent neurons across surgical incisions (130, 524, 841).

‡ See p. 153.

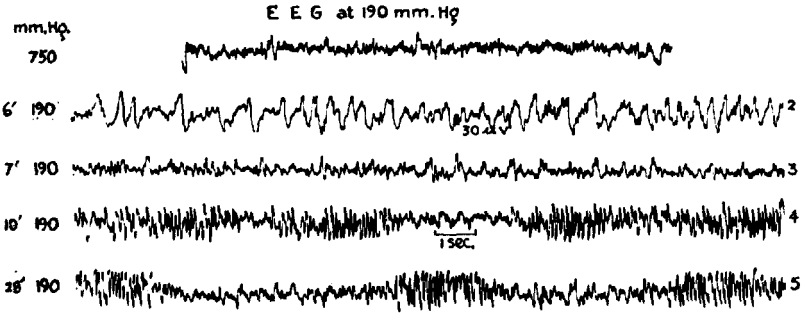

FIGURE 10. The effect of reduced barometric pressure on the electroencephalogram of the unanesthetized rat. (Kessler, Hailman, and Gellhorn, 772.)

tions of restricted brain circulation is much greater in animals than in man. Asenjo (43) found in the rabbit that ligation of one or both carotid arteries does not abolish brain potentials. The ligation of both carotid arteries together with the clamping of one vertebral artery reduces brain potentials, but they disappear completely only when the remaining vertebral artery is ligated. Bremer (127) observed in the unanesthetized cat a decrease in the amplitude of cortical potentials upon the clamping of both carotids, but these effects tended to disappear within a minute in spite of continued curtailment of the circulation.

The effect of anoxia on cortical potentials has been studied in animals with different procedures. Anemia of varying degrees was achieved by the ligation of arteries, a rise in the intracranial pressure, or a fall in the blood pressure, while hypoxia was induced by the inhalation of oxygen-nitrogen mixtures, a clamping of the trachea, or a lowering of the barometric pressure. That the oxygen tension of the brain is related to the blood pressure and to the oxygen tension of the inhaled oxygen-nitrogen mixture was shown by a polarographic method (1064). It is interesting to mention that when pure oxygen is inhaled instead of air, the oxygen tension of the brain rises very considerably, although the oxygen concentration of the arterial blood is increased but slightly. The effect of the different procedures inducing similar degrees of hypoxia is in essence the same (noted in studies on the human EEG). As is to be expected, the changes depend on the speed with which anoxia is reduced and on its degree and duration (772).

Figure 10 illustrates the appearance of large, slow potentials as the

barometric pressure is lowered to 190 mm. Hg.* At this time not only the cortex but also the midbrain is depressed: righting reflexes and frequently also cortical potentials are temporarily absent. However, in all experiments cortical potentials and righting reflexes reappear, although the animal is kept at the same barometric pressure. Under these conditions the potentials form distinct groups of large amplitude (spindles) at about 10 per second, which are separated from each other by trains of small frequent potentials. The EEG is similar to that seen in sleep and suggests that the hypothalamic center of wakefulness is still depressed, whereas owing to circulatory adjustments midbrain functions (righting reflexes) are restored.

These "spindles" occur at moderate degrees of hypoxia (barometric pressure 280 to 160 mm. Hg) except in animals previously injected with benzedrine, although the initial effects of anoxia on the EEG and on behavior (cortical silence and disappearance of righting reflexes) are the same in both groups. The interpretation of the "spindles" as an expression of anoxic hypothalamic depression leading to a sleeplike condition is supported by the finding that benzedrine, which is clinically used as a stimulus to counteract sleeplike conditions, restores

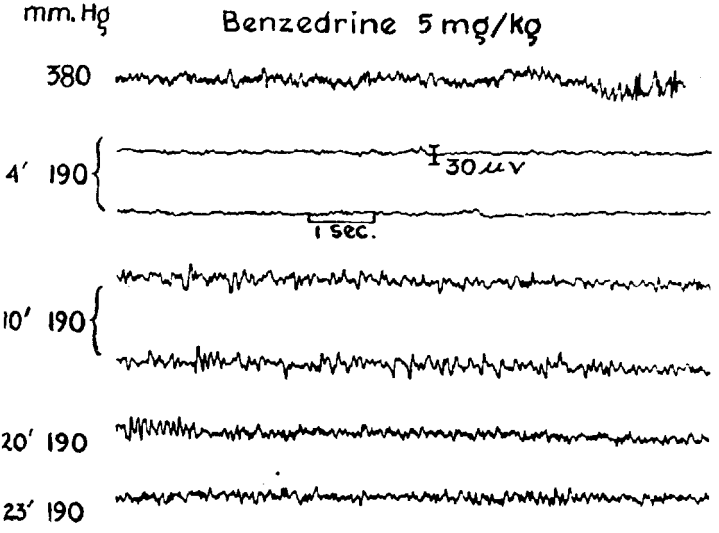

FIGURE 11. The effect of benzedrine on the electroencephalogram of the rat under conditions of reduced barometric pressure. (Kessler, Hailman, and Gellhorn, 772.)

* Experiments on rats show that a lowering of the barometric pressure per se does not alter the EEG as long as a fall in the oxygen tension of the inhaled air is prevented (586).

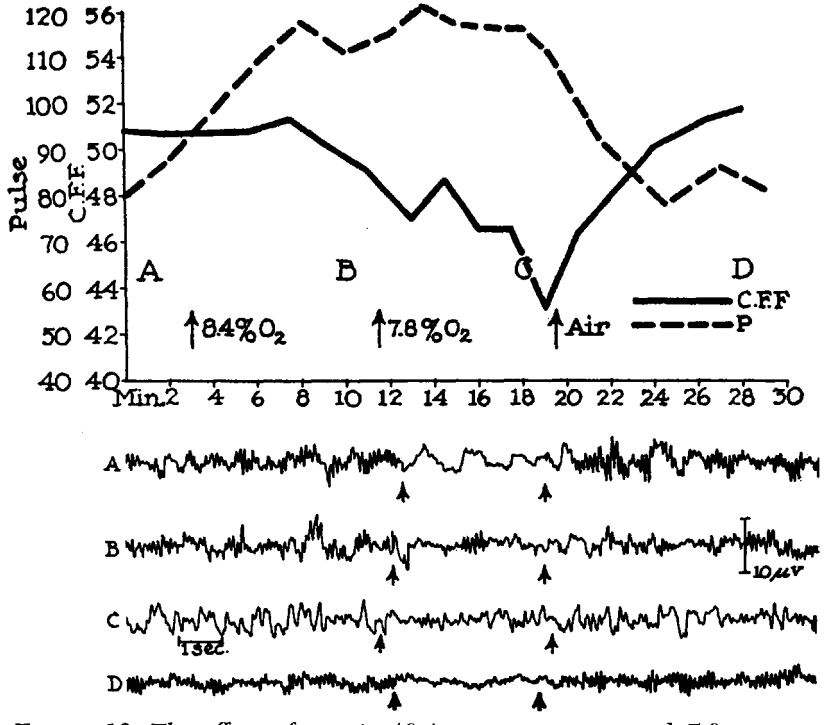

FIGURE 12. The effect of anoxia (8.4-per-cent oxygen and 7.8-per-cent oxygen) on the critical visual fusion frequency (C.F.F.), pulse rate (P), and electroencephalogram in man. Note the decline in the C.F.F. and the occurrence of slow potentials in the EEG. Between the arrows the eyes were opened and an object was fixated.

normal behavior at lowered barometric pressure.* At 190 mm. Hg normal potentials appear and the animals move freely (Fig. 11). However, when the pressure is lowered to 140 mm. or less, the electrical activity of the brain is progressively diminished in frequency and amplitude. Righting reflexes remain permanently absent, no "spindles" occur, and benzedrine is without effect. Apparently the diencephalon and midbrain remain greatly depressed, and a slowing of the pulse and gasping indicate the involvement of medullary centers.

The large factor of safety apparent from the study of anoxia on cortical potentials is likewise seen when the relation of the intracranial pressure to cerebral activity is investigated (376). When the blood pressure exceeds the intracranial pressure by 40 mm. Hg or more, the EEG is unchanged. This indicates that the rise in the intracranial

* Concerning the role of the hypothalamus in sleep see pp. 186ff.

pressure in clinical cases is insufficient to account for electroencephalographic changes. If the pressure difference is less than 40 mm. Hg, the potentials diminish in frequency and increase in amplitude. With the intracranial pressure equal to or in excess of the blood pressure the potentials disappear. Since not the absolute pressure but the ratio of the blood pressure to the intracranial pressure is the decisive factor, the experiments must be explained on a circulatory basis. As the intracranial pressure approaches the blood pressure, it interferes with the blood supply to the brain. This accounts for the similarity between the action of anoxia and an increased intracranial pressure on brain potentials.

The inhalation of 3- to 5-per-cent carbon dioxide greatly increases the resistance of man and animal to anoxia. Since a full discussion of this problem has been given elsewhere (436–439, 445, 446, 489) it may suffice to state that low concentrations of oxygen, which lead to slow, large potentials in the EEG, a decline of sensory functions, and a loss of consciousness, are well tolerated in the presence of carbon dioxide, so that the subjective and objective (EEG) signs of normal cortical activity are maintained (Figs. 12 and 13). An analysis of the

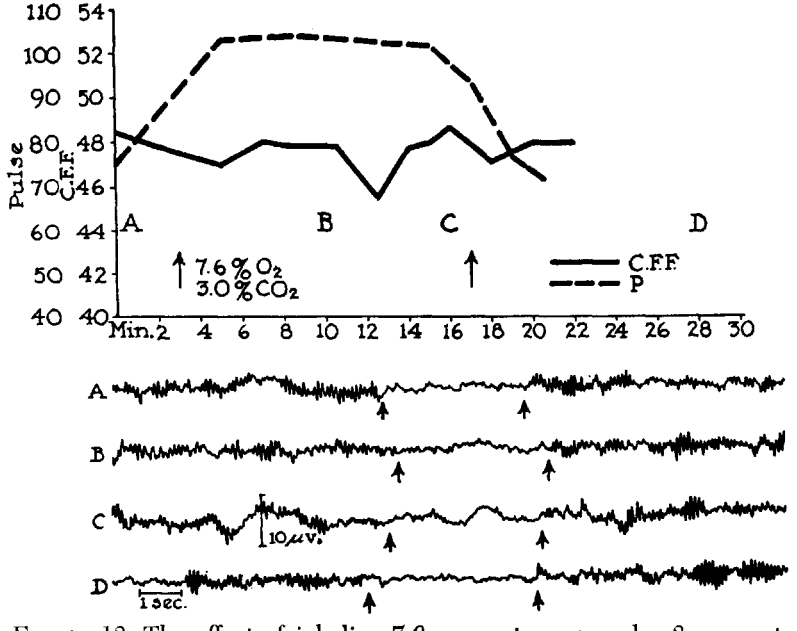

FIGURE 13. The effect of inhaling 7.6-per-cent oxygen plus 3-per-cent carbon dioxide on the C.F.F., P, and EEG of the same subject as in Figure 12. Neither the C.F.F. nor the EEG is altered! (Gellhorn and Hailman, 489.)

arterial and venous (internal jugular) blood shows that the greater tolerance of anoxia in the presence of carbon dioxide is in part due to the increased oxygenation of the brain. This improvement is due to the rise in the oxygen saturation of the arterial blood and to the increased cerebral blood flow, which is directly related to the carbon dioxide tension of the blood. The synergistic action of carbon dioxide and anoxia on the rise in the blood pressure is of particular importance (502). In addition the action of carbon dioxide on the neurons plays an important role, since at similar degrees of unsaturation of the internal jugular blood the EEG shows normal potentials when carbon dioxide is inhaled together with the oxygen-nitrogen mixture whereas large, slow potentials appear in such an experiment performed in the absence of carbon dioxide (543).

Some insight into the behavior of individual neurons in anoxia can be obtained from experiments on the influence of anemia on postganglionic potentials. Bronk (141) recorded them in response to preganglionic stimuli in the stellate ganglion. With prolongation of the anemia the potentials decline in amplitude, a fact indicating that the number of responsive neurons decreases. In addition it was found that this reduction in response is more rapid in the stimulated than in the resting stellate ganglion. In spite of the great difference in the sensitivity to anoxia existing between the cerebral cortex and an autonomic ganglion, which can recover from a complete anemia lasting for three hours, two important conclusions may be drawn from this experiment. First, the neurons of any part of the nervous system differ widely in the threshold to stimulation and to changes in the internal environment. Consequently the effect of anoxia is that of gradual decruitment. Second, the sensitivity to anoxia is directly related to the activity of the neurons. The validity of this statement for the convulsive state will be discussed later.*

Variations in the Blood Sugar Level

The utilization of hypoglycemic coma for the treatment of mental disorders initiated extensive investigations on the influence of variations in the blood sugar concentration on cortical activity. The action of anoxia and hypoglycemia is similar on the EEG. A sufficient diminution of the oxygen saturation or glucose concentration of the blood causes a decrease in cortical frequency and ultimately a disappearance of the potentials, and in both conditions there is a considerable margin of safety. A fall in the blood sugar from 100 to 60 mg. per cent is in general not accompanied by changes in the EEG. With a further

* See p. 148.

fall frequencies of 4 to 7 per second appear, and at comatose levels the low frequency band extends to the delta range (1 to 3 per second). Modern frequency analysis (544, 623) showed that, contrary to older findings (674) based on mere inspection of the records, alpha potentials persist even at a very low blood sugar level in spite of the prominence of large, slow potentials. The progressive changes in the EEG are associated with a decrease in the oxygen utilization of the brain, demonstrated *in vivo* and *in vitro* (657). The significance of glucose for brain metabolism has long been recognized, since the respiratory quotient is almost 1. Only small amounts of lactic and pyruvic acid are formed in the brain, so that more than 90 per cent of its metabolism appears to be due to the oxidation of glucose.

That the changes in cortical activity after the injection of insulin are due to the low blood sugar follows from the immediate return of the potentials to normality upon the injection of glucose. It should also be noted that hepatectomy and evisceration, which lead to a fall in the blood glucose, induce the same cortical changes as insulin hypoglycemia (883). Experiments on hepatectomized animals demonstrate conclusively the high specificity of carbohydrates for cortical activity. Aside from glucose, only mannose and maltose were found to restore the EEG in the hypoglycemic animal, while other carbohydrates (fructose, galactose) and substances closely related to the glucose metabolism and apparently utilized by the brain *in vitro* remained without effect.* In perfusion experiments on the isolated cat's brain the replacement of the glucose of the perfusion fluid by fructose reduced the oxygen consumption of the brain to 50 per cent. No utilization of fructose took place until glucose had disappeared from the brain (417, 418). Normal cortical potentials, oxygen consumption, and glucose utilization are apparently very closely interrelated.

Hyperglycemia within physiological limits, as after the ingestion of food, is without influence on the EEG, but at much higher levels (more than 300 mg. per cent) a slight increase in the rate of cortical potentials has been reported.

The Interaction of Anoxia and the Blood Sugar

It is known that hypoglycemia and anoxia in combination produce greater effects on the vasomotor center than either condition alone. In the dog the blood pressure response to mild anoxia increases with a falling blood sugar. These findings suggested that the interaction of

* It is of interest to mention that the changes in the reactivity of the medulla oblongata in hypoglycemia were eliminated by glucose and fructose but not by galactose (492).

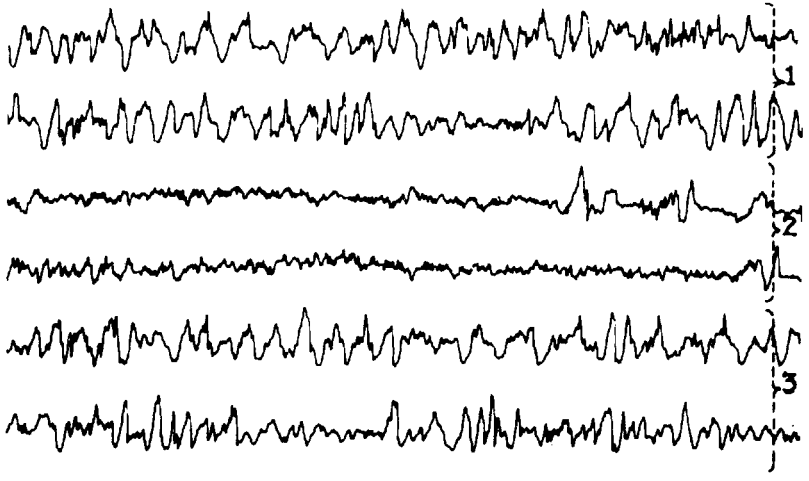

FIGURE 14. The action of oxygen in hypoglycemia on the electroencephalogram of the adrenalectomized rat. Five units of insulin was administered subcutaneously, and the records were taken 81, 85, and 90 minutes later. *Records 1 and 3:* taken while the rat inhaled air. *Record 2:* taken during the inhalation of 100-per-cent oxygen. (Gellhorn and Kessler, 498.)

these changes in the internal environment also affects the cortical potentials. A synergistic effect was established inasmuch as a mild degree of hypoglycemia greatly sensitized the cortex to the effect of hypoxia. The inhalation of 7-per-cent oxygen for three minutes did not appreciably alter the EEG in a rat when the blood sugar was normal, but it produced marked delta potentials when the blood sugar was reduced to a level which in itself did not cause any changes in cortical potentials (498). Similar observations were made in the dog in spite of the fact that the greater stimulation of the vasomotor center during the anoxic *and* hypoglycemic period created conditions for improved brain circulation (492). Gerard (527) suggests that the synergistic effect of anoxia and hypoglycemia on the cerebral cortex is due to interference with glycolysis as well as with oxygen utilization.

The recent studies of Edwards (313) show that the glucose uptake of neurons is enhanced in the absence of oxygen. Although the consumption of glucose is directly related to the glucose concentration in the blood, the lowering of the latter may be without effect as long as aerobic processes prevail. The reduction of oxygen makes the neurons more sensitive to hypoglycemia because the anaerobic processes play an increasingly greater role and compensatory glycolysis is limited by the low glucose level.

The effects of hypoglycemia on the EEG can be offset by the inhala-

tion of 100-per-cent oxygen. During hypoglycemia large, slow delta potentials appear while the animal inhales air. They disappear under the influence of 100-per-cent oxygen (Fig. 14). Apparently the rise in the oxygen tension of the brain in the latter condition offsets the action of hypoglycemia on cortical potentials. Whether this effect of 100-per-cent oxygen is accompanied by increased oxygen utilization is not known.

These investigations suggest that the changes in the EEG and the decrease of cortical functions in anoxia and hypoglycemia are due to a decreased metabolism of the cortical neurons. This interpretation is supported by the fact that alpha frequency is directly related to body temperature (667). Since the frequency of cortical potentials decreases gradually in anoxia and hypoglycemia, the decrease seems to be due to a progressive deceleration of the discharge rate of that population of neurons which accounts for alpha potentials of the EEG under strictly physiological conditions (Brazier, 125). Only when consciousness is lost do slow potentials appear abruptly.

*Carbon Dioxide and the Electroencephalogram**

The EEG and ECG are modified by variations in the carbon dioxide content of the blood brought about by the inhalation of gas mixtures rich in carbon dioxide or by hyperventilation. In animal experiments the changes induced by these procedures have been related to the *p*H of the brain. Since the action of carbon dioxide on the brain is subjected to closer analysis in a subsequent chapter, a few statements here may suffice. In spite of some controversy in the literature it is generally agreed that raising the carbon dioxide content of the blood increases the frequency of the potentials and reduces their amplitude, whereas blowing off carbon dioxide, as in overbreathing, causes slow, large potentials to appear. Frequency analysis has confirmed these findings. Because of its significance for the diagnosis of petit mal epilepsy, the action of hyperventilation has been studied extensively in man. Delta potentials of 2 to 3 per second appear with great regularity and are most prominent in the frontal areas, particularly in young persons. In normal persons the blood sugar level is of fundamental importance, since overbreathing for two to three minutes does not induce delta potentials if the blood sugar concentration is about 120 mg. per cent or higher. In epileptics and psychopathic patients, however, slow, large potentials may appear under these conditions (623).

The striking effect of the blood sugar on the reactivity of the brain

* For details see Heppenstall and Greville (623).

to hyperventilation cannot be explained by an influence of the blood glucose level on the acid-base balance of the blood; it rather shows that the stability of the brain, indicated by the EEG changes induced by stress (hyperventilation), depends on the concentration of the blood sugar. Since the effect of overbreathing can be offset by the inhalation of oxygen or by raising the level of the blood sugar, it may be assumed that it is at least in part due to anoxia. The latter is related to the degree of vasoconstriction which accompanies hyperventilation. This assumption is in agreement with the work of Darrow *et al.* (255) according to which the appearance of delta potentials can be prevented by stimulation of the parasympathetic nerves which dilate the brain vessels.*

The Electroencephalogram, Water Balance, and Cerebral Excitability

Increasing the water intake was shown by McQuarrie and Peeley (919) to precipitate convulsions in patients with grand mal epilepsy. This water test, reinforced by a simultaneous administration of pitressin, represents another condition of change in the internal milieu to which the cortex of the brain reacts distinctly. Under conditions of water intoxication the EEG shows delta potentials of large amplitude which are followed by or associated with spike potentials (465). The latter may be accompanied by overt convulsions. The injection of hypertonic sodium chloride solution reverses the EEG changes and restores the animal. Desoxycorticosterone, which has been shown to counteract the lethal effect of water intoxication (415), prevents the occurrence of spikes. However, delta potentials still appear, to be replaced by a normal EEG some hours later. The slow potentials seem to be the response of the cortex to a water intoxication of lesser severity and greater reversibility.

The problem of the relation of cellular hydration to brain excitability was further investigated by determining the electrical seizure threshold under several experimental conditions. The intracellular water can be increased by the oral administration of water or through the loss of electrolytes (induced by an intraperitoneal injection of glucose) (1145). Each of these procedures lowers the seizure threshold; in combination, they lead to convulsions. Dehydration (through hypertonic sodium chloride), however, raises the convulsive threshold (1146). There is an apparent discrepancy between the slowing of cortical potentials which appears under hydration and is generally interpreted as a sign of diminished cortical excitability and the in-

* See p. 408.

creased sensitivity to convulsions. Similarly it has been noted that anoxia, known for its depressing action on cortical neurons, may induce convulsions.* In both instances the convulsions are of subcortical origin: the excitability of the brain stem has a tendency to rise upon release from cortical inhibition.

The Action of Ions on Ganglion Cells

Numerous studies have shown that the excitability of nerve and muscle is altered by slight changes in the potassium/calcium balance of the medium (429, 676). There is an antagonism between potassium and calcium salts, since the effects of the former can be offset by the latter. Certain excitatory actions of potassium salts, such as the production of contractures in striated and smooth muscles, can be prevented by simultaneously raising the calcium ion concentration in the medium (426). The changes induced by the variation of potassium and calcium ion concentration in the medium appear closely related to alterations in permeability (430–432).† Moreover potassium is lost from muscle and nerve (242) on electrical stimulation,‡ and the exchange of potassium for sodium appears to be the basis of the action potential (686). It was to be expected that ganglion cells would likewise be modified by changes in their ionic environment leading to measurable alterations in the activity or excitability of central structures.

Bonnet and Bremer (112) showed in the unanesthetized "encéphale isolé"** of the cat that the intraarterial injection of fractions of a milligram of potassium chloride induces cortical excitation, indicated by an increase in the frequency of spontaneous potentials and an augmented after-discharge of the auditory cortex in response to acoustic stimulation. Calcium chloride causes the opposite effect and prevents the excitatory action of small concentrations of potassium chloride. The latter also produce signs of awakening in this preparation. The topical application of isotonic phosphate solution increases the responsiveness of the motor cortex to strychnine (20), presumably through its reduction of free calcium ions.

The effect of potassium is not restricted to cortical neurons. The

* See p. 151.

† On the other hand, the ion antagonism is quantitatively altered if the degree of permeability of the tissues is changed. A higher concentration of calcium is found to be optimal for the fatigued than for the resting muscle (430, 432).

‡ The increase in permeability of the indirectly stimulated muscle appears in the form of a greater susceptibility to potassium salts, as shown by their greater capacity to produce contractures (506).

** See p. 186.

occurrence of increased tendon reflexes, running movements, vocalization, and urination indicates that brain stem and medullary centers are likewise excited. The injection of calcium salts has a general depressing effect (297). Detailed experiments on the isolated frog's brain have shown that potassium increases frequency and diminishes amplitude reversibly, provided that calcium is present in the perfusion fluid. A reduction in the concentration of potassium ions has the opposite effect. The action of calcium is less than that of potassium and opposite in character. The frequency of discharge can be regulated within wide limits by varying the potassium content of the medium (1057). Increased synchrony (through calcium) and decreased synchrony (through potassium) seem to be the chief mechanism involved in these changes (841).

Experiments on autonomic ganglia have given additional valuable information on the action of potassium and calcium. Vogt (1188) noted that prolonged preganglionic stimulation leads to a loss of potassium from the ganglion, although antidromic stimulation (i.e., excitation of postganglionic nerves) of the normal ganglion and direct stimulation of the denervated ganglion fail to do so. Apparently synaptic transmission and excitation of nerve and muscle involve a loss of potassium. Potassium also excites postganglionic neurons (162) of the superior cervical ganglion, since the stimulating effect indicated by postganglionic action potentials and by the height of contraction of the nictitating membrane persists after degeneration of the preganglionic nerve fiber.

The omission of calcium from the perfusion fluid of the superior cervical ganglion exerts qualitatively similar but quantitatively greater effects than are seen when potassium is added to it. In both instances the potassium/calcium ratio is increased. The nictitating membrane contracts maximally, but this discharge is not accompanied by the liberation of acetylcholine and occurs likewise in the denervated ganglion. Since the excised peripheral nerve shows spontaneous action potentials in the absence of calcium, the influence on the nictitating membrane may be due to an increased activity of the postganglionic nerve (163). However, the failure of synaptic transmission under these conditions is clear evidence that lack of calcium has an additional central effect (613).

An excess of potassium chloride or calcium chloride induces the secretion of adrenalin, as indicated by the contraction of the denervated nictitating membrane and the nonpregnant uterus. This action seems due in part to the stimulation of autonomic centers and in part to action on the gland itself (Bacq and Rosenblueth, 58; Hermann,

630, 631). The intrathecal injection of potassium chloride or sodium citrate (the latter by reducing the concentration of ionized calcium increases the $\frac{K^+}{Ca^{++}}$ in the cerebrospinal fluid) calls forth a marked increase in the blood pressure, owing to a sympathetico-adrenal discharge and, in the case of potassium chloride, also as the result of a release of the hypophysial pressor hormone (Cicardo, 227).

Perhaps the most impressive changes in central functions through alterations in the ionic balance were reported from Bouckaert's laboratory. Leusen (834, 835) perfused the cerebral ventricles with a fluid of varying potassium, calcium, and magnesium content and studied the effect of this procedure on pressor and depressor reflexes. He found that as the potassium/calcium ratio in the perfusion fluid increases, vasomotor tone and the secretion of adrenalin are augmented, whereas lowering this ratio or adding magnesium to the perfusion fluid has the opposite effect. Under conditions of increased vasomotor tone, the pressor and depressor reflexes of sino-aortic origin are augmented, as is the pressor effect resulting from stimulation of the central end of the vagus. Changes in the ionic balance which lower the blood pressure lead to a diminution of these reflexes.

Similar changes in respiratory activity result from alterations in the ionic composition of the cerebrospinal fluid (1186). These effects persist after denervation of the sino-aortic areas and appear to be due to the direct action of these ions on the respiratory center. It was also shown that the activity of the stomach depends on the potassium/calcium balance of the cerebrospinal fluid (83). This action is mediated by the vagi. Under similar conditions the heart rate and its dependence on parasympathetic and sympathetic centers were determined. An excess of potassium was found to stimulate the accelerator and cardioinhibitory centers, whereas an increase in calcium ions slows the heart rate by inhibition of the former and excitation of the latter (284).

A detailed explanation of the mechanism by which changes in the ionic composition of the internal environment alter the reactivity of ganglion cells is beyond the scope of this book. Apparently the principles established through studies on muscle, nerve, and single cells apply to the neurons of the brain. Changes in membrane potentials and permeability occur as the potassium/calcium ratio is altered. Its increase augments permeability (427) and exerts a depolarizing (catelectrotonic) effect on the cell membrane, while its decrease is associated with a diminution in permeability and a prevention of depolarization (anelectrotonic effect) (364). The action of free cal-

cium ions is probably related to reversible changes in the organic constituents of the cell membrane which reduce its affinity to water (940). In general it has been found that the effect of potassium can be offset by bivalent cations, including magnesium. However, for the central nervous system an antagonism exists between the anesthetic action of magnesium and that of calcium which abolishes magnesium anesthesia.* But even in this case changes in the colloidal state of the cell membrane are probably involved (666), and a magnesium-calcium antagonism on the permeability of single cells has likewise been demonstrated (431).

Hormones and the Excitability of the Brain

The relation of the thyroid hormone to cortical activity is well known. The administration of thyroxin increases the alpha frequency of the EEG in man. Moreover, in hypothyroidism and hyperthyroidism the alpha frequency is related to the metabolic rate (1069). Alpha activity may be absent and slow potentials (3 to 4 per second) of low amplitude appear particularly in the congenital forms of myxedema.† The action of the thyroid hormone is generally interpreted as being due to the rise in brain metabolism. Although data on this point are controversial (657), the observation that the sensitivity of the brain to anoxia is increased in hyperthyroidism supports this argument. It has been found that the inhalation of 7-per-cent oxygen, which does not alter the EEG in normal rats for a long period of time, first slows, and within three minutes abolishes, the EEG of hyperthyroid rats (770).

The intensification of conditioned reflexes through thyroid feeding (1257, 1258), the increased sensitivity of the light reflex (1061), and the augmented response of the centers of the sympathetico-adrenal system in hyperthyroid animals (483) show that the excitability of all parts of the central nervous system is raised by the thyroid hormone. The converse statement is also true, as observations on nervous functions in thyroidectomized animals indicate.

The relation of adrenocortical hormones to brain functions has been investigated by several methods. The EEG of adrenalectomized rats shows a shift toward slower frequency. The normal range can be restored by adrenocortical extracts and $\triangle_5$-pregnenolone, but not by desoxycorticosterone (DCA). Whether the slowing which occurs in

* A diet deficient in magnesium ions causes a greatly increased excitability of the centers of the sympathetico-adrenal system (482). If the magnesium depletion is carried out far enough, spontaneous convulsions ensue (571).

† See Heppenstall and Greville (623) for further literature.

Addison's disease (623) is the result of decreased metabolism is not certain.

The relation of adrenocortical hormones to the excitability of the brain has been elucidated through electrically induced convulsions. The convulsive threshold is lowered after adrenalectomy and restored to normal by DCA or sodium chloride (257). When administered to the normal animal, DCA raises the convulsive threshold, and this effect can be counteracted by cortisone or ACTH (1245, 1246). These effects are apparently related to changes in the concentration of plasma sodium and consequently to those adrenocortical hormones which, like DCA, affect the sodium balance of the organism.

The greater sensitivity of the EEG of adrenalectomized animals than of normal animals to insulin hypoglycemia is discussed elsewhere.* The clinical observation that ACTH leads to changes in the EEG and in mental behavior is interesting but hardly amenable to a physiological analysis at the present time.

Concluding Remarks

The chief aim of this chapter has been to present evidence for the dependence of the activity of neurons on the internal environment. As in the peripheral nerve and muscle, changes in the ionic composition of the medium alter the membrane characteristics of the neurons and therefore their excitability. This alteration in turn determines both the rate of spontaneous discharge and the responsiveness to stimuli. The alteration in the composition of the blood with respect to oxygen, glucose, and other constituents may influence the ion (potassium, *p*H) concentration of the medium and thereby neuronal excitability or may exert more direct effects on the neurons by affecting their metabolism quantitatively or qualitatively. The action of rising temperature, indicated by the increasing frequency of the potentials (667), illustrates the former; the changes in brain metabolism resulting from hypoglycemia and from various drugs (675), including those which inhibit specific enzymes (eserine, DFP, etc.) (623), illustrate the latter. Recently it has been found that adenine derivatives, and particularly adenosinetriphosphate, whose role in carbohydrate metabolism is well known, inhibit acetylcholine spikes in the cortex (1059).

If electrical activity is recorded from large masses of neurons, as in electroencephalography and electrocorticography, the changes in frequency and amplitude depend on many factors, such as the number

* See p. 411.

of active neurons, their rate of discharge, and their degree of synchrony. The gradation of activity of the individual neuron is not fundamentally altered by changes in the internal environment, but the activity of larger portions of the brain is modified through alterations in the neuronal threshold, synaptic transmission, and the temporal relations of their discharges. The degree of synchrony of the potentials of individual cortical neurons, which is so important for the frequency and amplitude of the brain waves, is largely determined by subcortical structures such as the thalamus, the hypothalamus, and the reticular substance in the lower part of the brain stem. This aspect of the problem was purposely neglected in this chapter in order to emphasize the modifiability of neuronal activity by changes in the internal milieu. The mutual relation of cortical and subcortical structures in a variety of conditions will be considered later.

Only one other aspect of this problem should be mentioned now, i.e., the great differences between the cortex and subcortical structures in sensitivity. Anoxia and hypoglycemia may serve as examples. Clinical observations on man show that with progressive anoxia or hypoglycemia there is a gradual elimination of brain functions which begins in the phylogenetically younger structures and appears much later in phylogenetically older structures. Thus Himwich (657) distinguishes the initial cortical from subsequent subcortico-diencephalic, mesencephalic and myelencephalic phases during hypoglycemia, and a similar sequence appears under the influence of anoxia. This unequal sensitivity of different parts of the brain to these conditions is also borne out by anatomical and physiological studies. They show that anatomical lesions are produced predominantly in the cerebral and cerebellar cortex (359, 1215) in conditions of anoxia and hypoglycemia and that the electrocorticogram may be silent at a time when subcortical (hypothalamus) and medullary structures show ample electrical activity and continued function (maintenance of respiration). It is generally assumed that the different resistance of neurons at various levels of the cerebrospinal axis is due to variations in the metabolic rate of nerve cells, which decreases from the cortex to the medulla in the same order (243). By a complete elimination of the blood supply to the brain, the "survival times" measured by the disappearance of action potentials could be determined. They were found to increase from the cortex to the medulla oblongata, with diencephalic and mesencephalic structures at an intermediate position (1141).

PART II

Contributions to the Physiology and Pathology of Movements

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The Motor Cortex and the Physiology of Movements

"Attempts to express cerebral function in terms of the concepts of the reflex arc, or of associated chains of neurons, seem to me doomed to failure because they start with the assumption of a static nervous system. Every bit of evidence available indicates a dynamic, constantly active system, or, rather, a composite of many interacting systems. . . . Only when methods of analysis of such systems have been devised will there be progress toward understanding of the physiology of the cerebral cortex."

"The cortex must be regarded as a great network of reverberatory circuits, constantly active. A new stimulus, reaching such a system, does not excite an isolated reflex path but must produce widespread changes in the pattern of excitation throughout a whole system of already interacting neurons." K. S. Lashley (823).

IN ORDER to understand the foundations of neurology, a thorough discussion of the physiological basis of movements and their coordination is necessary. The study of movements, more than that of any other cerebral function, reveals the general principles which regulate the activity of the central nervous system as a whole and permits one to gain some insight into sensorimotor integration. Since Jackson's highest level of integration (730) is outside the reach of the experimental physiologist, the investigation of the cortical contribution to this function is mainly confined to the study of the motor cortex. However, our chief interest does not lie in the determination of anatomical foci in the motor cortex; it lies in the physiology of movement. Thus the emphasis will be on the interaction between impulses originating in the cortex and those coming from peripheral receptors because such conditions seem to imitate more closely the physiological interactions which take place under normal conditions.

Data will be presented which seem to indicate that the theory of

multiple representation of movements* in the motor cortex serves better than the mosaic hypothesis as a basis for the interpretation of movements induced by volition or electrical cortical stimulation or resulting from the spread of impulses in Jacksonian epilepsy. It will be shown that movements are modified through proprioception at spinal and supraspinal levels. On the basis of these experiments movement appears to be fundamentally an act of sensorimotor integration. A study of the interaction of nociceptive impulses with those originating in the motor area will be presented also, in order to illustrate the physiological foundation of some forms of the pathology of movements.

Multiplicity of Representation of Movements in the Motor Cortex versus the Mosaic Hypothesis

Following the fundamental discoveries by Fritsch and Hitzig of the electrical excitability of the motor cortex and the clinical studies of Hughlings Jackson, extensive investigations were performed by Ferrier, Sherrington, the Vogts, Hines, and many others (see Bucy, 174) in which the primary emphasis was placed on the exact delimitation of cortical foci. This work became the basis of the punctate, or mosaic, theory, according to which the muscles of the body are represented in numerous cortical areas of the precentral gyrus after a simple scheme familiar to the readers of any of our standard textbooks. The large somatotopical areas (leg, arm, face) occupy the medial, intermediate, and lateral part of the motor cortex, and the different muscles constituting these larger units are said to occupy more or less sharply delimited foci.

Since the cortical maps thus obtained were the result of only one method of stimulation, namely brief threshold stimuli, the question arises whether this method is adequate to give a true picture of the organization of the motor cortex. Would it not be more revealing to excite the motor cortex with stimuli which, rather than causing brief twitches in a muscle or part of a muscle, result in physiological movements showing all the characteristics of spatial and temporal integration – since the work of Sherrington (1111) considered the best indi-

* The term "multiple representation of movements" is understood to mean that movements are represented in the motor cortex in their total complexity. From the clinical analysis of lesions in the motor area and from the study of Jacksonian epilepsy, it follows that movements involving the same muscle or group of muscles are represented in many neurons distributed over relatively extensive areas of the motor cortex and that from every "focus" of the cortical motor area upon activation under physiological conditions, not contractions of a single muscle but movements composed of many muscles result.

cator of the activity of the central nervous system under physiological conditions? * This was the reason why Murphy and the writer (959) felt that instead of eliciting barely discernible muscular responses with brief threshold stimuli, the aim should be to evoke, by appropriate stimulation, the full potentials inherent in the gray matter of the motor area and then to determine whether or not the results obtained were the expression of purely local activity. Such a study should reveal whether the principle of multiple representation of movements proposed by Jackson and reiterated by Walshe (1202) could be validated experimentally.

The principal observation in the investigation, which applies to three species (rabbit, cat, monkey), may be summarized in the statement that under conditions of primary facilitation† multiple representation of movement is widespread in the motor cortex. The most common type of multiple representation is that found within large somatotopic divisions (leg, arm, face). There is a considerable overlap of the areas from which movements activating the various joints of the leg or of the arm are elicited, and a similar statement applies to the face and head area. Even in the monkey the cortical areas for movement of the hip, knee, ankle, and toes practically coincide, as do the boundaries for movements of the shoulder, elbow, wrist, and fingers.

The cortical overlap of two large somatotopic subdivisions is greatest in the rabbit and least in the monkey. It apparently decreases with progressive encephalization as the phylogenetic scale is ascended. The maps summarizing these observations in representative examples are far different from those accepted as indicative of functional localization in the animals investigated (Fig. 15).

The thesis that movements are represented severally rather than singly in the motor cortex is substantiated by experiments in which the cortical points stimulated were isolated from the surrounding gray matter. Not only the lateral connections of the various cortical layers but also the intergyral U-fibers were severed in these experiments. Since stimulation of such an isolated small block of cortical tissue elicits multiple movements similar to those obtained from the normal cortex, it may be concluded that the effect of stimulating a given focus in the motor area is little influenced by adjacent cortical

* This was the opinion of Horsley (707), as the following quotation shows: "It should not, in my opinion, be assumed that the effect of a minimal stimulus, evoking, as it often does, but a single movement of a single segment of a limb, is a criterion of all that is represented – that is, within that portion of the cortex cerebri." Cf. also the excellent critical papers of Walshe (1201–1204).

† I.e., repetitive stimulation.

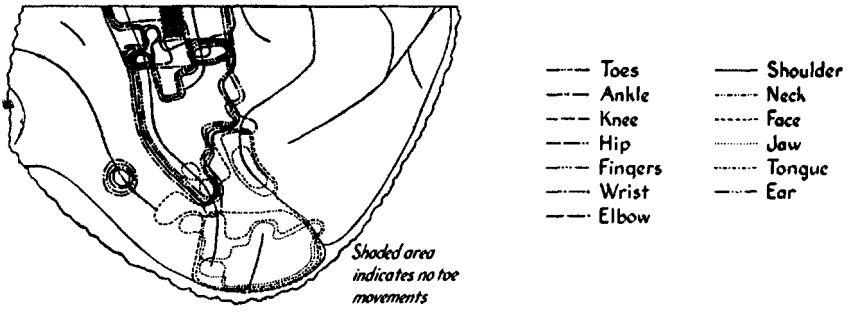

FIGURE 15. Maps of cortical motor response (right hemisphere) in the monkey (3 animals) under conditions of primary facilitation. The three major divisions (areas for the leg, arm, and face) are represented in a medial-lateral direction in the precentral and postcentral gyri, with less overlap of their borders than in the rabbit and cat. However, extensive multiplicity of representation exists within each of the three areas. (Murphy and Gellhorn, 959.)

neurons. Neither a physical spread of the current nor the physiological activation of neighboring neurons accounts for the appearance of activity in several muscles following focal cortical stimulation.

The divergent interpretations of experiments involving cortical stimulation can be reconciled in the following manner. It is probable that the ganglion cells which influence the biceps muscle, for example, through the anterior horn cells are distributed over a very wide area of the cortex. Where they are most numerous and closely arranged, stimulation may mainly evoke a contraction of the biceps with threshold stimuli—and this phenomenon has been stressed in the mosaic hypothesis—or under conditions of stimulation involving primary facilitation, a series of movements may occur which follow or are associated with a flexion of the elbow. These movements result from the activation of a neuron population of lesser density and possibly higher threshold than the neurons which account for the threshold or primary movement (elbow flexion).

Support for the assumption that multiple movements are represented in small, circumscribed areas of the motor cortex is found in the experiments of Denny-Brown (280) on the monkey. Focal electrical stimulation of the anterior part of area 4 frequently induced "synergic patterns" such as extension of the elbow and flexion of the leg. Complex movements resulted from stimulation of a small part of the area which was left intact when the remainder of area 4 was removed. The movements seen "separately and in various combinations" comprised flexion and extension of the fingers (including the

thumb), supination of the forearm, dorsiflexion of the wrist, and flexion of the elbow. It should be noted that in unanesthetized monkeys with aseptically inserted cortical electrodes, near-threshold stimuli frequently called forth movements of a whole extremity (Clark and Ward, 231).

If single shocks are applied at low frequencies so that facilitation is practically absent, multiple movements are likewise elicited from foci in area 4. As the intensity of the stimulus is increased, the area from which a given movement is evoked increases, and in addition other movements appear (Liddell and Phillips, 842). Apparently neurons which, for example, activate the muscle of the thumb are found over the whole precentral gyrus of the monkey and overlap even those activating the toes. The classical maps of the motor area do not indicate the complete distribution of the neurons which activate the muscles of the body, but record rather only the location of the neurons with lowest threshold!

In the unanesthetized human being focal stimulation with as low an intensity as one volt results in complex coordinated movements involving the muscles of several joints. Moreover the same muscle or muscle groups may be activated in several functional combinations. The lips are moved in speaking as well as in mastication, but the foci from which these movements are elicited are not the same. Similarly, the area from which flexion of the thumb may be evoked is quite different from that producing closure of the hand, but the latter clearly involves the activation of the thumb flexors.

It may therefore be said that the stimulation of the human brain with threshold currents gave in the hands of Penfield and Rasmussen (1002) little support to the mosaic hypothesis, which was still chosen by these authors for the schematic description of the organization of the motor area. The adherents of the mosaic hypothesis are inclined to interpret the occurrence of complex movements following focal stimulation by ascribing it to the physical spread of current or the physiological activation of adjacent parts of the motor cortex. The very rapid decline of the current in the immediate vicinity of the stimulated focus* and the persistence of complex movements upon stimulation of surgically isolated foci seem to discredit this interpretation.

Experiments on cortical fatigue (464) give further evidence that the lateral spread of excitation has been overrated. If a small fraction of the cortical biceps area (monkey) is fatigued, the stimulation of

* The voltage drops to 50 per cent of the original value 1 mm. away from the interelectrodal area (959)!

another part of this area may not reveal any decline in biceps response, although the linear distance of the two sites is only 2 mm. Moreover the anatomical studies of Lorente de Nó (867) indicate that the neurons constituting the various layers of the cortex are linked vertically and not horizontally. This explains Sperry's finding (1130) that gridlike sectioning of the motor cortex does not interfere with the execution of normal movements in monkeys. If the foci of the various muscles were strictly separated in the motor cortex as the mosaic hypothesis suggests, a functional interaction of various foci at the cortical level would be required for the execution of even the simplest type of movement, and disturbances in these lateral connections as produced in Sperry's experiments would greatly interfere with normal muscular coordination.

Observations on the restitution of movements after cortical ablation likewise point to the existence of cortical overlap. The recovery of function by the arm muscles is more delayed when the whole contralateral motor cortex, than when just the arm area, is excised (767).

The residual motor deficit resulting from the removal of the arm area depends on the method by which its boundaries are determined (956). If suprathreshold stimuli are employed, the subsequent paralysis is more severe than when threshold stimuli are used. Trendelenburg's observation (1169) that the restitution of function in the arm after cortical ablation is lost by temporary cooling of the cortex adjacent to the removed area can be similarly explained. Apparently the arm area had been removed incompletely, for threshold stimulation was employed for its delimitation. This interpretation holds for the observation (550, 551) that after the recovery of function following extirpation of the hand area, the stimulation of adjacent cortical parts elicits, on renewed exposure of the brain, hand movements. Since it is highly unlikely that a complete reorganization of the cortex can take place under any circumstances (Sperry, 1131), it appears more probable that either these parts had not been adequately stimulated on the first exposure or that their reactivity was obscured through functional factors.

The phenomenon of multiple representation in the motor cortex has been put on a firm anatomical basis by Glees's work. He found that lesions in the hand or thumb area in monkeys caused degeneration not only in cervical-thoracic segments of the spinal cord but also at the lumbar level (550, 551)!

The validity of the concept of multiplicity for the human motor cortex rests, in addition to the previously discussed work on stimula-

tion, on the course of recovery following lesions. Penfield and Rasmussen report "weakness and awkwardness in the whole upper extremity including the hand" after small cortical excision in the shoulder and elbow area. Finally, Walshe's interpretation of the Jacksonian march clearly reveals the extensive overlap of movements in the human cortex (1202).

The central overlap established for the motor area by these observations is, of course, not a unique feature of cortical organization but one of the essential characteristics of the central nervous system. Sherrington (1110, 1111) recognized it as the basis of functional interaction at the spinal level. Woolsey (1248) showed such an overlap to exist in the projection of cutaneous impulses to the sensory cortex in the postcentral gyrus, and Penfield and Rasmussen demonstrated it on the basis of electrical stimulation of this gyrus in the human being. It is of importance for processes of integration and also as a safety device. Cortical defects in the motor and sensory area must result in lesser damage than if the cortex were organized as a mosaic with sharply restricted areas for each individual muscle and various cutaneous areas. The fact that each muscle receives its supply of motor nerves from more than one segment fulfills the same purpose at the spinal level. Only fractions of muscles become functionless through a spinal lesion restricted to one spinal segment; not a single muscle is paralyzed (1110). Similarly, section of the posterior roots at one spinal level does not lead to a distinct cutaneous anesthesia, because of the overlap in the innervation through adjacent dermatomes.

Electromyography as an Indicator of Movements Induced by Stimulation of the Motor Cortex

Further insight into these and related problems depended on the development of appropriate techniques. To record the activity of numerous muscles through levers (219) is impractical and also undesirable, since it precludes knowledge of the actual movement. For this reason the electromyographic method was chosen, which allows one to determine the time course and the relative intensity of muscular activation during a cortically induced movement.

An analysis of the factors determining the electromyogram (EMG) showed (862) that the amplitude of the EMG is a reliable indicator of the magnitude of the mechanical response (contraction) and is directly related to the intensity or frequency of the stimulation (Fig. 16). Apparently an increase in the number of motor units accounts

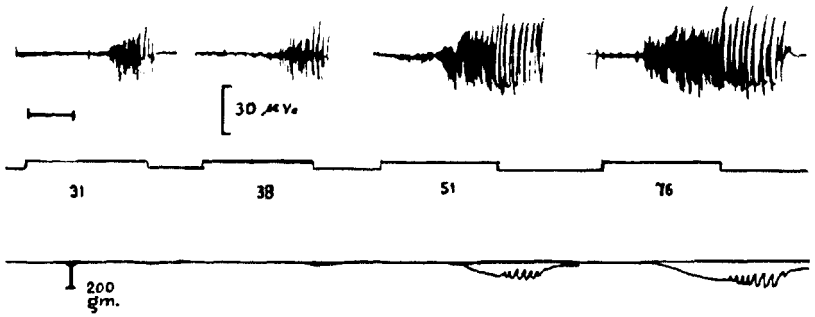

FIGURE 16. The effect on the amplitude of the electromyogram and on the isometric tension of m. tibialis of increasing the frequency of cortical stimulation. Stimulus: 12 volts. *From top to bottom:* EMG; stimulus signal; mechanogram. The frequencies (in stimuli per second) are indicated below the stimulus signals. Horizontal axis: 2 seconds. The figure shows that the amplitude of the EMG and the tension of the muscle increase as the frequency of stimulation is increased. The record also illustrates the shortening of the summation time and the increase in the after-discharge under these conditions. (Loofbourrow, 862.)

for the increased amplitude of the EMG seen on cortical stimulation of increasing intensity and/or frequency.* This interpretation is supported by studies of the EMG in a nerve-muscle preparation. The amplitude of the EMG was found to increase with increases in the intensity of the stimulation when submaximal stimuli were applied to the peripheral nerve, but it remained constant if supramaximal stimuli were used. Obviously the number of reacting nerve fibers remains unchanged in the latter case, since all of them discharge. If muscles are indirectly stimulated with supramaximal shocks under conditions of increasing initial stretch or with progressively greater load, the muscle tension increases; but alterations in these mechanical conditions of the muscle do not affect the EMG response in the nerve-muscle preparation, in which reflexes are eliminated since connections no longer exist with the central nervous system. However, these same factors call forth an increasing amplitude of the EMG if the motor cortex is stimulated. Apparently the greater tension set up in the muscle evokes proprioceptive reflexes which activate more motor units. That this interpretation is correct is proved by the fact that after deafferentation alterations in initial tension are without influence on the amplitude of the EMG (721). It may be concluded that under conditions of motor cortex stimulation and also in reflex experiments

* The frequency of asynchronously discharging neurons seems likewise to contribute to the amplitude of the EMG.

the amplitude of the EMG varies directly with the number of activated motoneurons and therefore parallels the degree of contraction or the tension developed by the muscle. The method is more nearly physiological, since in contradistinction to the mechanical methods which require tenotomy and interfere with the anatomical and physiological integrity of the extremity, the degree of muscle activity can be judged in various muscles of the intact limb.

That the electromyographic method is sufficiently specific – i.e., that potentials are picked up only from contracting muscles – is indicated by the following observations. If a muscle is acutely denervated, it fails to show action potentials when adjacent muscles are in a state of activity. In addition it was found that two functionally independent parts of the same muscle* may show different degrees of activity in the EMG records (495, 719).

General Characteristics of the Effects of Electrical Stimulation of the Motor Cortex

If stimuli are applied to the motor cortex for 5 to 10 seconds – i.e., under conditions favoring primary facilitation – while the activity of the muscles is recorded through EMG's, it is seen that with stimuli of low intensity prestimulatory tonic activity is inhibited, while with those of higher intensity increasing degrees of activity, characterized by an increasing amplitude of the EMG and a shortening of the latent period of response (summation time), are evoked (116).† The intimate relation existing between excitatory and inhibitory processes is indicated by two facts: first, that in a tonic muscle (Fig. 17) the excitatory processes may be preceded and followed by inhibition; second, that a contraction of the agonist, as Sherrington first showed, is accompanied by a relaxation of the antagonist.

Upon an increase in the intensity or frequency of stimulation, activity appears not only in the agonist but also in the antagonist (co-contraction, seen also in voluntary movements which are performed against a resistance). Figure 18 illustrates both reciprocal innervation and co-contraction for the biceps-triceps group in the cat. It shows in addition not only that different degrees of cortical stimulation induce these two types of response but also that the changes in tone occurring spontaneously may be responsible for the occurrence of one

* The biceps femoris consists of a flexor and an extensor part. These two parts react independently of each other – a fact clearly brought out by EMG records taken under a condition of stimulation of the motor cortex while the knee was fixed in flexion and extension respectively.

† See also Bubnoff and Heidenhain (168) and Hines and Boynton (663).

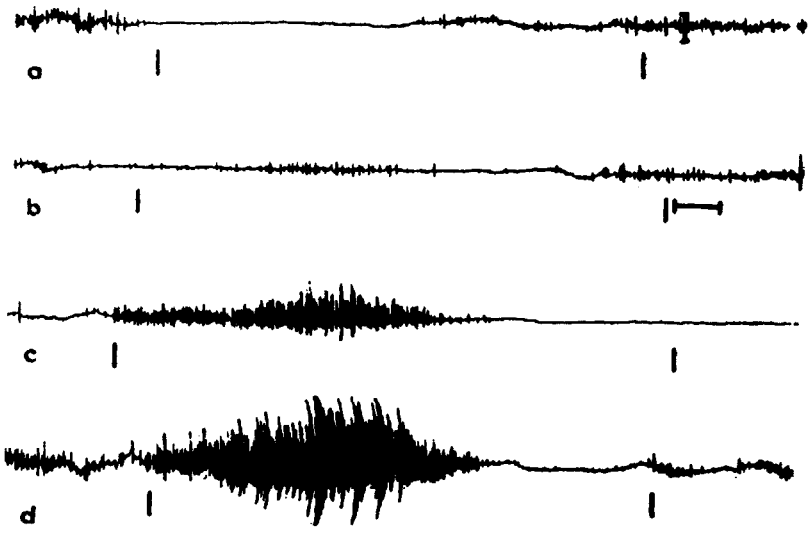

FIGURE 17. Inhibition and excitation resulting from stimulation of the motor cortex. The records show electromyograms of the hamstrings on stimulation of the motor cortex of the cat with (a) 4.0 volts, (b) 5.3 volts, (c) 6.3 volts, and (d) 7 volts. The stimulus is applied between the vertical lines at a frequency of 45 per second. *Read this figure from right to left.* (Bosma and Gellhorn, 116.)

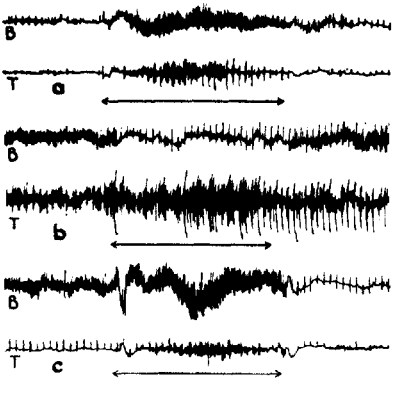

FIGURE 18. The effect of cortical stimulation on the biceps (B) and the triceps (T) in different states of tonus. The animal is the cat; the site, the middle of the cruciate sulcus; the stimulus, 3.3 volts. Note contraction of the biceps with co-contraction of the triceps in *a* and *c*, but contraction of the triceps with inhibition of the biceps in *b*. (Bosma and Gellhorn, 118.)

or the other response. It follows that muscle tone is one of the factors which modify the effect of cortical stimulation (118).

Since it will be seen subsequently that proprioceptive impulses greatly alter cortically induced responses, a study of the behavior of the deafferented limb under conditions of cortical stimulation is of interest. In such experiments a slight increase in the frequency or

intensity of the cortical stimulus increases the amplitude of the EMG, a result indicating that these factors increase the number of discharging neurons. However, the maximal amplitude of the EMG is always less after deafferentation (721). Apparently the number of discharging neurons depends on the cortical stimulus as well as on the recruitment of neurons as a result of proprioceptive reflexes.

Multiple Representation in Threshold Responses

The electromyographic method is adequate to decide the question whether the concept of multiple representation of movements established for suprathreshold stimulation is applicable for threshold conditions of stimulation. Experiments give an affirmative answer (458), since the thresholds of several muscles which are functionally interrelated are practically the same. Figure 19 illustrates a series of tests with a gradual transition from subthreshold to threshold stimuli as a result of increasing frequencies of stimulation. At a frequency of 21 per second there is no response; but at 26 per second a trace of reaction appears in several hind-leg muscles, and as the frequency is augmented further, these reactions increase in intensity, as indicated by the increased amplitude of the EMG and the decreased summation time.

Such observations were made on the precentral gyrus (area 4) as well as on the more anteriorally located parts of the motor cortex (area 6). The investigations give little support to the assumption that

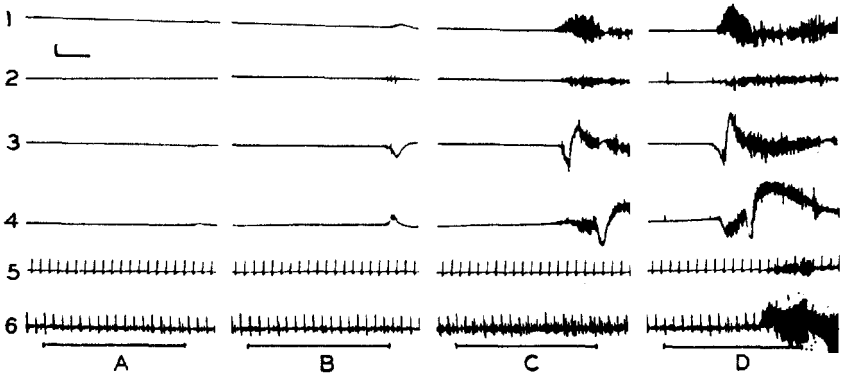

FIGURE 19. The effect of stimulating with increasing frequencies a site in the leg area of the motor cortex (area 4) of the Macacus rhesus. *Record 1*, hamstrings; *2*, quadriceps; *3*, tibialis anterior; *4*, gastrocnemius; *5*, biceps; *6*, triceps. Stimulus: 3 volts. Frequencies: *A*, 21 per second; *B*, 26 per second; *C*, 32 per second; *D*, 90 per second. (Gellhorn, 458.)

"discreteness" (1203) of response is a characteristic of area 4. However, not all muscles responding from a given focus have the same threshold. If a point is chosen which is located in the zone of overlap existing between the arm and the leg area, a reaction of the triceps may appear only upon further facilitation (Fig. 19). Upon stimulation of such foci either the hind-leg or the foreleg muscles contract at threshold, but in either case the threshold contraction is not confined to a single muscle but comprises functionally related muscle groups.

Apparently the mosaic concept of cortical organization does not hold even for conditions of threshold stimulation, nor is it valid for minimal willed movements. Inspection shows, as Walshe points out, that the apposition of index and thumb involves a contraction in the muscles of the hand and forearm, and the movement of one finger is associated with a change in the "tone" of other digital muscles (1170). It is concluded that movements, whether elicited by cortical stimulation or voluntary action or produced reflexly,* consist of specific combinations of muscles and not of contractions of single muscles.†

Patterns of Movements Resulting from Stimulation of the Motor Cortex

Stimulation of the motor cortex of the macaque under conditions of primary facilitation causes a multiple response of a definite coordinated type. From the lateral part of the arm area (biceps area) ‡ a flexion of the elbow combined with an extension of the wrist and a protraction of the arm is evoked, while the more medially located (triceps) area elicits on stimulation an extension of the elbow, a flexion of the wrist, and a retraction of the shoulder (117). Stimulation of the adjacent medial part of area 4 induces movements of the hind leg consisting of a flexion of the knee and a dorsiflexion of the ankle. These movements are accompanied by an extension of the elbow if the focus is located in the zone of overlap existing between the cortical representation of the triceps and the hind-leg muscles.

The functional significance of these movements is quite obvious. Stimulation of the biceps area results in a grasping movement; that of the triceps causes a supporting reaction used in walking. When

* See pp. 82ff.

† Denny-Brown agrees with these conclusions when he states that "the cortical mechanism probably does not use muscles individually, any more than a spinal reflex is made up of either a whole single muscle or all the movements represented in a spinal motor nerve root" (280).

‡ The terms "biceps area" and "triceps area" are used for the sake of brevity, the areas being named after the principal muscle.

the palm of the hands is placed on the ground, the triceps–flexor carpi complex is reflexly activated.

Electromyographic records reveal important details of the expected muscle activity during these movements. If EMG's are recorded from biceps, triceps, and carpal muscles while foci in the arm area are stimulated, it is found, in agreement with visual observations, that the activity of the biceps is commonly associated with that of the extensor carpi. Triceps and flexors carpi are similarly interrelated. If shoulder and arm muscles are recorded, the deltoid appears with the biceps, and the teres major with the triceps, a finding accounting for the combinations of flexion of the elbow with protraction, and extension of this joint with retraction of the arm (494). Between the cortical foci representing elbow extension and wrist flexion (triceps complex, consisting of triceps and flexor carpi) and those inducing elbow flexion and wrist extension (biceps complex, consisting of biceps and extensor carpi muscles) lies an intermediary zone from which both complexes are elicited, the biceps complex either preceding or following the triceps complex (biphasic area).

A close study of the EMG's frequently reveals activity in a muscle or groups of muscles which is not visible to the naked eye. Moreover electrical records give a more intimate insight into the muscular coordination of cortically induced movements and thereby contribute to phenomena such as reciprocal innervation.

New observations indicate that the concept of reciprocal innervation can be extended to include more than Sherrington's work indicates. Reciprocal innervation exists not only between individual muscles such as the biceps and triceps but also between functionally related muscle groups (456, 494) such as the biceps and triceps com-

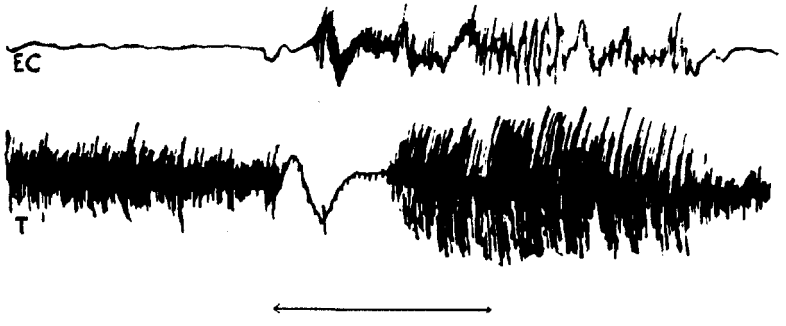

FIGURE 20. Excitation of the extensor carpi (EC) and inhibition of the triceps muscle (T) on stimulation of a site in the "biceps area" of the monkey. (Bosma and Gellhorn, 116.)

plexes. Thus activity in the biceps and/or the extensor carpi muscles is associated with a decrease or loss in tonic activity of the triceps and/or the flexor carpi muscles (Fig. 20).

Proprioception and Cortically Induced Movements

Physiologists and clinical investigators have emphasized the intimate interrelation of sensory and motor processes. Their separation appears to be more a necessity of analytic research and didactic simplification than an adequate description of the immediately given data of the physiology and pathology of movements.

It is known from Liddell and Sherrington's (843) and Hoffmann's (693) work that proprioceptive impulses set up phasic and static reflexes by themselves and quantitatively modify nociceptive spinal reflexes (244). Moreover contralateral reflexes are qualitatively altered by posture, i.e., by proprioceptive impulses (Magnus, 884). If a leg is flexed, a contralateral stimulus induces an extension, whereas if it is in extension, the same stimulus calls forth a flexor reflex.

That proprioception influences the motor cortex was shown by Bard's study (66) on the hopping reaction, a proprioceptive reflex requiring for its execution the integrity of the contralateral motor cortex. It suggests that proprioceptive impulses arrive directly or indirectly in the motor cortex and by their action modify neuronal activity in the motor area.

The direct action of proprioceptive impulses on the cortex can be demonstrated by action potentials (Fig. 21). Proprioceptive impulses

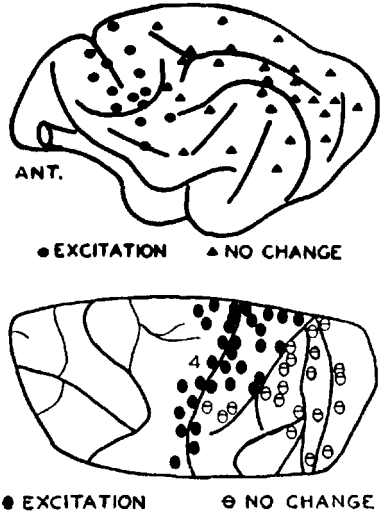

FIGURE 21. Cortical projection of proprioceptive impulses in the cat (top) and the monkey (bottom), based on the study of action potentials. (Gay and Gellhorn, 416.)

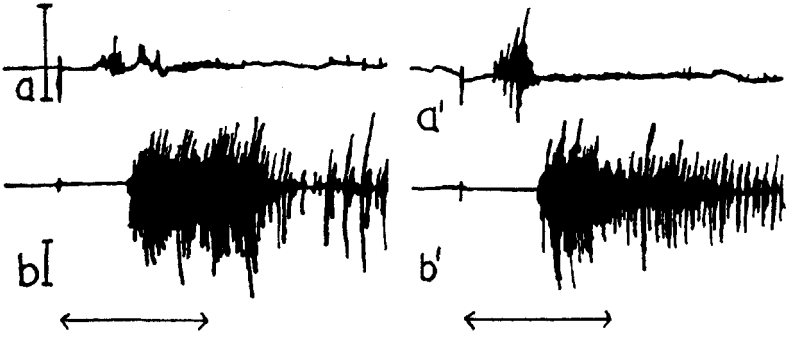

FIGURE 22. The influence of posture on the muscular response to cortical stimulation in the monkey. A site in the leg area was stimulated with 2.9 volts at a frequency of 90 per second for 5 seconds (arrow). Muscle: quadriceps in records a and a'; hamstrings in records b and b'. *Left:* knee at 110 degrees. *Right:* knee at 45 degrees. (Gellhorn, 454.)

elicited by passive movements or by the stimulation of the peripheral end of a motor root mainly alter potentials of the contralateral and, to a lesser degree, of the ipsilateral motor area (416). These impulses are conducted in the ipsilateral spinal cord, since its transection abolishes their cortical effect. They seem to reach the motor cortex via the cerebellum (Walker, 1198; Hassler, 614, 615; Hess and Weisschedel, 640). The observation that proprioceptive impulses project to the contralateral precentral gyrus supports the argument that movements invariably involve sensorimotor integration. This interaction is illustrated by the effect of proprioceptive impulses on cortically induced movements and may be divided into two groups, since proprioceptive impulses are set up not only when a muscle is stretched but also when it contracts and tension is developed (908, 909).

The first concerns the role which the initial length of a muscle or group of muscles plays in a cortically initiated response. If, for example, the knee is placed at an angle of 45 degrees, the quadriceps is relatively stretched and the hamstrings muscles are shortened, whereas with the knee extended the flexors are extended and the extensors are shortened. Under these conditions a given cortical stimulus induces a greater contraction of the stretched muscles than of the shortened ones. Thus Figure 22 illustrates a greater responsiveness of the quadriceps during flexion of the knee than during extension, in contradistinction to the knee flexors, which show the opposite behavior. It should be added that Clark and Ward (231) had already noted in unanesthetized animals that stimulation of the motor cortex through implanted electrodes induces different types of movements, depending on the

initial position of the extremity. If the limb is flexed, the cortical excitation results in extension; if it is extended, stimulation of the same cortical focus causes flexion. Apparently impulses originating in the stretched muscle shunt those coming from the motor cortex into those neurons which innervate the stretched muscle. *The von Uexküll-Magnus* (1177, 884) *rule according to which the central excitation has a tendency to flow into the stretched muscle is valid for movements elicited by electrical stimulation of the motor cortex.*

In these experiments the initial length of the muscles was varied, but the contraction was allowed to proceed without resistance (isotonic contraction). In a second group cortically induced movements were studied under conditions of the *fixation* of one or more joints so that the muscles contracted isometrically. These experiments serve to illustrate the role of proprioceptive impulses induced by tension rather than muscle stretch in movements resulting from cortical excitation. Proprioception is even more effective under these conditions; Cooper and Creed's observations (239) on spinal reflexes thus apply to cortically induced movements.

A fixation of the knee at an acute angle favors the response in the quadriceps, while the activity of the hamstrings is augmented in a fixation of this joint at an obtuse angle (Fig. 23). The marked differences between the amplitudes of the EMG's suggest, in the light of Loofbourrow's experiments (862) discussed earlier, that more neurons are recruited when considerable tension develops during isometric contraction and evokes proprioceptive impulses. This intensification is likewise apparent from the study of the summation time. Increased proprioceptive discharges shorten this interval (Fig. 24). It is notable

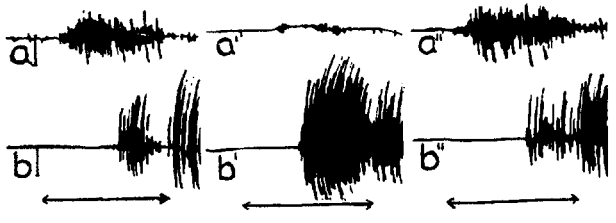

FIGURE 23. The influence of fixation of the knee at different angles on the muscular response to stimulation of the motor cortex in the monkey. The stimulation was with 2.3 volts for 5 seconds. Muscle: quadriceps in records a, a', and a"; hamstrings in records b, b', and b". *Records a, b, and a", b":* knee fixated at 45 degrees. *Records a' and b':* knee fixated at 165 degrees. (Gellhorn, 456.)

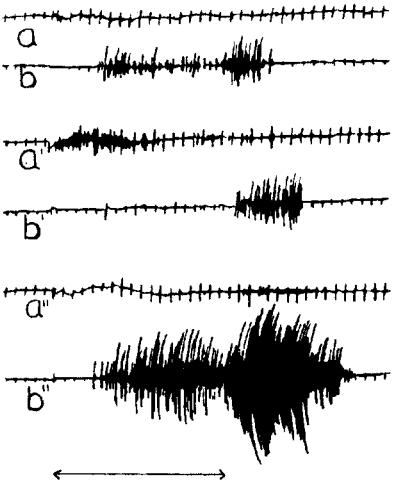

FIGURE 24. The influence of fixation of the elbow on the muscular response to stimulation of the motor cortex in the monkey. The stimulation (as in Figure 23) was with 2.3 volts for 5 seconds. Muscle: triceps in records a, a', and a''; biceps in records b, b', and b''. *Records a and b:* elbow at 90 degrees not fixated. *Records a' and b':* elbow fixated at 45 degrees. *Records a'' and b'':* elbow fixated at 140 degrees. (Gellhorn, 456.)

that under proper conditions the proprioceptive impulses decide which type of innervation pattern appears if the cortex in the biphasic (biceps-triceps) area is stimulated. With the elbow in flexion, action potentials appear in the triceps during stimulation and in the biceps only as an after-discharge;* with the elbow in extension, no activity is seen in the triceps, whereas potentials in the biceps occur during the stimulatory period and also as an after-discharge (Fig. 24).

The effect of proprioceptive impulses is not confined to the muscles whose length is altered by the fixation of a joint in an acute or obtuse position. On the contrary, it is exerted on other muscles according to well-defined functional patterns. These groupings are the same as those observed on stimulation of various cortical foci without a fixation of joints, but such functionally related groups become more distinct through conditions of fixation and demonstrate the far-reaching influence of proprioceptive impulses on complex movements.

It was mentioned earlier that the biceps complex includes biceps–extensor carpi and the triceps complex the triceps–flexor carpi muscles. The muscles of such a complex form one functional unit so that an increase in the responsiveness of one component of a complex as a result of increased proprioceptive impulses spreads to the other components as well. Thus a fixation of the elbow in extension intensifies not only the response of the biceps but also that of the extensors carpi to a given cortical stimulus, and flexion of the elbow diminishes the action potentials in both fractions of the biceps complex. Moreover a

* It was found earlier that with subthreshold stimuli a muscle or muscle group may show activity only in the form of an after-discharge (116).

fixation of the wrist in dorsiflexion, favoring the development of tension in the flexors carpi, intensifies the reactivity of these muscles and of the triceps, and corresponding relations exist between the extensors carpi and the biceps. Similarly it is found that proprioceptive facilitation of the hamstrings through a fixation of the knee in extension increases the reactivity of hamstrings and tibial muscles, and proper facilitation of the latter by appropriate fixation of the ankle joint affects not only the tibialis muscle but the flexors of the knee as well.*

The principle of reciprocal innervation persists under these conditions. Figure 25 shows that elbow fixation at an acute angle increases the amplitude of the action potentials and decreases the summation time in both components of the triceps complex (triceps and flexor carpi), whereas the reactivity of the extensor carpi, which is part of the antagonistic biceps complex, is diminished. This again is seen both in the amplitude and the summation time of the reaction.

The effect of proprioceptive excitation and inhibition is not restricted to the muscles of the same limb. Thus a fixation of the elbow in flexion greatly increases the triceps *and* hamstrings response, although the position of the hind leg remains unchanged (Fig. 26).

The fact that proprioceptive reinforcement through the fixation of a joint is not confined to those muscles which, under the conditions of stretch and fixation, develop considerable tension on stimulation of the appropriate cortical foci, may be used to gain more insight into the organization of the motor cortex, i.e., into the grouping of those muscles that show themselves to be functionally related on stimulation of the motor area. The electromyographic technique allows one to determine those muscles whose reactivity parallels that of the triceps or biceps as the elbow is alternately fixated in flexion and extension. On the basis of this criterion it was found that the flexors of the elbow, the extensors of the wrist and fingers, and the acromio-deltoid constitute the biceps complex, while the extensors of the elbow, the flexors of the wrist and fingers, and most of the shoulder muscles with the exception of the acromio-deltoid comprise the triceps complex. The principle of reciprocal innervation regulates the relations between the two complexes (494) in the same manner as Sherrington (1111) has described it for spinal reflexes and simple cortically induced movements.

There are still other proprioceptive effects which modify the execu-

* That this increased responsiveness is not due to mechanical factors associated with the fixation of a joint in a certain position but to proprioceptive reflexes is attested by the effectiveness of the latter from arm to leg and by observations on tenotomized muscles (see pp. 75 and 83).

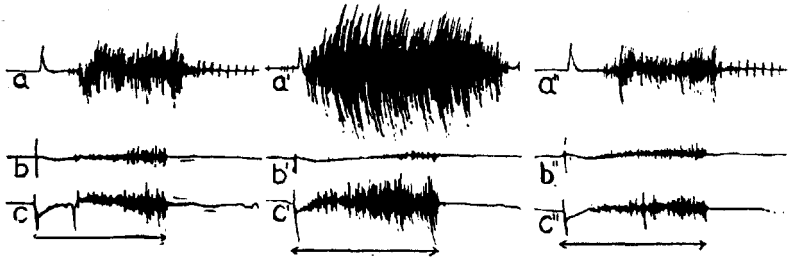

FIGURE 25. The influence of fixation of the elbow on the muscular response to stimulation of the motor cortex in the monkey. A site in area 4 was stimulated with 2.9 volts for 5 seconds. Muscle: triceps in records a, a', and a''; extensor carpi radialis in records b, b', and b''; flexor carpi radialis in records c, c', and c''. *Records a, b, c, and a'', b'', c'':* elbow at 75 degrees not fixated. *Records a', b', c':* elbow fixated at 45 degrees. (Gellhorn, 456.)

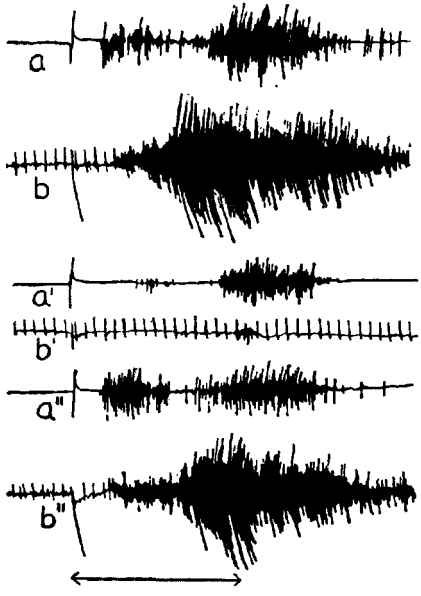

FIGURE 26. The influence of fixation of the elbow on the muscular response to stimulation of the motor cortex in the monkey. The cortical stimulus was 3.3 volts for 5 seconds. Muscle: hamstrings in records a, a', and a''; triceps in b, b', and b''. *Records a, b, and a'', b'':* elbow fixated at 45 degrees. *Records a' and b':* elbow at 110 degrees not fixated. In all three experiments the hind leg was in the same position (hip at 90 degrees, knee and ankle at 100 degrees) and was not fixated. (Gellhorn, 456.)

tion of cortically induced movements. Changes in the position of the shoulder influence the reactivity of arm muscles in a characteristic manner. A protraction of the arm facilitates the response to cortical stimulation nonspecifically, since the responsiveness of the muscles of the biceps *and* the triceps complexes is increased. This suggests a tendency toward fixation of the elbow and wrist under these conditions

(Fig. 27). However, even then the principle of reciprocal innervation is not abolished, since with the arm protracted the cortically induced response is changed by the position of the elbow according to the previously stated rules.

A novel type of proprioceptive facilitation was found in studies involving fixation of the arm in pronation and supination. *Depending upon the cortical site stimulated,* the activity in the biceps or the triceps complex is facilitated by pronation of the forearm. The rule is summarized in the following table.

Triceps Site	*Biceps Site*
PRONATION	
Triceps complex increased	Biceps complex increased
Biceps complex decreased	Triceps complex decreased
SUPINATION	
Triceps complex decreased	Biceps complex decreased
Biceps complex increased	Triceps complex increased

It should be emphasized that pronation as such does not favor the response of a certain muscle group in the way that fixation of the elbow in extension favors the response of the biceps complex but that the proprioceptive modification induced by pronation depends on the type of movement involved. Only if the biceps group is the agonist – i.e., if the cortical site stimulated is a biceps site – will pronation increase the responsiveness of the muscles of this complex. Obviously the effects of pronation and supination on the responsiveness of the motor cortex cannot be stated solely with respect to a muscle or muscle group but must take into account the cortical site stimulated. Figure 28 illustrates these findings.

The upper section shows the EMG activity in the triceps and a group of biceps-complex muscles when a triceps cortical site is stimulated (with the elbow flexed). The triceps is facilitated by a fixation of the forearm in pronation, whereas supination of the forearm is the favorable position for activity in response to cortical stimulation in the extensor digitorum proprius II and III, abductor pollicis longus, and extensor digitorum proprius III and IV – i.e., muscles which form part of the biceps complex. In the biceps there is a small co-contraction that increases in pronation along with the increased activity in the triceps.

The lower section of Figure 28 shows the change in the response when the stimulating electrodes are shifted to a biceps cortical site. The activity of the triceps in response to cortical stimulation is now confined to a small co-contraction paralleling the biceps activity. The

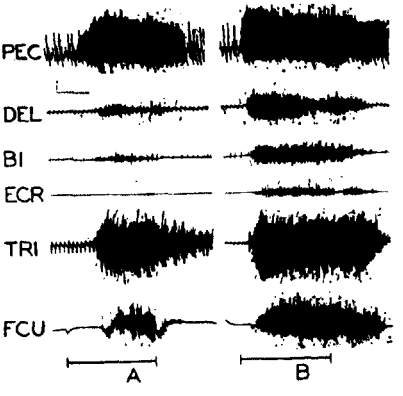

FIGURE 27. The effect of fixation of the shoulder in protraction and retraction on the activity induced in the muscles of the arm, forearm, and shoulder by stimulation of a triceps cortical site. The elbow was fixated in flexion; the stimulus was 3.8 volts at 80.3 per second. *Records A*: retraction. *Records B*: protraction. Protraction increased the response in the pectoralis major (PEC), triceps (TRI), and flexor carpi ulnaris (FCU). The contractions of the biceps (BI), acromiodeltoid (DEL), and extensor carpi radialis (ECR) were also facilitated. (Gellhorn and Johnson, 494.)

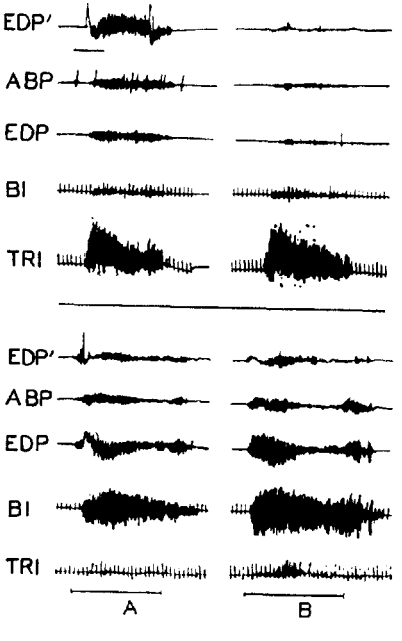

FIGURE 28. The effect of fixation of the forearm in pronation and supination on the activity induced in the muscles of the arm and forearm by stimulation of a triceps and a biceps cortical site. *Records A:* supination. *Records B*: pronation. *Upper half:* stimulation of a triceps site. The elbow was flexed; the stimulus was 1.9 volts at 90 per second. The triceps (TRI) and biceps (BI) responses (the latter a co-contraction) were greater when the forearm was pronated. The extensor digitorum proprius II and III (EDP), abductor pollicis (ABP), and extensor digitorum proprius III and IV (EDP) responses were greater in supination. *Lower half:* stimulation of a biceps site. The elbow was extended; the stimulus was 3 volts at 50 per second. The biceps complex (biceps, extensor digitorum proprius III and IV, and abductor pollicis) was facilitated in pronation. The extensor digitorum proprius II and III was essentially unchanged. (Gellhorn and Johnson, 494.)

biceps complex is facilitated by a fixation of the forearm in pronation, whereas on stimulation of a triceps cortical site supination had been the more favorable position for the optimal responsiveness of the biceps group.

The investigations showing the role of pronation and supination in the responsiveness of a cortical point illustrate perhaps better than any other data the fact that movements and not muscles are represented in the motor cortex. The effect of cortical stimulation on the biceps – e.g., in a certain condition of fixation – is not exclusively determined by the physical characteristics of the muscles (their length and tension), but it depends also on the functional significance of the cortically induced activity. The response of the biceps and biceps complex to cortical stimulation is increased in pronation if the movement executed * is a flexion of the elbow, but it is decreased if the movement is an extension. The biceps and triceps may receive impulses from a biceps as well as a triceps site; the anatomic relation is similar, at least as far as this antagonistic pair of muscles is concerned; but the functional significance of the cortically induced innervation pattern is different, and the latter, as the experiments on pronation and supination indicate, is decisive.

Finally, proprioception is a factor which apparently determines the responsive area in the brain (719). This is illustrated for foreleg and hind-leg muscles in Figures 29 and 30,† showing not only that the response of the flexor complexes is increased when the joints of the foreleg and hind leg are fixated in extension but also that the actual area from which a flexor movement may be elicited is larger in this setting than on fixation in flexion. The latter condition, of course, provides the largest responsive cortical area for the extensor group.

It should be added that proprioceptive end-organs are not the only structures whose activity contributes to the responsiveness of the motor cortex. Apparently the tonic function of the vestibular apparatus exerts a similar effect, since section of the vestibular nerve reduces the height of contraction on electrical stimulation of the motor area (764).

It is of interest to mention that Leyton and Sherrington (840a) found a forward extension of the anterior border of the motor cortex under the influence of temporal facilitation.‡

* Or the potential movement under conditions of strict fixation.

† These figures illustrate for many points of the motor area of the monkey the validity of the principle of multiple representation of movements under near-threshold conditions.

‡ The significance of this finding for the alleged functional differences between areas 4 and 6 is discussed by Walshe (1202).

Nociceptive Impulses and Cortically Induced Movements

That afferent impulses other than proprioceptive may either increase or diminish the effects of electrical stimulation of the motor cortex has been known since the classical studies of Bubnoff and Heidenhain (168) and Brown and Sherrington's work (164) on the instability of the motor cortex. For example, stimulation of a cortical biceps site was seen to become more effective when it was preceded by stimulation of a nerve ipsilateral to the recorded muscle. These observations indicate that the action of the motor cortex resulting from electrical stimulation may be altered greatly through impulses originating in the sense organs and in nerve fibers which mediate pain. The question therefore arises whether the effects of nociceptive impulses are similar or not to those induced by proprioception.

In order to compare the role of proprioception and nociception in the performance of movements, the interaction of nociceptive impulses and impulses induced by stimulation of the motor cortex was studied in a manner similar to that described in the preceding section dealing with proprioceptive impulses. Just as proprioceptive impulses may be restricted to one or a few muscles by the fixation of a single joint, nociceptive impulses may be confined to a single muscle by injecting into it a hypertonic sodium chloride solution. This gives rise to strong pain impulses, leading to referred pain (838) and dilatation of the pupil. The latter reaction is a useful indicator of nociceptive excitation, since pupillary dilatation increases in degree and duration as the nociceptive stimulus increases in intensity. Moreover the autonomic and somatic nervous systems are influenced in a similar manner by nociceptive impulses, since a close parallelism exists between pupillary effects and alteration to cortical stimulation. It has also been found that the effect of cortical stimulation remains in general unchanged if the diameter of the pupil is unchanged by the pain stimuli (519).

Nociceptive impulses produced in this manner alter the responsiveness of the motor cortex to stimulation in several ways. Frequently a marked intensification of the cortically induced movement is observed. The movement may be the same as that seen before the injection of sodium chloride solution, but it occurs with a shorter summation time and each of its components is intensified. The effects are reversible within a few minutes. Furthermore it may be seen that, whereas the movement under control conditions was confined to the contralateral side, it involves as a result of added nociceptive impulses an ipsilateral movement as well. Finally, the character of the movement is altered under the influence of nociceptive impulses. Thus extension may

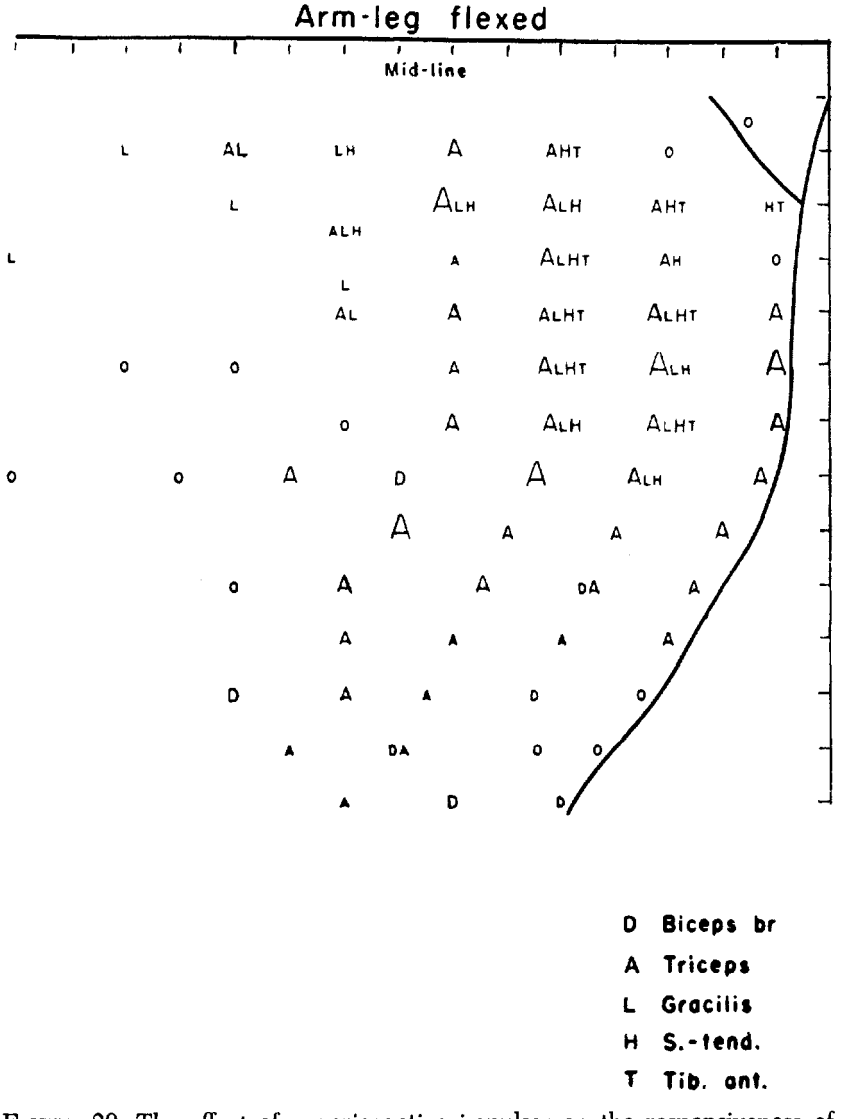

FIGURE 29. The effect of proprioceptive impulses on the responsiveness of the motor cortex. Cynemolgus, left hemisphere. The central sulcus indicates the posterior border of the stimulated area; the divisions on ordinate and abscissa indicate distances in millimeters. The size of the letters indicates the amplitude of the electromyograms of five muscles on stimulation from different cortical foci while the extremities were held in a flexed position (hip 90 degrees, knee 70 degrees, ankle 60 degrees, shoulder 90 degrees, elbow 80 degrees, wrist dorsiflexed to 30 degrees). (Hyde and Gellhorn, 719.)

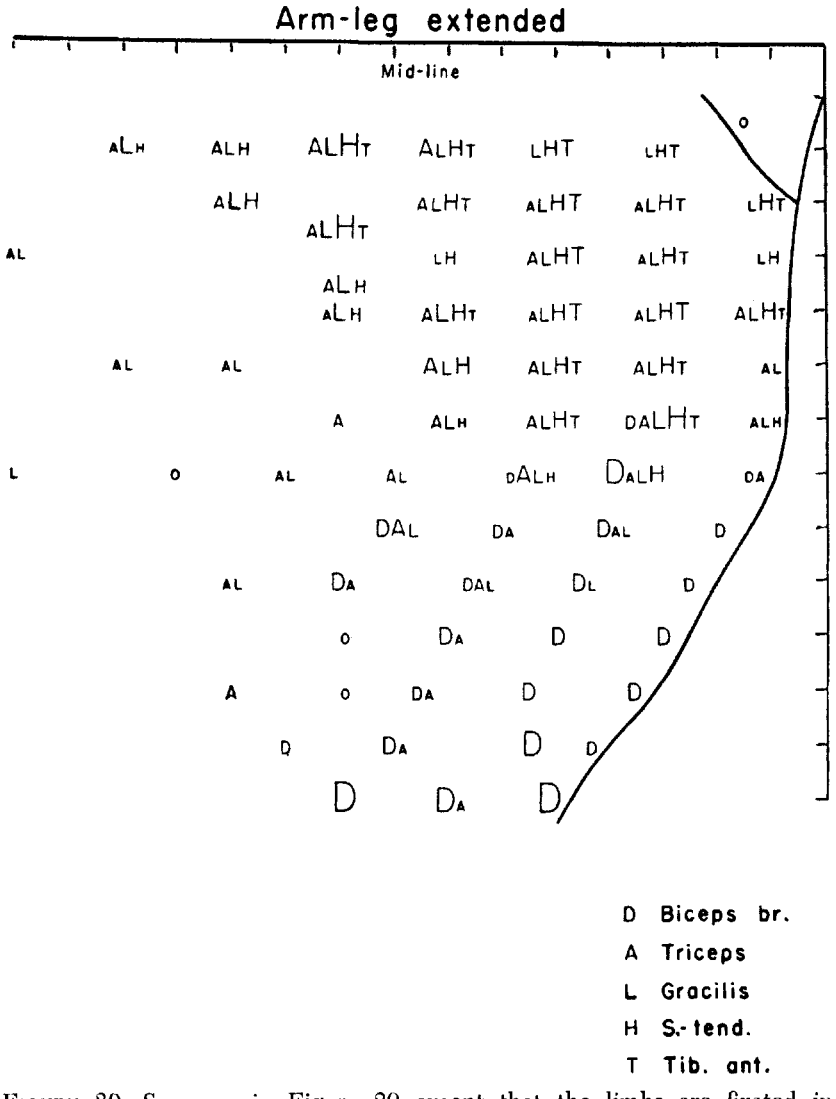

FIGURE 30. Same as in Figure 29 except that the limbs are fixated in extension (hip and shoulder 90 degrees; knee, ankle, and elbow 160 degrees; wrist volar-flexed to 80 degrees). (Hyde and Gellhorn, 719.)

appear instead of flexion; or abduction of the arm, not seen before the elicitation of pain impulses, may occur in addition to flexion.

These changes seem to be fundamentally different from those observed under increased proprioceptive impulses. In general the effect of the latter is confined to the muscles directly involved and

to the functional groupings (e.g., biceps complex and triceps complex) with which they are linked. Thus the fixation of the elbow in extension will increase the reactivity of the biceps complex but not that of other muscles of the arm. Most certainly it will leave unchanged the reactivity of the extremities of the other side and will not affect the hind leg.* On the contrary, nociceptive impulses originating in any muscle of an extremity may alter qualitatively not only the reactivity of the muscles of this extremity to cortical stimulation but also that of other limbs which under control conditions did not respond to stimulation from this particular cortical focus. In contradistinction to the specific effects of proprioceptive impulses, the excitation of pain fibers seems to exert an unspecific facilitatory effect on the central nervous system which results in an intensified, more widespread, and even qualitatively altered response to cortical stimulation. The extent to which these profound changes are due to alteration at the spinal and at the supraspinal (including cortical) level is not known.

Proprioception and Reflex Activity

The classical work of Liddell and Sherrington (843) has established the myotatic reflex as the basis of posture. This reflex was shown to remain confined to the stretched muscle and even to the stretched portion of a muscle, whereas nociceptive stimuli elicit complex functional reflex patterns frequently extending over a whole extremity or even beyond these limits. However, there is scattered evidence in the literature that the myotatic reflex is not restricted to the stretched muscle and its synergists acting on the same joint (Lloyd, 852) but may involve other muscles as well.

If potentials are recorded from several muscles of the limb, the EMG's indicate that the myotatic reflex activates striated muscles in functional patterns similar to those previously described in the work on stimulation of the motor cortex (863). Thus extension of the elbow induces in anesthetized animals not only a stretch reflex in the elbow flexors (biceps and brachioradialis) but also in the extensors carpi, which have previously been shown to be a part of the biceps complex. This effect is not due to mechanical alterations in the extensors of the wrist, since it is also seen after their tendons have been cut. Likewise it was shown that a load on the tenotomized biceps activates the extensor carpi when the elbow is fixed. Similar synergistic myotatic reflexes exist between triceps and the flexors of the wrist (Fig. 31).

* Except for the fact that fixation of the elbow increases both triceps *and* hamstrings responses as shown earlier. However, this reaction is quite specific and seems to be part of a proprioceptively reinforced walking pattern.

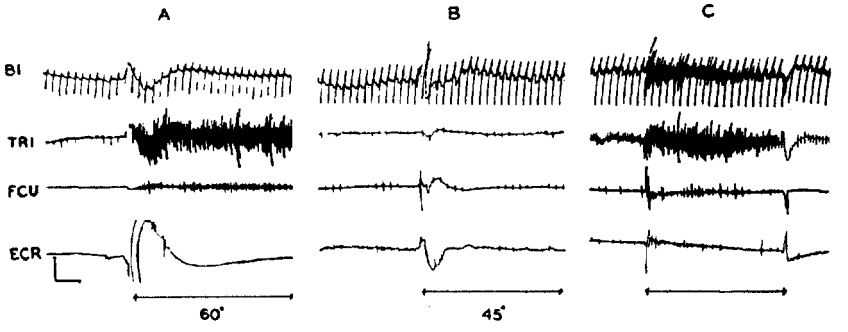

FIGURE 31. A proprioceptive spinal reflex elicited in the monkey by flexion of the elbow before and after tenotomizing the triceps brachii (TRI) and by a pull on the triceps tendon. *Records A:* The flexor carpi ulnaris (FCU) has been tenotomized. Flexion of the elbow to 60 degrees, indicated by the horizontal line, excites the TRI-FCU complex. *Records B*: After triceps tenotomy, flexion of the elbow to 45 degrees elicits no response. *Records C*: A pull on the triceps tendon, indicated by the horizontal line, excites the TRI-FCU complex. Co-contraction occurs in the biceps (BI), the response of which is favored by an obtuse elbow angle (120 degrees). (Loofbourrow and Gellhorn, 863.)

From these experiments it may be concluded that reflexes of proprioceptive origin result in the activation of muscle patterns which are similar to those due to cortical stimulation. The myotatic reflex arising in a single muscle excites not only this muscle and its synergists at the same joint but also those synergists which act on a neighboring joint and form with the stretched muscle a functional association such as the biceps or the triceps complex. These indirect effects of the myotatic reflex are quite strong, since in a muscle even greater activity may be evoked by impulses arising proprioceptively in other muscles than by autogenous proprioceptive stimulation, i.e., by stretching the muscle.

It was mentioned earlier that cortically induced patterns of movement are accompanied by the inhibition of their antagonists. Thus activation of the biceps complex is accompanied by inhibition of parts or of the whole of the triceps complex and vice versa. This statement applies also to proprioceptive reflexes. Thus it was noted in experiments in which several muscles showed a spontaneous tonic activity that the application of a load to the tendon of the flexor carpi not only increased the tonic activity in this muscle and in the triceps but inhibited that of the biceps.

The parallelism between cortically induced movements and myotatic reflexes goes even further. The quantitative relation between

antagonistic complexes depends in both instances on the degree of activity of the agonists. Relatively mild contractions may be accompanied by the reciprocal inhibition of part or of the whole of the antagonistic complex; stronger reactions frequently lead to co-contractions.

It is of interest to inquire still further into these similarities of cortically and reflexly induced movements. Is it possible to elicit movements reflexly which are similar to those caused by cortical stimulation? The work of Sherrington (1111) seems to give a negative answer to this question. Reflex movements as far as the extremities are concerned seem to consist of a few stereotyped patterns. Nociceptive stimulation elicits an ipsilateral flexor complex and contralateral extension. If different cutaneous nerves are stimulated, the total reflex pattern seems to be the same, and only the relative distribution of the activity in the muscles involved is different (Creed and Sherrington, 245). More recent studies, however, in which the activity of numerous muscles was recorded at the same time, indicate that stimulation of various cutaneous nerves in the foreleg and hind leg may produce reflex movements similar to those seen on cortical stimulation (864). The biceps complex is activated on stimulation of cutaneous branches of radial, ulnar, and median nerves, while the triceps complex contracts in response to stimulation of the cutaneous antibrachii nerve.* Apparently reflex movements are not only different in type if different receptors are involved (cf. Sherrington's extensor thrust on stimulation of pressure receptors on the sole of the foot), but even nociceptive impulses may activate the spinal cord to a fractional degree, thereby causing the appearance of activity patterns of considerable variety.†

Before these findings are utilized for a further clarification of the mutual relations between cortically and reflexly induced movements, the question should be discussed to what extent these nociceptive reflex patterns can be modified through proprioceptive impulses (864). Experiments in which the elbow and/or wrist were fixated at obtuse

* In the hind leg various patterns of response are likewise elicited on stimulation of different cutaneous nerves.

† This idea of well-differentiated reflexes originating in different afferent nerves of a limb is supported by the recent observation of Hagbarth (585) on the influence of cutaneous stimulation on bineuronal reflexes. The ventral and dorsal parts of the skin of the hind leg exert diametrically opposed effects on such reflexes. Dorsal cutaneous stimulation increases the gastrocnemius reflex and inhibits the reflex contraction of the tibialis anterior, whereas ventral cutaneous stimulation acts in an opposite manner.

or acute angles while stimulation of various cutaneous nerves* activated either the biceps or the triceps complex showed that here again those results could be duplicated which were described earlier in the section dealing with proprioceptive modification of cortically induced patterns of innervation. Thus proprioceptive facilitation of the biceps resulting from the fixation of the elbow at an obtuse angle or the application of a load to the tendon of the biceps while the angle of the elbow remains unchanged causes an increase in the biceps complex

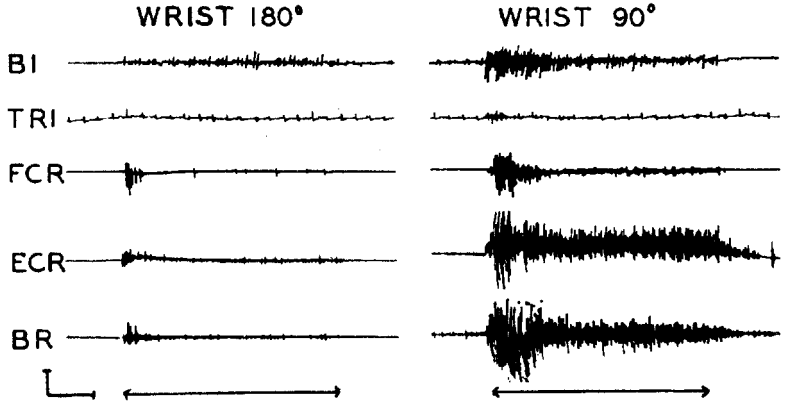

FIGURE 32. Facilitation of the biceps–extensor carpi radialis–brachioradialis response (BI-ECR-BR) to stimulation of the superficial radial nerve by fixation of the wrist in volar flexion. The increase noted in the flexor carpi is considered to be co-contraction associated with an intense response of the extensor carpi. Stimulus: 1.68 volts at 25 per second. (Loofbourrow and Gellhorn, 864.)

(biceps, brachioradialis, and extensor carpi muscles). A similar reflex action is induced by the fixation of the wrist in volar flexion. This position facilitates not only the responsiveness of the extensors carpi to reflex stimulation of the radial nerve, but also that of the biceps and brachioradialis, which are part of the biceps complex (Fig. 32). A similar interaction of proprioceptive and nociceptive reflexes occurs for the triceps complex when the cutaneous antibrachii nerve is stimulated. The contraction of the triceps *and* flexor carpi muscles is increased in such reflexes as the fixation of the elbow is changed from an obtuse to an acute angle. Apparently the modification by posture (fixation of a joint, etc.) of patterns of innervation resulting from

* These nerves transmit not only nociceptive impulses; however, the latter are stressed since they are more apt to elicit reflexes than non-nociceptive sensory nerves.

stimulation of the motor cortex or of afferent nerves follows the same rules and is understandable on the basis of specific proprioceptive facilitation and inhibition of spinal centers. However, Gay and Gellhorn (416) have recently found that proprioceptive impulses induced by passive movements or by stimulation of the peripheral end of a motor root reach the contralateral motor cortex. These findings raise the question whether in addition different points in the motor cortex are differentially facilitated and inhibited.

Nociceptive Impulses and Reflex Activity

Proprioceptive impulses have been shown to modify spinal reflexes and movements induced by electrical stimulation of the motor cortex in exactly the same manner. This similarity of action suggests that the change is in both instances either exclusively or partly of spinal origin. It has likewise been shown that nociceptive impulses alter the effects of stimulation of the motor cortex. These observations pose the question whether these profound changes may, again, not be chiefly or solely of spinal origin. In order to elucidate this problem, nociceptive impulses were set up by the injection of sodium chloride into striated muscles, and their action was studied on the knee jerk and flexor reflex. Under these conditions the effect of nociceptive impulses was not characterized by the great variability noted in similar experiments involving stimulation of the motor cortex, but followed more stringent rules (448, 520, 1155). Thus flexor reflexes (elicited by the stimulation of ipsilateral nerves) were intensified by ipsilateral and diminished by contralateral injection of a hypertonic solution of sodium chloride. The knee jerk reflex likewise was altered by pain impulses, but was diminished by ipsilateral impulses and increased by contralateral.

These results are easily understandable in view of the fact that ipsilateral nociceptive stimuli elicit flexor and inhibit extensor reflexes, whereas contralateral stimuli act oppositely. No such laterality, however, exists in the effect of nociceptive impulses on cortically induced movements. This suggests that the modification of the effects of cortical stimulation by nociceptive impulses is not explainable on the basis of spinal changes alone. Aside from subjective experience, there are other indicators of cerebral changes following nociceptive stimulation. Grouped potentials seen in the anesthetized (barbiturate) animal disappear in both hemispheres on sciatic stimulation (466). Muscular coordination, as tested by handwriting with closed eyes, is greatly altered as the result of muscle pain (520).

The autonomic nervous system furnishes evidence that nociceptive impulses act on the cortex. Ury and Oldberg (1181) showed in the cat that a cortical component is involved in the pain-induced pupillary dilatation which is based on inhibition of the tone of the third nerve nucleus. For the study of autonomic changes in man an observation by Richter (1049) was used. This author found on the hand and the foot, as well as the face, areas of low resistance to electrical current which expand during wakefulness and constrict during sleep. Their size is obviously due to the degree of tonicity of sympathetic discharges to the sweat glands, but their form is not explainable on the basis of the distribution of the spinal nerves or as a result of the activation of spinal segments. Consequently they appear to be of supraspinal (cortical?) origin. These areas are markedly extended in pain (1156) (Fig. 33). Apparently somatic and autonomic processes are altered by nociceptive impulses at spinal and supraspinal levels.

It follows from these observations that afferent impulses, nociceptive and proprioceptive, modify the activity of the central nervous system in a different manner. Proprioceptive impulses are responsible for similar quantitative changes of reflexes and of movements induced by electrical stimulation of the motor cortex. They appear to be due to facilitatory processes which are chiefly confined to the spinal cord

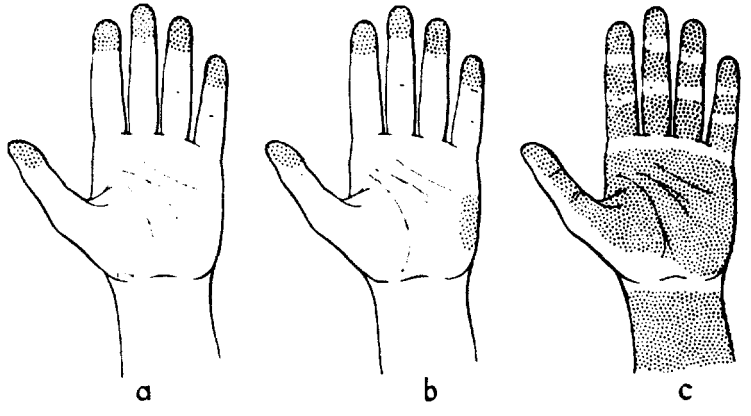

FIGURE 33. The effect of ischemic pain in the right foot on the skin resistance of the left hand. *Hand a:* control. *Hand b:* in ischemia; shows the same distribution of the low-resistance area except for a small area appearing on the hypothenar. *Hand c:* ischemic pain in the right foot; shows increased low-resistance area in the left hand. Ten minutes after the restoration of circulation the low-resistance area is the same as in the control (a). (Thompson and Gellhorn, 1156.)

and leave the pattern of innervation unchanged. Nociceptive impulses, however, involve cortically induced movements and spinal reflexes in a different manner. Their action suggests that spinal and supraspinal levels are modified as a result of nociception. Through nociception the effects of stimulation of the motor cortex are changed quantitatively and qualitatively. Proprioceptive impulses alter these movements in a predictable manner; nociceptive impulses may result in the occurrence of movements not seen under control conditions.

~ 4 ~

Voluntary Movements, Motor Cortex, and Reflex Activity

"No one ever touched anything (had a vivid tactual image) without moving his fingers. No one ever saw anything (had a vivid visual image) without moving his eyes." Hughlings Jackson (730).

"The pyramidal system of itself initiates nothing, and to speak of it as 'responsible for' this or that category of movements is to ignore the source and motive power of its activities. It is simply the channel through which pass the impulse volleys by which willed movement is activated and continuously moulded by controlling cortical afferent patterns of excitation." F. M. R. Walshe (1204).

On the basis of the data presented in the preceding chapter it seems appropriate to compare voluntary movements with those elicited reflexly or by stimulation of the motor cortex and to evaluate their interrelation.

Proprioception and Willed Movements

Proprioception is obviously of great importance for all movements no matter whether they are simple reflexes studied in the spinal animal or highly complex and skilled movements executed through will power. The experiments showing that proprioceptive impulses modify in a similar manner reflexes and cortically induced movements suggest the spinal cord as an important site of proprioceptive facilitation and inhibition. The study of movements after deafferentation and of clinical cases with varying degrees of loss of proprioceptive sensations illustrates the significance of proprioception for reflexes and voluntary movements. The crossed extensor reflex no longer shows the gradual development and steady maintenance of tension after deafferentation (Sherrington, 244, 1108, 1111). Postural reflexes involved in

the maintenance of normal standing are lost in tabes dorsalis, as indicated by Romberg's sign.

No detailed studies seem to exist on the cortically induced movements of deafferented limbs. Sherrington (953) noted that deafferentation does not significantly alter the excitability of the motor cortex to electrical stimuli. In collaboration with Hyde (721) the author found that deafferentation greatly reduces the maximal discharge which can be evoked through cortical stimulation. It was further observed that even with strong cortical stimuli co-contractions are slight or absent. This suggests a disturbance in muscular coordination, although investigations of the patterns of movements of deafferented limbs under conditions of stimulation of the motor cortex in higher animals than cats have not been performed as yet. Extensive material, however, is available on the influence of deafferentation on voluntary movements in man and animals.

Pigeons fail to fly after bilateral deafferentation of the wings (1168), and monkeys are unable to use the hand and fingers after deafferentation of the arm (953). In lower forms (frog, toad) locomotion is less affected by deafferentation than in mammals. Bickel (99) and Hering (627) had previously noted that sensory denervation of two extremities did not greatly alter the coordination of all limbs in various types of locomotion, including swimming and jumping. After deafferentation of all four extremities the animals are lethargic, but a "low level" activity persists (Weiss, 1217) and ambulation is still possible, although with gross deviations from the normal pattern. But these ambulatory patterns disappear after sensory denervation of all spinal nerves from segments II to XI. Apparently at least one spinal segment must possess both motor and sensory innervation, but its site is relatively unimportant. Thus Gray (569, 570) observed walking in toads with all segments deafferented except the eleventh, which supplies the pelvic region.

According to Foerster (370) simple movements of the human deafferented arm, such as lifting it to the horizontal plane, are performed accurately even without visual control. Finer movements, however, particularly of the hand and fingers, are abolished. Thus in the attempt to stretch the fingers a flexion may occur or the impulses intended for the fingers may instead reach the hand or forearm. Associated movements, normally absent under these conditions, may become prominent and obscure the originally intended movement.

The interaction of various synergists, which is apparently based on the activation of the functional complexes previously described in our

experiments on stimulation of the motor cortex, suffers in patients with a deafferented extremity. A simple movement such as the dorsiflexion of the foot involves the activation not only of the tibialis anterior and peronei but also of the extensor digitorum longus and extensor hallucis longus. A disturbance in the quantitative interplay of these muscles accounts for the fact that the foot may be dorsiflexed upon supination or pronation. Clenching a fist, which presupposes contraction of the flexors of the fingers and fixation of the wrist in dorsiflexion, may become ineffectual because the extensors carpi fail to contract. Of other characteristic disturbances it may be mentioned that if a glass is raised to the mouth in order to drink, this simple act is performed in an awkward manner, without the usual abduction of the arm.

There is in these cases, as well as in patients with cerebellar lesions and tabes, evidence that ataxia interferes with a normal agonist-antagonist relationship. Thus the forward movement of the leg in walking shows that in the normal individual, of the tibialis and gastrocnemius only the former is active, whereas in tabes the activity of the tibialis alternates with that of the gastrocnemius (Foerster). The lesser promptness of the antagonist to stop the movement is a familiar symptom in tabes and cerebellar disease.

The absence of proprioceptive impulses is not the only condition that alters the performance of movements at spinal and supraspinal levels; excessive afferent impulses do likewise.* As has already been mentioned, the cortical area from which contractions of a given muscle can be elicited increases when afferent impulses from such a muscle are augmented by its fixation in stretch. It is interesting to add that even qualitative alterations in cortical response occur in spontaneously tonic muscles (118). Thus it was found in the lightly anesthetized monkey with spontaneous activity in the biceps that this muscle was activated from the medial (instead of the lateral) part of the precentral gyrus and appeared in combination with the hamstrings, whereas normally a triceps-hamstring complex appears from this area. These and similar experiences not only may serve as physiological models of the great variability of cortical responses but also indicate that focal cortical excitation may cause abnormal movements as the result of an excessive tone in the striated muscles.†

* If the stretch reflexes are greatly augmented, disturbances in muscular coordination may occur which are described in Chapter 6.

† Gellhorn and Thompson (521) observed in the decerebrated cat that changes in tone induced by nociceptive impulses may quantitatively and qualitatively alter spinal reflexes and lead to a reflex reversal.

Sensorimotor Integration in the Visual Sphere

The far-reaching influence of the sensory impulses on motor performances may be illustrated by Rademaker's work (1030) on visual-motor integration. The spatial separation of the motor cortex from the visual projection area of the occipital lobe is favorable for an analysis of the relation of the latter to the movements of the eyes and limbs (Fig. 34).

The occipital cortex is concerned with impulses originating in the retina and with movements of the eye. Electrical stimulation of the mesial side of the medio-caudal part of the occipital lobe (dog) elicits conjugate eye movements to the contralateral side. They persist after bilateral removal of the precentral motor cortex and are consequently not due to activation of the frontal eye field (area 8) but are probably mediated by a path to the oculomotor nuclei via the superior colliculi. Destruction of the medio-caudal part of the visual cortex abolishes conjugate movements of the eyes to visual stimuli. The animal remains always staring and gives therefore the impression of being blind.

The optic placing reactions show in an even more striking way the dependence of motor reactions on sensory perceptions. If the rostal parts of the occipital lobes are removed, the dog fails to place the forelegs on a table when brought close to it. The animal does not

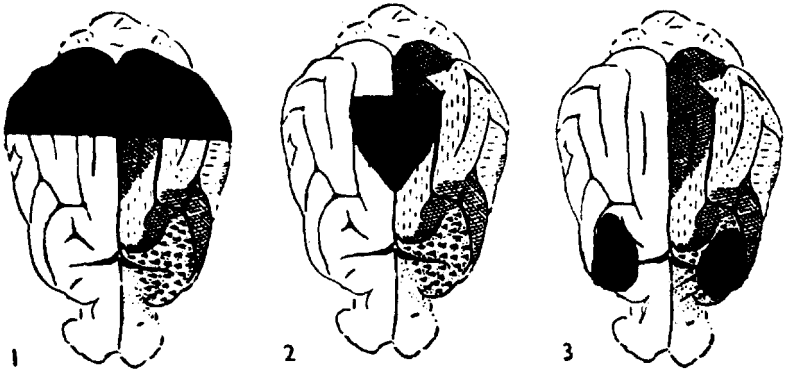

FIGURE 34. The effect of removal of parts of the occipital cortex on visual reactions. *Section 1:* removal of the caudal poles of the occipital lobes ("Munk-dog"). Blinking in response to threatening movements and optic conjugate ocular movements are abolished, but optically induced placing reactions are preserved. *Section 2:* bilateral extirpation of the rostral part of the striate area. The blinking reaction to threatening and conjugate ocular movements is present, but optic placing reactions are lost. *Section 3:* bilateral extirpation of the foreleg area in the dog. Optic placing reactions are lost. (Rademaker and Ter Braak, 1030.)

avoid obstacles and bumps into the walls of the room, although owing to the preservation of optically induced conjugate eye movements, it impresses the observer as one having normal vision. Finally, it was noted that destruction of the lateral-caudal part of the visual cortex abolishes the lid closure in response to a threatening gesture, whereas the blinking reflex in response to touching the cornea is preserved. The latter is a subcortical reflex, the former a reaction involving the visual and motor cortex of the same side.

The close interdependence of sensory and motor reactions in the visual sphere is illustrated by the fact that even trained observers may confuse a motor deficit with a sensory disturbance. Munk (954) extirpated the caudal parts of both occipital lobes in the dog and characterized its behavior as being due to the loss of recognition of objects ("Seelenblindheit," or psychic blindness). The repetition of this work by Rademaker showed that such an animal, having lost the cortical blinking reflex and the ocular movements to optic stimuli, appears to be blind. However, the dog avoids obstacles, shows optical placing reactions, and jumps from a table. Its inability to react to visual stimuli is not due to a lack of recognition of objects but rather to the absence of the conjugate eye movements in response to visual objects. On the other hand, a dog whose optic placing reactions are abolished by bilateral removal of the motor cortex seems to see normally, since it shows eye movements and blinking when it is suddenly confronted with a visual object. But the same animal having lost the optical placing reactions* bumps into the walls of the room and falls off a table. This work is a striking illustration of sensorimotor integration. It shows in addition that different parts of the sensory (occipital) cortex are related to the activity of the forelegs, the external muscles of the eye, and the muscles of the eyelids.

Clinical experience suggests a similar organization of visual-motor reactions in man. Centers for eye movements are likewise found in the frontal and occipital lobes. Permanent paresis of voluntary eye movements results from bilateral frontal lesions, but the patient is able to follow a slowly moving object with his eyes. Reading is still possible unless the individual letters are too widely spaced. On the other hand, bilateral occipital lesions eliminate the fixation reflex, particularly when the head is moved, in spite of the integrity of voluntary eye movements. There seems to be a finely adjusted balance between the frontal and occipital oculomotor centers, since after the loss of the

* It is hardly necessary to stress that these placing reactions are absent in adult man; however, Rademaker mentions that they occur in children of about one year of age.

former the fixation reflex is so exaggerated that no nystagmus results from galvanic or caloric stimulation of the vestibular nerve (Holmes, 697).

The Unity of Sensation and Movement

The intimate interrelation between sensory impulses and voluntary movements has led several authors to stress the unity of sensation and movement in the act of volition. Walshe (1204) speaks of the "receptor system as initiating and directing willed movements." Gooddy (558), emphasizing the loss of voluntary movements in cases of cerebral lesions in the sensory parts of the cortex and the importance of sensory control in the acquisition of skilled movements, suggests that "in voluntary movement, sensation and motion form a single, indivisible, continuous process." *

It seems, however, advisable not to overlook the fact that ontogenetically motor innervations and generalized movements precede sensory innervation (Coghill, 234). Also, if a fragment of the spinal cord and a limb are transplanted to the dorsal fin of a salamander larva, the limb may show periods of spontaneous activity which precede by many weeks the establishment of reflex movements (Weiss, 1218). Even in the human being movements of deafferented limbs are possible,† although qualitatively and quantitatively altered. The disturbance is greatest for the fine movements of the fingers, which require continuous readjustments based on sensory (proprioceptive) control. Apparently *the foundation of voluntary movements lies in a diffuse motor discharge which originates in the cerebral cortex and is sustained,‡ modified, and directed into the proper pattern through proprioceptive impulses.*

Proprioceptive impulses have still another function. They minimize synaptic resistance, as shown by the proprioceptive reinforcement of nociceptive reflexes and cortically induced movements. In addition the motor cortex itself is excited by proprioceptive impulses. This excitation, presumably increasing the susceptibility of the motor cortex to afferent stimuli (including those originating in other parts of the cerebral cortex), leads to an actual discharge of the large ganglion

* See also von Weizsäcker (1222).

† Jewsburg (740) cites unpublished observations by Lorber and Carmichael on apparently normal movements in a three-year-old child with a congenital absence of postural, tactile, and pain sensitivity.

‡ Foerster (370) mentions the following characteristic observation: A patient with a deafferented arm attempts to extend the fingers. The movement starts correctly, but before it is completed, the extensors relax and the flexors contract.

cells in the fifth cortical layer, since the activity of the pyramidal tracts is increased as a result of proprioceptive excitation (464). The activation of the final common path in voluntary movement seems accordingly to be due to impulses originating in the cortex of the brain* and proprioceptive reflexes acting on segmental and suprasegmental portions of the central nervous system, including the motor cortex.

Even without stimulation of the motor cortex the internuncial neurons and the motor horn cells of the spinal cord appear to be bombarded by impulses through bineural and multineural proprioceptive spinal reflexes and through the pyramidal tracts whose cortical neurons have been activated by proprioceptive and other impulses. These processes form an important part of the physiological basis of muscle tone.† They set the stage for voluntary movements and may contribute to their initiation.

Afferent impulses, including those that act below the level of consciousness, play a part in the performance of normal movements. The importance of the distance receptors for the development of the motor cortex and for the initiation and execution of movements was emphasized by Sherrington (1111). The role of proprioception is particularly stressed in this book, but the action of other receptors is likewise significant. Von Frey (389) has shown that after the elimination of cutaneous sensations through anesthesia, the degree of active movement of a finger, for instance, contracting against a spring can be judged accurately, although fine movements, such as writing, may be disturbed greatly. Apparently in the performance of skilled movements the final action depends on more than one sensory modality. A study of the development of movements in the infant, as well as observations on patients with tabes or a deafferented extremity, shows the significance of optic perception for the learning and relearning of movements.

Parsons (992) emphasized recently that as far as a sensation is concerned, the "natural form of stimulation is always a receptor *pattern* of less or greater complexity, in which probably invariably more than one adequate stimulus is involved." This statement holds

* The possible relation between the discharge originating in the motor cortex and that of other parts of the cortex needs further clarification. It is of considerable interest that Penfield and Rasmussen (1002) observed that stimulation of the secondary motor area in man elicits an "intention of movement."

† Extrapyramidal influences, the reticular formation (Magoun, 886), and vestibular effects (Magnus, 884a) likewise play a decisive role in the maintenance and modification of muscle tone in physiological and pathological conditions.

true for the physiology of voluntary movements, which are the result of the integration of various sensory and motor impulses at several levels of the central nervous system.

Stimulation of the motor cortex with a single shock may induce a contraction in a single muscle or in a fraction of a muscle, but this form of activation is as far removed from that involved in a normal voluntary movement as a stimulation of a single Meissner corpuscle with a von Frey hair is removed from the arousal of a pressure sensation under physiological conditions. The value of analytic procedures, which have given much insight and have led to an understanding of the excitation of a single neuron on a quantitative basis, is by no means deprecated, but without some synthesis that is mindful of sensorimotor interaction the interpretation of physiological processes in general and of the central nervous system in particular remains inadequate.

The Central Position of the Spinal Cord

Since motor impulses, whether induced reflexly, by cortical stimulation, or by the cortical mechanism involved in volition, ultimately reach the final common path of the motor neurons of the anterior horn cells, the functional characteristics and anatomic distribution of these neurons and of the internuncial spinal neurons associated with them must be a determining factor in all movements. Consequently it is not surprising to find that certain reflex patterns, as represented by the biceps and triceps complexes, are the same as those seen after stimulation of the motor cortex. These patterns seem to agree with the synergism described by Foerster (369, 370) as the basis of voluntary movement in man.*

There is, however, one important difference between movements induced reflexly or by cortical stimulation and voluntary movements. In the former, biceps and triceps complexes are fixed; i.e., biceps contraction is primarily associated with contraction of the extensor carpi muscles, and the flexor carpi muscles are activated only secondarily (in the form of co-contraction). In voluntary movements the association of muscles in groups is more variable and solely determined by the intended movement (452). Thus voluntary flexion of the wrist against a resistance is aided by the biceps in supination but by the triceps in

* As another example may be cited the observation that voluntary flexion of the arm against gravity involves the following muscles: brachialis, biceps, brachioradialis, extensor carpi longus, and pronator teres. These muscles are part of the biceps complex, as determined by stimulation of the motor cortex (Gellhorn and Johnson, 494).

pronation. The effect of various movements of the wrist on the innervation of the biceps and triceps is shown below.

Movement	*Agonist*	*Associated Muscle*
Flexion in pronation	Flexor carpi	Triceps
Flexion in supination	Flexor carpi	Biceps
Extension in pronation	Extensor carpi	Biceps
Extension in supination	Extensor carpi	Triceps

This simple example may serve to illustrate the fact that the neurons of the spinal cord which, activated in a certain temporal and spatial order, produce movement patterns seen in reflexly and cortically induced movements, may be combined into new forms. Precision, rapidity, and individuation progress under the influence of training. They lead to elimination of the associated movements or of the changes in muscle tone of associated muscles that ordinarily accompany movements of a single finger (1170). Whether the individuation (flexion of a single finger) seen on stimulation of the motor cortex in apes is the result of a unique analytical power of the motor cortex, as Leyton and Sherrington (840a) suggest, is not certain. Impulses reach the anterior horn cells from the motor cortex of the brain or through reflexes activated by cutaneous and proprioceptive end-organs. In either case the individuation of movements seems to be determined by the selective activation of neurons. Voluntary action refined by training may result in highly specialized and restricted movements. But reflexes can likewise show an increasingly specific character. Through the utilization of smaller nerves for stimulation, the classical ipsilateral flexor reflex of the arm can be divided into reflexes involving either the biceps or the triceps complex (864), and a further specialization is probable for nociceptive reflexes and well established for stretch reflexes.

The similarity in the motor effects obtained on reflex stimulation, excitation of the motor cortex, and voluntary effort indicates that certain fundamental characteristics of movements are determined by the spinal cord. The motor cortex on the one hand, the cutaneous and proprioceptive receptors on the other, represent the "afferent" areas through which the spinal cord is activated. Under strictly physiological conditions – i.e., in the absence of pain – the cutaneous afferent field contributes through reflexes to muscle tone, the spinal cord thereby being made more responsive to cortical impulses. Gross injury calls forth Sherrington's ipsilateral flexor reflex or more widespread reflex

patterns, but nociceptive impulses of lesser intensity originating in a restricted area will result in selective reflex responses.

The Interaction of Willed Movements with Spinal Reflexes

The resemblance existing between motor effects arising from nociceptive reflexes and from the motor area of the cortex should not obscure the fundamental differences between these two forms of activation of the motor apparatus of the spinal cord. This is well illustrated by the study of the interaction of spinal reflexes with cortically initiated movements.

As far as proprioceptive reflexes are concerned, it was shown that they are closely integrated with cortically induced movements. Similar results were obtained in experiments involving an interaction between nociceptive and proprioceptive reflexes. In either case the pattern set up by stimulation of the motor cortex or through nociceptive end-organs or nerves can be specifically intensified. Apparently the activation of the spinal cord through the cortex and through multineural reflexes follows similar laws, and the two forms of activation are different only in the degree of complexity.

Further light on the nature of willed movements is shed by the study of their interaction with proprioceptive and nociceptive reflexes. A fine integration exists between the phasic form of proprioceptive reflexes (the stretch reflex) and voluntary movements (Hoffmann, 693). If the hand or foot is placed on a vibrating rod, no reflexes are elicited. However, if the muscles are voluntarily excited in an attempt to reduce the size of the vibration, action potentials appear in them at the frequency of the vibration even if its rate is altered within fairly wide limits. As Hoffmann expresses it, "The voluntary innervation is changed into a reflex series." Apparently the stretch reflexes, although elicitable in the spinal animal and isolated for purposes of analysis in the physiological experiment or the clinical test, are an important part of the voluntary movement. Hoffmann emphasizes that the final type of a movement is not solely determined by the will but that the "distribution of innervation" is influenced by these tendon reflexes.

On the other hand, no such integration is present between voluntary movements and nociceptive reflexes. If an ipsilateral flexor reflex is interacting with a voluntary flexion of the same muscle one does not find any summation but, on the contrary, an inhibition of the flexor muscles (694). It may be remembered that nociceptive impulses greatly modify movements which are initiated by stimulation of the motor cortex, but in contradistinction to the alteration induced by proprioceptive impulses, the effect of nociceptive excitation is unpre-

dictable (519). This shows that the proprioceptive reflexes in their phasic and static form are an integral part of cortically induced movements. Only when they are greatly increased in intensity, as in certain spastic conditions, or considerably weakened, as in cerebellar disease, do they qualitatively alter the motor act. Nociceptive impulses, on the other hand, may be responsible for abnormal patterns of innervation in willed movements. It need hardly be added that nociceptive reflexes are primarily protective mechanisms operating independently of cortically induced movements.

The Motor Cortex and the Variability of Movements

The question arises whether the elementary character of the movements elicited by electrical stimulation of the motor area is actually in conflict with the assumption that the excitation of this structure through volition is the basis of complex and skillful movements. The large pyramidal neurons of the motor cortex have often been compared to the strings of a piano. Since, like the keys of the piano, the muscles of the hand have been activated singly (and in fractions) as well as in various combinations with other muscles by electrical stimuli, there is no fundamental difficulty in explaining the great variety of hand movements through the activation of the neurons of the cortical hand area in different spatial and temporal relations. There is good reason to assume that the motor cortex functions in a similar manner on electrical stimulation and in volition, since both procedures lead to the same type of motor discharges * and, as reported earlier, volitional effort and electrical stimulation of a peripheral nerve can be exactly matched. Consequently it is highly probable that the forms of activity resulting from stimulation of the motor area constitute basic elements of voluntary movements. The instability of the motor cortex (164) – i.e., the fact that a preceding stimulation modifies the reactivity of a given group of cortical neurons – is a phenomenon of intrinsic interest, but in addition it contributes to the variability of voluntarily induced movements. Other factors involved are: (1) differences in the optimal frequency of neurons activating the same muscle from different cortical foci or functionally related muscles from the same focus (722); (2) differences in threshold among a population of neurons which activate a given muscle (842); (3) the interaction of excitation and inhibition operating not only between the agonist and antagonist of individual muscles but also between functional muscle groups of varying degrees of complexity (456, 494).

* See p. 23.

Levels of Integration in Willed Movements

In the light of this discussion the motor cortex appears to be only a more refined and specialized afferent area through which the spinal cord is activated *under the guidance of other parts of the cortex, including the sensory projection areas.* This interpretation is based on the fact that the planning and the execution of a purposeful act are not prevented by partial lesions in the motor area. If, for example, through lesions of the thumb-finger foci the apposition of thumb and index is lost and the opening of a box requiring such a grip is impossible, the monkey may substitute an entirely different movement (pull on the handle of the box with the teeth) and achieve the same goal (550). The fact that apraxia in the human being results less from lesions of the motor cortex than from those of the parietal and frontal lobes is in agreement with these observations (939).

Obviously, volitional movements are carried out at different levels. For the simpler types of movements it appears adequate to "look upon the pyramidal system as an internuncial, a common, pathway by which the sensory system initiates and continuously directs, in willed movements, the activities of the nervous motor mechanisms. This sensory afflux is a condition of willed movement, and unless we consider both in association we cannot hope to see the purpose of either" (Walshe, 1204). These movements are greatly altered by deafferentation, which eliminates the effect of sensory impulses on the spinal and cortical level. Ablation of the sensory projection area in the postcentral gyrus is less serious and causes only temporary loss in the sense of movement and in two-point discrimination. On the other hand, removal of the parietal lobe induces no sensory disturbance in the contralateral arm, but in one such case Penfield (1002) reported that the patient "had difficulty in visualizing what he was to do with the left hand on the side of the body when tasks were set him. He had trouble in dressing and was apt to ignore the left arm as though it did not belong to him." Even after two years his relatives had "to remind him to use his left hand." The defect in this case is probably related to what have been called "sectional disturbances of consciousness." * Apparently the parietal and the frontal lobes supply impulses to the motor cortex in addition to those reaching this structure directly or through cortical projection areas. Interference with these systems will eliminate willed movements of varying degrees of complexity or abolish their execution by certain parts of the body.

A few additional remarks are necessary to clarify the role of the

* See bibliographical entry 225.

motor cortex in voluntary movements. There is a general consensus that the motor cortex is an indispensable link in the chain of structures and events which culminate in volitional movements. The restoration of movement after focal cortical lesions appears to be due to the neurons which remain functioning in adjacent areas. It is also conceded by all workers in the field that the motor cortex does not represent the highest level of motor integration. Penfield and Rasmussen (1002) stress the relative simplicity of the movements which result in the human being on stimulation of the motor cortex. "There is represented in the sensorimotor convolutions only elementary movements such as might be expected of an infant, and yet ablation of precentral gyrus produces paralysis of all the complicated, skillful movements which do not seem to be represented there!" To solve the problem they propose to make the diencephalon the highest integrating mechanism for motor as well as for sensory processes.* This idea appears to have no support in experimental or clinical work. The importance of diencephalic-cortical discharges for cortical activity in general and consciousness in particular is discussed elsewhere.† Suffice it to say that this stream of impulses is the *conditio sine qua non* of specific cortical activity. With regard to the motor cortex it could be shown that these impulses increase its responsiveness greatly (957). But there is no evidence that further *elaboration* of motor (and sensory) phenomena is a specific contribution of the diencephalon.‡

That motor activity in its simplest form, i.e., in reflexes, is intimately related to sensory function is evident from the classical investigations of the Sherringtonian school (244). The disturbance in speech resulting from lesions in the temporal cortex (sensory aphasia) is the most impressive example of similar relations at the cortical level. No attempt can be made here to discuss the complexity of the physiology of speech even in its most elementary feature, but it is important for an understanding of the highest level of motor activity to stress that the motor (Broca) and sensory (Wernicke) centers of speech are definitely located in the cortex. The action of these two areas is necessary to supply the foci of articulation and vocalization in the motor cortex with a plan which will result in a spoken sentence. The sensory

* "Within the diencephalon there are neurone circuits which may be considered the highest level of neuronal representation and re-representation. But much of the function at this level is made possible and is elaborated by the special areas of the cerebral cortex."

† See pp. 197ff.

‡ The significance of the diencephalic-cortical discharges for the problem of emotion is dealt with in Chapter 14.

control of the proper execution of this plan lies in Wernicke's center.* Similarly every deliberate action presupposes a plan which must be supplied to the motor cortex in the form of spatially and temporally determined sequences of impulses. Lesions in the frontal and parietal lobes may interfere with the formation of such a plan. The result is apraxia. Obviously the highest level of motor activity lies in the cortex outside of the precentral gyrus. If this is, at least in principle, a correct scheme of the mechanism of volitional movement, is it surprising that the stimulation of a small area of the cortex with an electrical current of a given intensity and frequency produces a rather primitive movement? Is not this result due to the rather inadequate method of stimulation? Electrical stimuli applied to the occipital cortex give rise to primitive elements of vision ("a brilliant ball, a star, a streak, a wheel, a spot or a flash, a light" – 1002), but nobody doubts that optical impulses induced by physiological stimulation of the retina initiate through excitation of the visual cortex complex visual phenomena characterized by color, shape, and depth.

If this analogy is valid, it may be said that the complexity of willed movements appears to be fully accounted for by the established relations of the sensory projection areas and the frontal and the parietal lobes to the motor cortex. Impulses from these areas activate in ever varying relations the pyramidal cells of the fifth layer of the Rolandic cortex and produce thereby an infinite number of combinations of movements, the elements of which are demonstrable in experiments on the electrical stimulation of the motor cortex.

* For further details see Nielsen (971).

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The Restitution of Movements after Central Lesions

"Compensation does not, in this scheme, mean that nervous arrangements take on duties they never had before, but that having more or less closely similar duties, they serve – not as well, but only – next as well as those destroyed." Hughlings Jackson (730).

THE restitution of movements following lesions in various parts of the central nervous system is of theoretical interest because the function of structures such as the motor cortex can be properly evaluated only if the results of stimulation *and* ablation are taken into account. In addition the functional recovery from cortical motor lesions is obviously of great practical import from the point of view of prognosis and therapy. That the axon outside the central nervous system has considerable recuperative powers not only in laboratory animals but also in man is attested by the restoration of motor and sensory functions after injury or complete severance of the nerve fibers. On the other hand, the restitution of axons in the central nervous system after injuries such as transection of the spinal cord has never satisfactorily been proved for the mammalian nervous system, although in lower forms nerve fibers regenerate and function is completely restored even after transection of the brain stem (1131). Since this discussion is confined to the effect of lesions of the central nervous system in mammalian organisms, and particularly in primates, the restitution of function here cannot be presumed to be the result of growth processes (regeneration) of previously sectioned axons. Rather it must be explained either by the restoration of normal function in uninjured neurons after the initial shocklike phenomena (von Monakow's diaschisis, 939) have disappeared or by the assumption of new, compensatory functions on the part of the uninjured neurons, or by both. An attempt

will be made to arrive at a decision between these different possibilities.

The Restitution of Muscle Function after Partial Denervation

The problem of the recovery of muscle function after partial denervation is of great interest for diseases which, like poliomyelitis, affect preferentially the anterior horn cells of the spinal cord. Since each muscle receives its motor nerves from several spinal segments and since each of the segments from which the cervical and the lumbar plexus originate carries nerves to numerous muscles (1110), a lesion confined to one or a few segments is apt to damage several or many muscles only partially. This poses the question whether the remaining neurons can contribute to the restitution of muscle power. Since muscle function, at least in the experimental animal, is best measured by the tension produced by the muscle on stimulation of its nerve (indirect stimulation), the problem is whether a restitution of muscle function takes place spontaneously after the muscle has been partially denervated as the result of a spinal lesion. Since it would be difficult or impossible to produce practically identical spinal lesions in a number of animals, a different procedure had to be chosen, allowing one to answer this question on a quantitative basis.

In view of the fact that a certain muscle receives its motor supply through at least two motor roots, the effect of a partial destruction of the motor horn cells at a given spinal level can be duplicated by sectioning a single motor root provided that its regeneration is prevented by proper surgical procedures. Then the contribution of the remaining root or roots to muscle function can be determined by stimulating these roots with maximal currents and recording the effect on muscle tension at various intervals following the root section, and by comparing the results thus obtained with those of similar experiments performed on the other, unoperated side. In such studies (1183) it was found that after the sixth lumbar nerve has been removed in the rabbit, stimulation of the intact fifth lumbar nerve yields a considerably greater tension in the paretic sartorius and quadriceps muscles than is observed under analagous conditions of stimulation in the contralateral control muscles. This increase in tension begins after two weeks and is not yet completed after six months. Similar results were obtained on rats and cats (662, 1221). It was also noted that the muscle loses weight at first, but this atrophy is checked eventually and its disappearance is confirmed by histological studies. No hypertrophy of muscle fibers occurs, but the previously atrophied muscle fibers regain, through re-innervation, their normal size and

TABLE 4. A Summary of Average Values for the Gastrocnemii of 15 Cats Subjected to Bilateral Section of the Seventh Lumbar Nerve (Hines, Wehrmacher, and Thomson, 662)

No. of Days after Section	Muscle Weight, in Grams	Total Tension When Activated through		Tension per Gram Muscle When Activated through	
		Nerve	Muscle	Nerve	Muscle
3	12.683	3,400 Gm.	10,223 Gm.	257 Gm.	756 Gm.
18	10.207	5,809	8,023	557	730

appearance. Table 4 shows that while the muscle is still losing weight, the tension produced on indirect stimulation increases. A startling augmentation of the tension per gram muscle is observed in the course of a few weeks following this partial denervation.

Further analysis shows that the compensatory reaction is due to intramuscular branching of the intact nerve fibers, since the tension produced by indirect stimulation increases with the duration of the recovery, although the number of nerve fibers entering the muscle remains unchanged. This sprouting of the intact nerve fibers occurs after the terminal part of the fiber has degenerated. It is important to note that the stimulus which apparently originates in the degenerating nerve or muscle fibers and which accounts for the re-innervation through nerve branches is not a "neurotropic" influence which extends over appreciable distances. On the contrary, if denervated and normal muscle fibers are clearly separated, as in the diaphragm following unilateral section of the phrenic nerve, re-innervation does not occur. Since intact and degenerated muscle fibers are located in the same fascicle and consequently are closely intermingled if the lesion is of spinal and not of peripheral origin, the recovery studied experimentally by Hines, Van Harreveld, and Weiss can be expected to take place spontaneously following partial segmental destruction of motor horn cells as in poliomyelitis. As Weiss suggests, there may be no need for the neurotripsy of Billig (101) unless this surgical procedure will greatly accelerate the process of regeneration by inducing nerve branching (cf. Hodes, 680).

For the fundamental question of the nature of the restitution of function following lesions in the central nervous system these investigations are of great interest. Since there is no essential difference between the loss of muscle innervation engendered by partial lesions in the anterior horn of the spinal cord and that produced by sectioning of a motor root, it appears likely that the mechanism of nerve branching initiated by the degenerating nerve and muscle fibers plays an

important part in the recovery from lesions caused by the polio virus. Obviously the degree of recovery will depend on the number of surviving normal nerve fibers. Perhaps the factor of age is of importance, and the regenerative power may be much greater in lower forms than in man. But it should be stressed that this restitution does not involve any change in the function of the motor horn cells. The motor units which leave the spinal cord at various segmental levels to innervate a certain muscle such as the gastrocnemius are not functionally different. The process of growth and development limits the number of muscle fibers which are innervated by each motor root, since each muscle fiber is supplied with only one nerve ending. The loss of innervation initiates the regenerative processes described above and may lead to an enlargement of the terminal area supplied by the remaining motoneurons, but their functional properties remain unchanged.

The Restitution of Motor Functions after Lesions in the Motor Area

Some facts about recovery after experimental lesions of the motor area * have been mentioned earlier. It was emphasized that apparently neurons in the vicinity of the extirpated area account to a large extent for the restitution of function. The extensive overlap in the representation of movements in the motor area explains the fact that even after the extirpation of the "arm zone," neurons supplying the muscles of the upper extremity are still present in the adjacent somatotopic cortical areas. The conclusion that multiple movements are represented in minute parts of the motor cortex was established for the monkey through stimulation of the intact structure and of surgically isolated parts of cortical tissues (Murphy and Gellhorn, 959; Denny-Brown, 280); it is also valid for man (Walshe, 1202). Even in very small lesions "damage to any part of the limb area results in weakness of

* Cytoarchitectonically the motor area is divided into area 4, located immediately adjacent to the Rolandic fissure, and area 6, which comprises the anterior part of the precentral gyrus. The assumption that these two parts of the motor cortex subserve different functions (Fulton, 397) has been criticized on the basis of experimental and clinical findings (Walshe, 1201; Denny-Brown, 279). In stimulation experiments it was noted in the writer's laboratory that in moderately anesthetized animals the threshold increases considerably as the electrode is moved more anteriorly in the precentral gyrus, and at the same time the summation time increases and the tendency to after-discharges is greatly augmented. However, in very lightly anesthetized animals the threshold and type of response to electrical stimulation show little change (719). These observations support the concept stressed by Walshe of the precentral motor cortex as an area of unitary function. Denny-Brown suggests for it the term "Rolandic cortex."

movement of many muscles and at several joints within the general limb or body segment represented" (Denny-Brown). Since electrical stimulation of the human cortex produces multiple effects, the restitution of function through adjacent intact neurons is highly probable for man.

As to the role of homologous areas of the contralateral intact cortex no consensus exists. The better recovery of movements of proximal than of distal joints could be explained through the function of the intact precentral gyrus because the former are said to be more bilaterally represented in the cortex than the latter. However, as will be shown presently, other (nonhomologous) cortical areas of the same side could equally well account for this fact. Direct experiments do not favor the assumption of an important role of the opposite cortex in the restitution of movements. If several weeks after a cortically induced monoplegia of the left arm, the right arm is paralyzed by a similar cortical operation of the left brain, the left arm is used with greater advantage than before the second operation (1169). Similarly, with the left arm removed and consequently great motivation to use the right arm, recovery after a left cortical lesion is rapid if parts of the arm area are left intact, but after more thorough extirpation the fingers remain permanently useless and the movements of hand and arm are clumsy. Moreover no movements of the right arm are elicited on stimulation of the right cortex several months after the left cortical lesion.

The observation (280) that the degree of recovery tends to parallel the number of the pyramidal cells of the specific part (e.g., arm area) remaining intact, whereas the removal of other parts of the motor cortex has little influence on the restored movements, suggests likewise that the restitution of movements is due to specific parts of the motor cortex and that these functions cannot be taken over by other parts of the Rolandic cortex.

Movements of the extremities can also be elicited by the electrical stimulation of extra-Rolandic areas, and the possible contribution of these areas to the restitution of motor function following lesions in the motor area must now be discussed. Just as the sensory cortex is represented in two separated cortical areas of each hemisphere (1247), it is found that movements of the limbs are also represented laterally to the face area of the classical motor cortex of the cat (413) and in the insular cortex of the monkey (1140). Penfield and Rasmussen (1002) present suggestive evidence for such a second motor area in the human being, located between the lower end of the Rolandic fissure and the fissure of Sylvius. They also found a "supplementary"

motor area within the longitudinal fissure just anterior to the representation of the foot in the motor cortex. Stimulation of this area produces complex combinations of movements "in which the contralateral hand is typically raised before the face and the head and eyes turned to the hand."

Under conditions of facilitation movements may be elicited from large parts of the frontal and parietal cortex. They consist not only of adversive movements (turning of head and eyes to the contralateral side) but also of flexion of the contralateral fingers and toes and the elbow. The former effects are obtained from the frontal eye area (area 8), the latter from area 9 of the frontal lobe. An extension of the contralateral elbow and knee occurs on stimulation of the postcentral gyrus of the monkey, and these effects persist after ablation of the Rolandic cortex. These observations show that movements of the limbs are elicitable outside the classical motor cortex (279, 939).

As mentioned before, the recovery from cortical lesions of the motor area is characterized by the fact that distal muscles regain function to a much lesser degree than proximal muscles. Furthermore the movements of the distal muscles appear commonly only in association with other muscles. Foerster (367, 369) lists among such functional synergisms the abduction of the arm in combination with flexion of the forearm and pronation, and he noted that with the intention to extend the forearm, the upper arm was abducted and the leg extended at the same time. Flexion of the leg was combined with that of the arm or with dorsiflexion of the foot and toes. If an extension of the leg was attempted, plantar flexion of the ankle and toes appeared simultaneously and was occasionally accompanied by an abduction of the hip. In cases in which the ability to flex and extend the fingers returns, these movements are performed with all fingers together, but flexion or extension of individual fingers is impossible. Moreover flexion of the terminal phalanges of the fingers, particularly against resistance, is associated with adduction and opposition of the thumb (Wartenberg's sign).

Since the stimulation of extra-Rolandic areas commonly produces such combinations of movements, it is understandable that recovery from lesions in the motor area has often been explained through the activity of these parts of the cortex. This interpretation is implied in an observation in which the removal of the arm area in man was followed by the restitution of arm movements only, not finger movements. At this time the stimulation of the adjacent areas of the postcentral gyrus induced "gross movements in the arm much like the ones of which (the patient) was . . . voluntarily capable" (1002).

However, the larger part of the recovery of function following partial lesions of the precentral motor cortex appears best explained by the activity of the remaining parts of this area. The overlap in the motor cortex of representation of movements accounts for the fact that removal of the hand area abolishes only a fraction of the pyramidal cells which send impulses to the hand muscles. The cortical injury and the consequent reduction in the number of functioning Betz and large pyramidal cells raise the threshold for stimulation and voluntary innervation. Several factors are probably involved. The injury causes a shocklike condition (diaschisis, 939), which gradually disappears. Even under optimal operative conditions which tend to minimize local effects such as edema, the diaschisis lasts for a considerable time in the higher-developed brains of apes and man. But also after the disappearance of diaschisis the excitability of the cortical "hand area" in our example must remain low, for several reasons. It was shown earlier in studies on cortically induced movements resulting from voluntary effort (845) or electrical stimulation (512) that the chief factor in the gradation of movements is the number of activated motor units. If the cortical "hand neurons" are reduced below a certain number, no movement will occur; if somewhat more neurons are available, even weak movements will require greater effort, and consequently movements of the hand and fingers will appear not individually but in combination with those of the arm, etc. In addition, the necessity of overcoming spasticity demands a greater influx of impulses (Foerster).*

The Significance of Sensorimotor Disintegration

The mechanism involved in the initiation of normal movements and of those appearing during recovery following cortical injury or pathology cannot be understood without recognition of the importance of sensory factors. The loss or great reduction in voluntary movements following deafferentation of an extremity or after lesions of the parietal lobe which lead to a partial breakdown of the body scheme† has been pointed out. The destruction of parts of the motor area must lead to a diminution of proprioceptive impulses which reach the precentral

* How the associated symmetric movements of the paretic limb which occur in monoplegia (707) with strong movements of the corresponding healthy extremity are to be explained is uncertain. Suffice it to say that the differences between physiology and pathology are also in this case only quantitative, since with maximal contraction of one arm action potentials appear in homologous muscles of the contralateral side, although overt movements are absent (464).

† In such cases of autotopagnosia the patient is unaware of the contralateral side of his body.

gyrus (416), and disturbances in the relation of the postcentral to the precentral gyrus and consequently a partial failure in the integration of movements and cutaneous sensations are to be expected. Horsley (707) emphasizes diminution in the accuracy of tactile localization and Penfield notes a reduction in two-point discrimination after removal of parts of the precentral gyrus in man. On the basis of animal experiments Munk (954) stresses the importance of the motor cortex for tactile reactions, and Denny-Brown (279) adds new material through a study of the grasp reflex. The latter reflex is dependent on the combination of tactile and proprioceptive stimuli and is abolished by lesions in the Rolandic cortex. Denny-Brown suggests that with the loss of tactile reactions the proprioceptive reflexes are exaggerated and spasticity ensues. Although the problem of spasticity appears to be more complex,* it seems important to emphasize with Denny-Brown that the disturbances in movements resulting from lesions of the motor area are the result of sensorimotor disintegration as well as of a direct motor deficit. In this connection it should be mentioned that the cutaneous abdominal reflexes and tactile placing reactions† are permanently lost following lesions of the motor cortex.

The rise in the threshold of the motor cortex following lesions appears to be due not only to the reduction in pyramidal cells but also to sensorimotor disintegration. Adrian and Moruzzi (17) have shown that in the anesthetized animal a discharge of the pyramidal tracts occurs which is increased by various afferent impulses. Consequently it may be assumed that in the normal organism proprioceptive and cutaneous impulses bombard the motor cortex continuously and thereby lower the threshold to voluntary innervation.‡

The So-Called Plasticity of the Central Nervous System

An attempt was made in one of the preceding sections to explain the recovery of movements following lesions of the motor area without assuming that pyramidal neurons of the same and the contralateral cortex would change their function in order to compensate for the loss.

* See the recent brilliant investigations of Magoun (886, 889).

† In the normal animal, contact of the dorsum of the foot with a flat surface leads to placement of the limb on it (Bard, 66).

‡ The threshold of the motor cortex to *electrical* stimulation is not raised by deafferentation (721), but it should be remembered that voluntary effort activates the cortex in a more subtle way than does electrical stimulation. This is best illustrated by Foerster's experience (369) that electrical stimulation of the motor speech center of Broca resulted in a logorrhoea which was coordinated at first but soon became ununderstandable, while Penfield (1002) reports that stimulation of this area caused hesitation, and with stronger stimuli, cessation of speech but in no instance initiated normal speech.

We followed therein Jackson's clear statement quoted earlier rather than the clinical and experimental literature which has used concepts of reorganization freely with respect to the central nervous system. Such suppositions are based to a large extent on the apparent readjustment in function after nerve crossings and muscle transplantation, but the fundamental work of Weiss (1218, 1219) and Sperry (1129, 1131) makes it abundantly clear that there is little if any basis for such sweeping generalizations.

In the earlier work it was assumed that the nervous system adapted itself so rapidly that immediately after the restitution of conduction between central and peripheral structures normal functions were restored in spite of nerve crossings. Bethe (97) suggested that the rapidity of the adjustment in locomotion seen immediately after the removal of one or more extremities in vertebrates and invertebrates was due to a "plasticity" of the central nervous system and was not based on relatively slow learning processes, and Goldstein (555) attempted to show that this new quality accounted for the restoration of function following lesions of the motor and sensory cortex in man. If correct, this concept of plasticity would indeed be of a revolutionary character since central-nervous activity has been explained heretofore on the basis of preformed neuronal pathways, the laws of synaptic transmission, and factors influencing neuronal excitability. However, Sperry (1129) showed in a critical review that the rapid adjustment was due in part to mechanical factors, the activity of muscles with similar function whose innervation had remained undisturbed, and the fact that muscles which were thought to be completely denervated had actually retained some (anomalous) nerve supply. At any rate, the experimental results did not necessitate the assumption that a fundamental alteration in function of the central neurons had resulted from experimental transposition of muscles or nerves.

Weiss (1219) has shown in particular that in lower animals (amphibians) additional limbs can be transplanted and receive innervation from other than the normal limb nerves. The muscles of these supernumerary limbs contract synchronously with normal muscles of the same name, and with similar intensity. Weiss speaks of a myotopic response and emphasizes the fact that this type of innervation persists even when it is definitely harmful from a functional point of view. "Synonymous muscles being in mirror-image positions, the synchronous movements of these twin limbs occur in exactly opposite directions and therefore counteract each other. Three or four limbs supplied from a common plexus merely triplicate or quadruplicate the myochronograms of each other, regardless of the wholly

absurd functional effects resulting therefrom. Never has there been any sign of an adaptive remedial change" (Weiss). Since similar results are obtained with deafferented limbs and after decerebration, learning and adaptive processes are obviously not involved.

This conclusion is supported by the study of certain phenomena involving the sensory nervous system. Sperry (1131) rotated the eyeballs in amphibians through 180 degrees and allowed them to remain in the new position. Optokinetic reactions occurred promptly but were reversed because of the rotation of the retinae. "The predatory reactions involving approach, pursuit, and striking at small moving objects are directed toward corresponding points in the opposite sector of the visual field from that in which the bait is located. The maladaptive responses persist indefinitely without correction. This refractoriness to reeducation suggests, in itself, that the structure mediating these reactions is not organized by the learning process" (Sperry).

These and many other ingenious experiments show that at least in lower forms coordination patterns are not readily altered and that the ganglion cells of the central nervous system do not change their inherent motor and sensory function in spite of maladaptive functional effects.

Experiments on mammals (1131) give in essence similar results. Nerve crossings in rats lead to permanent disturbances and even in monkeys such experiments reveal only a slight adaptive correction. Most interesting is the observation that in cases of human poliomyelitis the crossing of flexor and extensor tendons acting on the knee leads at first to a reversal of movements. Later a corrective adjustment takes place so that the coordination of movements in walking is correct. However, Weiss and Brown (1220) noted that even after years of learning, the old, maladaptive pattern may return. Apparently the old pattern persists, but is altered through a learning process operating at a higher level.

THE CROSSED PHRENIC PHENOMENON

The so-called crossed phrenic phenomenon* likewise seemed to give evidence for neuronal plasticity at the level of the medulla oblongata. Porter (1025) and others observed that hemisection of the spinal cervical cord above the exit of the phrenic nerve leads to a cessation of the respiratory contractions of the ipsilateral half of the diaphragm. If, however, the contralateral phrenic nerve is then sectioned, the ipsilateral diaphragm again shows respiratory movements. It was recognized that this activity is apparently due to crossed

* See Cannon and Rosenblueth (206) for the literature.

descending pathways, but it was not understood why the previously resting diaphragm should resume activity at the moment when, owing to the unilateral sectioning of the phrenic nerve, this function became of vital importance. Does this phenomenon suggest that the outflow of impulses from the phrenic neurons into the intact half of the spinal cord proceeds through uncrossed pathways in the normal animal, but that these impulses cross over to the opposite side as soon as the uncrossed path is blocked? And if so, is this observation the expression of a mysterious adaptability of neuronal pathways, or can it be explained by the generally recognized laws of nervous conduction?

The work of Renshaw (1066) and Brookhart (837) has given convincing evidence for the second alternative, as indicated by the following observations. Through electromyographic recordings it can be shown that the diaphragm is normally innervated by uncrossed and crossed pathways. Hemisection of the cord leads, through the elimination of the uncrossed tracts, to greatly diminished activity in the ipsilateral diaphragm, but this activity is determined, as at the normal side, by the intensity of the discharges from the respiratory center. On diminution of these impulses through hyperventilation the contractions disappear. They return progressively with decreases in the artificially maintained respiratory volume or with other forms of excitation of the respiratory center. If the respiratory volume is kept constant, no changes occur in the crossed impulses after the phrenic nerve on the intact side of the spinal cord has been cut. If respiration is not kept constant, however, the "crossed phrenic phenomenon" occurs; i.e., following section of the right phrenic in an animal with left hemisection of the cervical spinal cord, contractions are initiated or increased in the previously inactive left half of the diaphragm. This phenomenon is simply the result of increased respiratory impulses which are due to reflexes induced by mechanical changes in the lungs subsequent to phrenicotomy. The lesser inflation of the lung and the reduction in the respiratory volume lead through vagal reflexes and anoxic stimulation of sino-aortic chemoreceptors to an excitation of the respiratory center. The classical laws covering the conduction and gradation of nervous activity are adequate to explain the crossed phrenic phenomenon, and no mystic plasticity is needed to interpret the interesting adjustment reactions on which it is based.

Learning and the Hierarchical Structure of Motor Functions

The observations discussed in the preceding sections suggest that the function of motor neurons cannot be changed either in the spinal cord

or in the motor cortex. A reorganization through learning can be accomplished under steady sensory control from only those parts of the cortex supplying the Rolandic area with that sequence of innervation patterns which results in a well-coordinated movement. The learning process is still understood but little (see Lashley, 820, and Smith, 1121) and the highest level of motor action is at present beyond the reaches of physiological research, but clinical observations on apraxia suggest that the frontal and parietal cortex are involved.

Jackson (730) pointed out in his theory of the dissolution of the nervous system that the highest forms of movements – i.e., those which are acquired latest – are the most easily lost. The skillful movements of the distal muscles of the extremities are consequently more vulnerable than the more automatically controlled movements of the proximal joints. Thus it is seen in various forms of apraxia that the more recently acquired movements are lost first and in severe cases "the apractic is reduced to a state of babyhood, being unable to speak, to stand, to walk, to turn over in bed, to control his excreta" (967). The study of the nervous system reveals that sensorimotor functions are established with varying degrees of complexity at different spinal and supraspinal levels. The contributions of the spinal cord, the various sections of the brain stem, and, finally, the cortex to posture, and the increasing complexity and variability of movements as one experiments with the spinal, the decerebrate, the thalamic, and, finally, the intact animal, are well established. Hess (640) called attention to the complex movements which are obtained on electrical stimulation of the diencephalon in the cat. But it appears doubtful whether, at least in adult man, these subcortical structures can account for the restoration of willed movements unless they receive impulses from the cortex.

In cases of infantile hemiplegia subcortical structures appear to be responsible for voluntary movements, since removal of the motor cortex (1223) or hemispherectomy (806) may actually improve movements. If the injury is one that has occurred at birth or in the prenatal period, this circumstance seems to favor adaptation processes, which are hardly ever encountered subsequent to cortical lesions occurring in later life. The studies of Edinger (312) and Gamper (409) on children born without a forebrain indicate that willed movement, including mimic expressions, can be executed if the absence of the forebrain was due to disturbances in embryonic development. If the hemispheres were destroyed later as the result of an injury at birth, however, willed movements remained absent. Apparently the hierarchical organization of movements develops during the embryonic period,

and the fixity of the motor function of a given neuron becomes established.

Re-education after Central Motor Lesions

The question must now be discussed whether the investigations on the motor cortex and the principles elaborated in this chapter give any guidance for a re-education program for cases with lesions of the central nervous system. Whether the lesions are located in the motor cortex (or in the internal capsule) and eliminate certain groups of upper motor neurons originating in the Rolandic cortex, or whether they are located in the spinal cord (anterior horn cells or internuncial neurons), a weakening of voluntary movements is to be expected.* The therapeutic effort must consequently be directed toward an increase in the effectiveness of the remaining corticospinal motor system.

Two principles may be applied:

1. The responsiveness of this system may be increased by chemical agents which augment neuronal excitability and/or increase synaptic transmission.

2. The effect of voluntary effort may be improved by those physiological processes which have been found to increase the height and tension of the contractions elicited by a given stimulus applied to the motor cortex.

RE-EDUCATION AND CHEMICAL TRANSMISSION

Among the chemical agents which may be considered of possible value in the therapy of central nervous disturbances are acetylcholine or one of its more stable derivatives, such as Doryl, and the inhibitors of cholinesterase. It has been shown † that the normal and the convulsive reactivity of cortical neurons (including those of the motor area) are greatly increased by these substances. Moreover the threshold to electrical stimulation and possibly to voluntary innervation is lowered. There is suggestive evidence that synaptic transmission at the spinal level involves acetylcholine and may be aided by physostigmine and related drugs which increase the stability of acetylcholine. This seems to be the basis of the observation that acetylcholine derivatives enhance voluntary power after cortical lesions (1209) and that neostig-

* Upper and lower motor neuron lesions are clinically fundamentally different inasmuch as the former lead to spasticity, the latter to flaccidity and muscular atrophy; but these differences are not of major importance for the re-education program, since the same principles can be applied in both groups.

† See pp. 142ff.

mine (an inhibitor of cholinesterase) improves the range of movement and the endurance in various forms of nervous diseases in which the site of pathology is located either in the brain or in the spinal cord (745, 746).* It is of interest to mention that according to these clinical observations the increased tone of the muscles diminishes as voluntary action is augmented. This is analogous to the previously mentioned finding that spasticity disappears after Rolandic lesions in the monkey when movements of cortical origin in response to a slight contact (Munk's "Berührungsempfindungen," 954) are restored.

RE-EDUCATION THROUGH PHYSIOLOGICAL FACILITATION

The second principle concerns the various procedures described in Chapter 3 which enhance the effects of cortical electrical stimulation and henceforth presumably facilitate willed movements. Under these conditions proprioceptive facilitation mediated by stretch and tension receptors greatly augments the effect of cortical stimulation and makes even subthreshold stimuli highly effective. In cases with central lesions these procedures have actually been applied by initiating movements against large resistances; in Kabat's systematic studies (747–750) they were found to be very successful.

It was shown earlier that excitation of the motor cortex and reflex stimulation of the spinal cord result in certain compound movements involving, for instance, the biceps or triceps complex. It was further proved that the laws of proprioceptive reinforcement are valid within these complexes. Thus, to cite one example only, fixation of the elbow in flexion increases the responsiveness of the triceps as well as of the flexor carpi and the shoulder muscles (with the exception of the acromio-deltoid, which belongs to the biceps complex), although the shoulder and wrist joints need not be fixated. The application of these findings to re-education is obvious and should take into account the fact that proprioceptive facilitation is also effective from the muscles of the distal to those of the proximal joints. If a patient has a paresis of the triceps and not of the flexor carpi, fixation of the wrist in extension may increase the responsiveness of the triceps sufficiently so that actual movements result.† In the leg of the monkey these complexes were not found to be as distinct as in the arm, but the functional relation between the dorsiflexors of the foot and the flexors of the knee was as clearly established as that between the antigravity muscles

* Kabat reports favorable effects in poliomyelitis, hemiplegia, and multiple sclerosis. In poliomyelitis this action of physostigmine may in part be due to its effect on the neuromuscular junction, which is also impaired in this disease (679).

† Unpublished experiments on poliomyelitis patients with electromyographic recordings.

(454, 456, 719). Consequently here again the fixation of one joint may facilitate the responsiveness of muscles innervating another joint.*

The fact that after cortical lesions a muscle may be effectively innervated only in one certain movement – i.e., in combination with one definite group of muscles, but not in other muscle patterns – may also form the starting point of a re-education program based on physiological principles. Thus it was found that, in some cases, of the two functions of the peroneal muscles (plantar flexion and eversion) only the former was preserved. If plantar flexion is carried out isometrically (i.e., against resistance), the apparently lost function may then appear as eversion is attempted (747). This favorable result seems again to be due to proprioceptive reinforcement. Since movements are commonly based on the activation of synergic groups (e.g., flexion of the elbow, involving biceps and brachioradialis), the paresis of one muscle may be overcome by innervating a "normal" synergist under conditions of proprioceptive reinforcement. Kabat further mentions that adduction of the fingers is facilitated by flexion of the metacarpal-phalangeal joints, while abduction of the fingers is reinforced by their extension. Both flexion and extension are carried out against heavy resistance so that the contractions are performed nearly isometrically, as in our fixation experiments. The effect of cortically induced impulses is apparently augmented by proprioceptive reflexes evoked through tension receptors.

Pathological proprioceptive reflexes causing reflex spasms may likewise be utilized for the reinforcement of movements of paretic muscles. In cases of upper motor neuron lesions, passive flexion of the big toe leads to flexion of the hip, knee, and ankle, thereby providing the condition of proprioceptive reinforcement through which the voluntary contraction of these flexors becomes possible.

In a recent study Twitchell (1175) showed the importance of proprioceptive facilitation for the restitution of willed movements of the fingers in hemiplegic patients. Several days before the fingers could be flexed voluntarily, this movement appeared through repeated elicitation of "finger jerks" (i.e., brief stretches of the flexors digitorum) and gradually grew in intensity. After these movements had returned, even tactile stimuli applied to the palm of the hand facilitated willed flexor movements of the fingers.

It is apparent that the principle of proprioceptive facilitation can be extended considerably. The extensor thrust reflex induced by pressure on the sole of the foot and resulting in fixation of the joints

* For further details such as the influence of pronation and supination or protraction and retraction of the shoulder, see Chapter 3.

of the leg may provide an adequate background for the execution of voluntary movement with paretic leg muscles. The neck reflexes of Magnus, leading to increasing extensor tone of the arm toward which the face is turned, can likewise be utilized if they are sufficiently pronounced. The gag reflex may make possible the voluntary contraction of paretic palate and pharyngeal muscles (Kabat, 748, 749).

Kabat introduced two more physiological principles for the retraining of paretic muscles. The first, "reversal of antagonists," is based on Sherrington's successive induction of reflexes. Immediately after a flexor reflex has been elicited, the responsiveness of the spinal cord to the extensor reflex is increased (1108). This phenomenon is also valid for flexor and extensor movements following stimulation of the motor cortex (164). The application of these findings in clinical cases showed that a maximal effort against resistance aids in the subsequent contraction of the paretic antagonists.

Kabat's second principle involves the cerebellum. He found that exercises, probably invoking specific cerebellar functions, are important aids in physiological re-education. It is well known that in cerebellar lesions the quick alternation of antagonistic movements is impaired (adiadochokinesis). Kabat's principle of "rhythmic stabilization" is apparently closely related to this phenomenon. A joint is held rigidly against strong external forces which would tend to bring about extension and flexion in rapid succession. This procedure has been found to be of particular value in motor disturbances of cerebral or spinal origin, but is not applicable to cerebellar lesions.

The older therapeutic procedures emphasized passive movements and electrical stimulation of the muscles. The latter will aid in the delay of atrophy, but neither will help in the reactivation of central neurons. The new procedures are based on training in which corticospinal impulses can become effective owing to optimal conditions of facilitation, particularly of proprioceptive origin. These forms of therapy are said to be successful even years after the onset of paralysis, a fact indicating that loss of function does not lead to fundamental disturbances in the neuron.* This is in agreement with Tower's studies (1166) on spinal neurons, which in spite of complete surgical and consequently functional isolation retain their structural integrity for long periods of time. It has also been shown that denervated striated muscle retains its striation and other morphological characteristics for more than one year in spite of gross atrophy (1142).

* After spinal cord injury with apparently complete loss of sensation and volitional motor function, training under conditions of optimal proprioceptive facilitation led to the restitution of some voluntary movements (750).

There remains the question of the mechanism through which these movements are improved. It is easy to understand that in the acute experiment facilitation in its various forms augments the contraction and the development of tension of paretic muscles in willed movements; however, the more permanent effects are ill understood. The latter are in essence similar to those underlying any kind of training, as in motor skills, the establishment of conditioned reactions, etc. Whether training affects primarily the precentral gyrus or is equally effective on extra-Rolandic areas is not known. To assume that after lesions in the Rolandic area the extrapyramidal system plays a greater part in the restitution of movements seems unjustified, since the motor area is composed of both pyramidal and extrapyramidal neurons. It is certainly correct that normal movements involve a balance of the Rolandic and extra-Rolandic systems (279), but it is not certain that this balance is altered during the restitution of movements following lesions in the motor area. Although purely quantitative changes affecting the excitability of those corticospinal neurons which remain intact after a lesion seem primarily responsible for whatever recovery of movements can be achieved through re-education, it should not be forgotten that at least in cases of early acquired lesions compensatory processes may lead to anatomically verified hypertrophy. Déjérine, von Monakow, and others reported hypertrophy of ipsilateral pyramidal tracts in infantile hemiplegia, and Foerster (367) states that years of training may lead to a restitution of arm and hand movements in the adult in spite of anatomically verified complete degeneration of the pyramidal tracts. In these cases new motor functions may appear through learning processes involving the highest level of integration, but even here the execution of these movements would not involve a change in function of the individual neurons of the motor cortex.

Concluding Remarks

A final remark on the restitution of movement is in order. It was noted by the writer that polio-infected monkeys with marked paralysis showed a surprisingly good muscular performance under conditions of emotional excitement, and similar changes were recently reported after lesions of the motor cortex (280). These phenomena were shown to be due to hypothalamic facilitation of the motor cortex (957) and in addition to summation processes which result from the interaction of the cortical and the hypothalamic discharges on the motoneurons in the spinal cord (1045). This hypothalamic effect is perhaps deserving of more attention, and a properly guided training program should take advantage of this powerful facilitating mechanism.

It is obvious that in spite of decades of research our knowledge of the physiology of restitution following central motor lesions is very incomplete. Nevertheless it seems unjustified, even in the present state of understanding, to explain the change in the character of the movements and the gradual improvement by assuming that the extrapyramidal system or the motor area of the intact hemisphere has "taken over" the functions normally fulfilled by area 4. Such concepts presuppose a plasticity of neural functions which is not borne out by the careful investigations of Weiss, Sperry, and others. Moreover the loss of relatively "discrete" movements, which were erroneously considered to be characteristic of area 4,* appears to be due to the reduced excitability of the motor cortex following removal of some of its parts. Only very strong cortical excitation is apt to elicit any movements at first, and consequently the character of these movements is massive and accompanied by associated movements. If the cortical lesions are small, the permanent decrease in cortical excitability is less, and willed movements involving a relatively small effort are bound to be effective, with the result that movements of individual fingers etc. reappear. But even mass movements and associated movements do not represent a new phenomenon, since they can be seen, although to a lesser degree, with strong movements in the normal individual. In the absence of overt associated movements, changes in reflex excitability indicate that voluntarily initiated discharges are not restricted to the intentionally innervated muscles. It is an old clinical experience that a strong pull exerted with both arms facilitates the knee jerk. This effect appears to be due to the associated activation of small motor fibers which innervate the muscle spindles in the leg muscles and initiate a discharge from these proprioceptive organs (695, 715). Thus a previously ineffective stimulus elicits a knee jerk. It seems that primarily by creating optimal conditions for these physiological processes of facilitation and secondarily through learning processes a centrally induced paresis can be improved.

* See the critical and experimental studies of Walshe (1203) and Gellhorn (458).

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Electromyography

Physiological Observations of Muscle Action

To ascertain the degree and the temporal relations of activity in individual muscles in reflexes and willed movements is of greatest importance for an understanding of central nervous functions in physiology and pathology. In animal experimentation the performed work or the developed tension gives a direct measure of muscle function, but these data cannot be obtained without sectioning of the muscle tendon and fixation of the limb. These procedures introduce unphysiological conditions and are not applicable to man. It is, however, possible to measure muscle activity through a recording of action potentials either through surface electrodes or through the insertion of needles into muscles. The results of such studies involving proprioceptive reflexes and voluntary movements in a variety of conditions will be reviewed.

If through a sudden stretch of a tendon the knee jerk or ankle jerk is elicited, it is accompanied by a biphasic potential in the agonist. The discharge of the various units activated is essentially synchronous. The behavior of the antagonist of the stretched muscle is variable. There may be no activity or a potential of lesser magnitude may appear, and even in successive experiments on the same subject electrical silence in the antagonist may alternate with activity in an irregular manner (Altenburger, 27). The effect on the antagonist is not due to muscle stretch, since it occurs before the agonist is shortened; nor is physical spread involved, since it is absent when the antagonist is denervated. The results suggest that even for the tendon reflex there is some tendency toward physiological spread, and such

an interpretation is in agreement with the behavior of the closely related myotatic reflexes.*

The effect of passive movements depends on their speed and degree.† Small and slow movements do not elicit any action potentials in man. As the speed is increased, potentials appear in the agonist while the muscle is lengthened and cease at the end of the passive movement, provided that the stretch was moderate and no pain was involved. If such a movement is repeated while the muscle is voluntarily innervated, the proprioceptive reflex is magnified and persists as long as the muscle remains stretched (facilitation). With increases in the rate and degree of passive motion, the action potentials increase in amplitude and appear also in the antagonist. Apparently the number of activated units and their frequency, as was discussed earlier, increase under these conditions, and the reflex spreads to the antagonist.

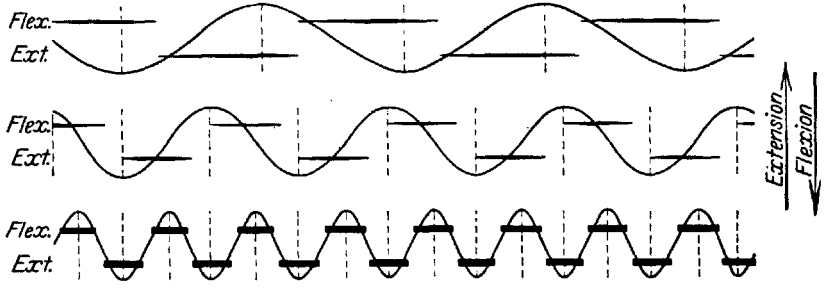

FIGURE 35. The influence of the speed of to-and-fro movements (flexion and extension of the elbow) on the appearance of action potentials and their temporal relation to the phases of movement. (Wachholder, 1195.)

In voluntary movements the degree of movement and the amplitude of the EMG are related. The study of the agonist-antagonist relation is of particular interest (1195). Figure 35 shows the effect of alternating flexion and extension of the elbow on action potentials in flexor and extensor carpi radialis. Periods of activity in the flexor alternate with those in the extensor. With increases in speed the action potentials increase in amplitude, but in addition the time relations of these potentials to the two phases of movement are markedly altered. As the movement changes from flexion to extension, the activity in the extensor muscle appears progressively earlier as the speed of the

* See pp. 82ff.

† The gradual lengthening of a muscle elicits the static form of the stretch reflex (myotatic reflex). The sudden lengthening evokes its phasic response (e.g., knee jerk).

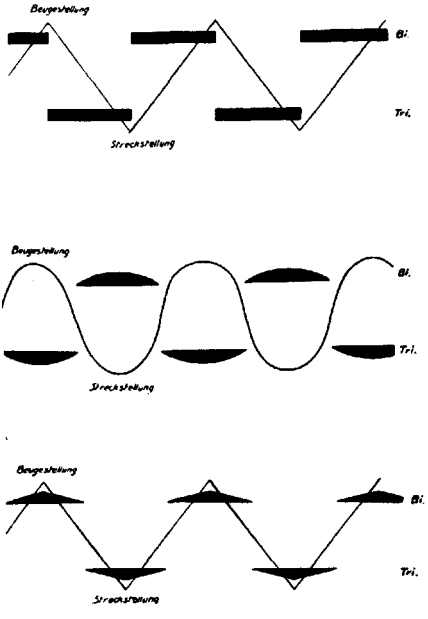

FIGURE 36. The influence of friction (top), inertia (middle), and elastic forces (bottom) on the temporal relation between action potentials and to-and-fro movements of the arm. "Beugestellung," flexor position of the elbow; "Streckstellung," extensor position of the elbow. (Wagner, 1197.)

movement increases. With fast movements action potentials in the extensor are noted during the last phase of the flexor movement and continue until the middle of the extensor phase. Apparently this muscle acts first as an antagonist to flexion and then as an agonist for extension, whereas with slower movements no brake action of the antagonist is necessary. The fact that the period of activity in flexor and extensor muscles does not coincide with the duration of flexion and extension shows that other factors, such as elasticity and inertia, in addition to the contraction induced by nervous impulses, play an important role in the performance of movements.

Wagner (1197) has been able to show that the innervation patterns of biceps and triceps in an alternating horizontal movement of the elbow on a turntable depend on the external forces involved. Increasing the mass by the addition of a weight leads to conditions in which the external forces are determined largely by inertia. If the movement is performed in a very viscous medium, the effect of friction is predominant, whereas the flexion and extension of the elbow against springs are primarily modified by elastic forces. As the diagram shows (Fig. 36) these external conditions alter the innervation pattern, for in the friction experiments the amplitude of the potentials remains the same whereas in the two other conditions a rising and declining phase appears. Furthermore it is evident that the onset of activity

of the flexor relative to the onset of the movement of flexion is fundamentally altered under the three conditions.

Electromyographic studies have shown that the patterns of innervation depend also on the degree of joint fixation involved in a particular movement. If the elbow is flexed or extended against minimal external forces, activity periods between flexors and extensors alternate. If, however, a movement is performed with active fixation of the elbow (by holding a weight), agonist and antagonist are activated during the movement and reciprocal innervation no longer exists. Similarly, it is seen in experiments on the motor cortex that as the intensity of the stimulation is increased, the antagonist is brought into action to an increasing degree (116). The augmentation of volitional effort is accompanied by the spread of activity to synergistic muscles. Thus, as shown earlier, flexion of the wrist in pronation under nearly isometric conditions calls forth activity in the triceps (452). Common experience shows that when effort is increased, particularly in fatigue, more muscles are activated.

Electromyographic experiments show that strong volitional efforts are accompanied by the spread of activity to homologous muscles of the contralateral side. In experiments in which the dynamometrically measured pressure of the hand muscles was correlated with the appearance of slight action potentials in contralateral muscles, it was found that the latter appeared only at nearly maximal pressure and the associated activity was very slight (464). If, however, patients with chronic poliomyelitis of several years' standing were asked to contract the almost completely paralyzed arm, it was found that in spite of minimal activity in this arm the associated activity was considerable (464). Obviously the latter is not related to the effect of the voluntary action on the muscle, but to the volitional effort.

It should be emphasized that agonist and antagonist are not anatomical but physiological concepts. Thus the internal recti of the eye are synergists during the movement of convergence, but antagonists when the eyes are moved to one side. Active fixation of a joint is a prerequisite for a certain forceful contraction under load, but if the same movement is performed slowly and without load, contraction of the antagonist would actually interfere with it. Nevertheless even under nearly identical conditions innervation patterns differ for different individuals and for the same person at different times. Even such a primitive muscular action as is involved in standing shows individual differences (Hoefer, 687). Strong flexion of the wrist may be accompanied by co-contraction in the extensor carpi or by reciprocal inhibition. The tendency to co-contraction increases with increasing

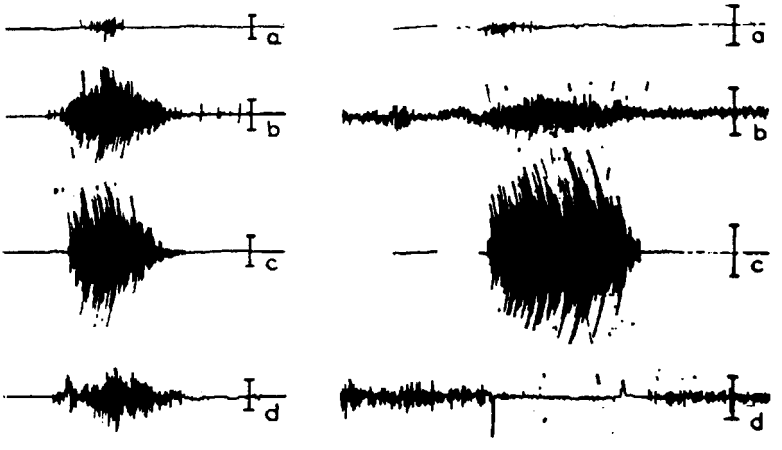

FIGURE 37. Electromyograms during voluntary flexion of the wrist in pronation. *Records a:* biceps; *b,* triceps; *c,* flexor carpi radialis; *d,* extensor carpi radialis. Nearly isometric conditions. *Left:* tension = 6 lb. *Right:* tension = 8 lb. *Read the records from right to left.* (Gellhorn, 452.)

volitional effort. The experiment represented in Figure 37 shows that in two different subjects reciprocal innervation may be present in one person with a greater effort and co-contraction in another subject with a somewhat lesser tension (452). Perhaps these individual differences are related to those in gait, although other factors (training) contribute to it.

Since the gradation of muscular contraction has been discussed earlier, it may suffice to add that according to observations by Denny-Brown (279) different motor units are activated when the same muscle is used in different movements.

Electromyography in Diseases of the Central Nervous System

SPASTICITY

Spasticity results from partial or complete interruption of the upper motor neurons and is most commonly seen after lesions in the motor cortex or the internal capsule.* It is associated with weakness or motor paralysis and is further characterized by increased resistance to passive movements, which is said to be due to an increased myotatic reflex. Electromyographic tests (Hoefer, 688) reveal that, with proper effort on the part of the investigator, the spastic may not show any spontaneous activity at rest, although it is sometimes difficult to find

* Concerning the role of pyramidal and extrapyramidal neurons in spasticity see Fulton (397) and Walshe (1201, 1204). At the spinal level, spasticity can be produced by sectioning of the reticulo-spinal tract (Wagley, 1196).

the resting position. Even slight passive movements elicit marked potentials, and these appear not only in the stretched muscles but also, though to a lesser extent, in their antagonists. This type of innervation explains both the weakness and the stiffness of movements characteristic of the spastic patient. The abnormal intensity of the stretch reflex is also apparent from the fact that the passive movement of a joint may lead to activity in muscles of the contralateral side or in those of other joints. Obviously a widespread excitation in the spinal cord results from moderate passive movement. By the insertion of several microelectrodes into the same muscle, records are obtained in voluntary movements which indicate similar patterns of discharge in all parts of the same muscle. These records may indicate synchrony of discharge in spasticity, but the data thus far published do not prove this interpretation conclusively.

RIGIDITY

Patients with Parkinsonism show, in contradistinction to spastics, action potentials in their rigid muscles at rest (Hoefer, 688). Under the influence of a slight muscular effort, rhythmic discharges occur in the agonist and, after a slight delay, also in the antagonist. These potentials are based on nearly simultaneous bursts of activity in several muscle units. Passive stretch leads likewise to such bursts of activity in the stretched muscle as well as in its antagonist. Such rhythmic bursts are recorded in the absence of any clinical tremor (Hoefer). There is apparently an increased tendency toward synchrony in rigidity, and Hoefer suggests that under these conditions the fine gradation in voluntary contraction which is due to an increase in the frequency of asynchronously discharging units is lost and movements can be stepped up solely by the recruitment of new units.

TREMOR

Even authors (Denny-Brown, 278) who do not believe that the discharges in Parkinsonism are strictly synchronous admit that with the occurrence of tremor the discharges of all units occur in groups separated from each other by periods of electrical silence. The bursts show a frequency of about 5.5 per second, and the ratio of activity to rest is 1:2 or 1:1. These bursts appear practically simultaneously in different muscles of the body. They tend to be the greatest at rest and to diminish or disappear with voluntary effort, whereas cerebellar tremors appear with volitional activity. Moreover records with multiple microelectrodes in the same muscle show that cerebellar

tremor, just like normal innervation, is characterized by asynchronous discharges.

A recent study on tremor by Bishop (102) is valuable because it shows the gradual transition from physiological to pathological conditions. He found that strong voluntary innervation of muscles leads in healthy persons to tremor, mostly of a higher frequency than that seen in Parkinson's disease. An increase in muscle tension may augment the tremor frequency, and relaxation may have the opposite effect. However, the variation in rate is small and the effort to vary the rate may abolish the tremor and result in an irregular tetanus. The tremor of normal individuals is characterized by alternating bursts in agonists and antagonists. Synergists, such as the brachioradialis and the biceps, discharge synchronously. When flexion is induced, the amplitude of the flexor EMG increases while that of the extensor decreases, but the alternating rhythm persists. However, when there is great effort, bursts appear not only alternately but also in phase. Thus the increased bursts of the triceps during extension induce biceps bursts simultaneously, and the latter also appear during the period of inactivity of the triceps. Under these conditions the frequency of the biceps bursts is doubled, and the principle of reciprocal innervation is partially invalidated, just as with increasing voluntary effort or with increasing intensity of cortical stimulation movements change from reciprocal innervation to co-contraction.

These rules hold, to a certain degree, for pathological forms of tremor. In mild forms the tremor may be of the reciprocal type as in normal individuals, and slight voluntary flexion or extension may induce continuous activity in the agonist but abolish the activity of the antagonist. Under these conditions tremor may persist in some muscles. Thus Bishop shows a record in which with flexion the activity of the biceps becomes continuous and that of the triceps disappears, while the brachioradialis shows typical tremor bursts. In these cases the principle of reciprocal innervation is obviously valid. In other cases flexion or extension leads to a doubling of the rate of the tremor, and agonists and antagonists discharge at the same time. Under these conditions there is no longer a reciprocal inhibition in amplitude, but, on the contrary, the increased amplitude of the agonist is accompanied by a similar augmentation in the activity of the antagonist. The principle of reciprocal innervation is superseded by that of co-contraction. The increased myotatic reflexes in these pathological conditions, which induce activity in the stretched muscle as well as in its antagonist, appear to be primarily responsible for this form of tremor.

ATHETOSIS

The involuntary movements observed in disturbances of the extrapyramidal system (chorea, athetosis) are grossly characterized by a great variety of forms. Involuntary bizarre movements may result in abnormal postures of the fingers, hands, and feet (athetosis), whereas jerky movements are characteristic of choreiform conditions. The degree of activity may vary within wide limits. Tremor may likewise occur. In agreement with the great variability in the forms of muscular activity, the patterns disclosed by electromyography show little constancy. Sudden shifts in activity occur in some muscles without affecting others, but even the same muscle may show in different parts different forms of activity. Hoefer (688) mentions that a part of a muscle may contract in a jerklike manner, while another maintains sustained activity. No consistent pattern in the relation of agonist to antagonist exists. Obviously the discharges in this condition are asynchronous.

CEREBELLAR HYPOTONIA

The diminution of the myotatic reflex in cerebellar lesions appears clinically in the loss of tone of skeletal muscles, indicated by a lack of resistance of the muscles to passive movements of the joints. Electromyographically it is seen that these movements, even if they are performed quickly and carried on to an extreme angle, do not elicit any action potentials. On the basis of clinical and electromyographic observations, the myotatic reflexes increase according to the following series: cerebellar disease, physiological state, spasticity, rigidity. Voluntary movements in cerebellar disease show normal innervation patterns (reciprocal innervation) and asynchrony.

The well-known defects in the performance of movements seen in cases of cerebellar lesion appear in the mechanical records as alternating acceleration and slowing, instead of the steady movement of the normal limb. Rhythmic discharges of the agonist, separated by periods of isoelectricity, are seen in the EMG. Antagonists may or may not show potentials. Upon increase in the speed of movement the "brake" action of the antagonist is less precise (delayed) or absent (Altenburger, 26). In cerebellar tremor the bursts appear at the rate of 4 per second.

FASCICULATION

Fasciculation is due to the activation of one or more motor units in abnormal states of the anterior horn cells. Spontaneous discharges, often of a repetitive character, are seen, particularly in amyotrophic lateral sclerosis. The muscle fibers of the unit contract simultaneously,

causing a twitch visible to the naked eye. Such twitches may also follow voluntary effort in this condition and are fused into a tetanus if the rate of firing reaches 25 impulses per second. Activation of a motor unit, with consequent fasciculation, appears not only in diseases of the spinal cord, including poliomyelitis, but also in disorders of the peripheral nerves (polyneuritis and injury of motor roots) (281). It may be produced experimentally through ischemia of a nerve. Finally, it should be mentioned that spinal cord tumors may elicit fasciculation. The determination of the spinal segment which induces these unit discharges can be accomplished by electromyography. If muscles innervated by D_3 show a spontaneous discharge while those supplied by the adjacent segments remain silent, the lesion is probable at D_3 (Hoefer, 689).

POLIOMYELITIS

The testing of the myotatic reflex, particularly during the acute phase of this disease, shows an exaggerated response, which appears clinically as increased resistance to passive movements. In the EMG it is seen that the duration of the myotatic reflex is increased. It is not confined to the period of progressive stretching, as under physiological conditions, but persists as long as the muscle remains stretched. As in other pathological states showing an intensified myotatic reflex, activity may appear in the antagonist and in other muscles of the body, particularly those of the contralateral side which are innervated by the same spinal segment.

The mechanism which accounts for the increased myotatic reflex is not fully understood. It is possible that nociceptive impulses arising from meningeal irritation of the posterior root (Moldaver, 937) or lesions in the spinal root ganglia increase the reactivity of certain spinal segments to all impulses, including those from the muscle spindles. This interpretation would explain the spread of activity to contralateral muscles. On the other hand, the profound role of the reticular substance in the medulla oblongata on the stretch reflex (886) should not be forgotten, particularly since in experimental poliomyelitis of the monkey lesions in this area were accompanied by widespread "spasticity" (Bodian, 107). However, to what extent the inhibitory portion of the reticular substance is invaded during the acute condition of the disease in the human being is not known.

THE ELECTROMYOGRAM AND MOTOR DEFICIT

In numerous studies in conjunction with several collaborators it was shown in the writer's laboratory that the EMG obtained with wires sewn into a muscle in animals (495) or, in the human being,

through surface electrodes (452) gives a good indication of the functioning of a given muscle. Loofbourrow's analysis (862) showed that the amplitude of the EMG is determined by the number and frequency of the discharging units. In spite of the fact that surface electrodes are said to pick up potentials from adjacent active muscles, it could be shown that the simple procedure of placing surface electrodes in regular distances over several longitudinal axes of the leg clearly reveals specific motor deficits (283) which, for instance, result from the sectioning of anterior roots. This objective method appears to be of value for clinical investigations both in localizing spinal cord lesions and recording the progress of nerve regeneration.

The Temporal Relations of Unit Discharges

With a growth in activity induced by volitional effort or, in reflex movements, as the result of an increase in the stimulation, the frequency of unit discharges and particularly the number of discharging units increase. Whereas under the artificial condition of electrical stimulation of a peripheral nerve the various axons discharge synchronously, reflexes (with the exception of tendon reflexes) and volitional movements show asynchronous discharges. This is to be expected, since multineuronal systems of varying degrees of complexity are activated under these conditions and it is hence impossible for the various impulses to reach the final common path at exactly the same time. Moreover the voluntarily initiated movements elicit reflexes which through proprioception likewise invade the final common path. Finally, different neurons show widely different characteristics in threshold, frequency of discharge, and rate of adaptation. These are the reasons why the earlier investigators who attempted to study the relation between intensity of movement and frequency of discharge were unsuccessful. With electrodes which record the activity of many motor units the frequency cannot be determined, since the records represent an interference curve (owing to the superimposition of many unit discharges of varying frequencies). The introduction of microelectrodes by Adrian (5) made such investigations possible, provided that strong movements are not included. Under the latter conditions discharges from closely adjacent units may be picked up by the microelectrode, and again interference curves will result.

It follows from this discussion that ideal conditions for the recording of unit activity even at maximal effort would exist in cases in which, owing to central or peripheral lesions, such a large number of motor neurons were functionally eliminated that in the muscle small normal

areas were surrounded by large parts of degenerated muscle tissue. If the lesion is not in the central nervous system but in the muscle itself, as in progressive muscular dystrophy, dystrophia myotonica, and disuse atrophy, the change does not consist in a selective loss of motor units but rather in a reduction of muscle fibers in these units. Consequently the EMG's will show interference curves in myopathies, as in normal muscles, even with moderate muscular effort, whereas unit potentials can be recorded under similar conditions in cases of central lesions, such as amyotrophic lateral sclerosis. Thus an objective differentiation between lesions of nervous and muscular origin is obtained through electromyography (Buchthal, 170, 171) (Fig. 38).

If several microelectrodes are inserted into the same muscle, the records may reveal synchrony or asynchrony of the central discharge in voluntary effort. The former is seen frequently in fatigue and, to a greater degree, in pathological conditions. Buchthal thought that synchrony suggests an unfavorable prognosis in chronic poliomyelitis. Perhaps such synchrony occurs during the acute phase of poliomyelitis, but important observations speak against its presence in the chronic phase of this disease. Kugelberg (813) showed that stimulation of the *peripheral* nerve with slowly rising currents produces synchronous discharges in chronic poliomyelitis which are practically identical with the discharges seen under conditions of volitional innervation. The synchrony which occurs with peripheral stimulation is obviously not explainable as the result of an abnormal (synchronized) central discharge, and an influence of the action potentials in the peripheral nerve on adjacent nerve fibers, although theoretically possible, is highly improbable in these cases in which the threshold of the nerves is not decreased but rather increased. It seemed, therefore, to be more probable that the synchrony of discharge seen in poliomyelitis does not indicate an abnormal form of central nervous activity but is

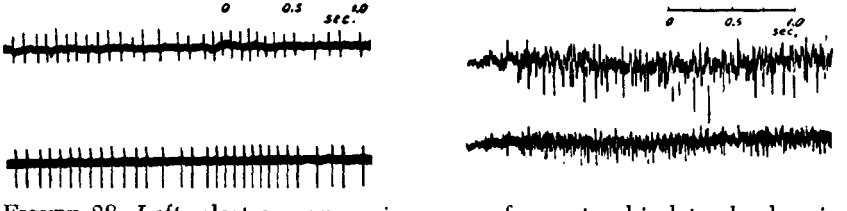

FIGURE 38. *Left:* electromyogram in a case of amyotrophic lateral sclerosis during moderate voluntary contraction of the anterior tibial muscle; synchronization of discharges of single motor units. *Right:* electromyogram in a case of idiopathic muscular dystrophy; moderate to maximal effort in the biceps muscle; asynchronous discharge of many units. (Buchthal, 170.)

due to the fact that the electrodes pick up the activity of one large unit from different parts of the muscle.*

However, synchronous discharges of varying degrees have been noted by several investigators in spasticity and in Parkinsonism and seem to be due not to an abnormal interaction of motor horn cells as the result of pathological processes within the spinal cord but to the greatly increased myotatic reflex. Such an interpretation appears justified on the basis of studies in decerebrate rigidity. In this condition the units discharge continually, yet in asynchrony, as long as no proprioceptive stimuli are applied. But if, for example, the elbow is flexed, the discharge in the triceps not only is increased but becomes grouped. The synchrony of central discharges results in an increase in the amplitude of the action potentials during the flexion and is also recognized by the similar appearance of action potentials recorded from two different parts of the muscle (Bernhard, 92). Since myotatic reflexes have no synchronizing effect when they reinforce cortically induced movements in the normal animal (Gellhorn and Riggle, 512), it follows that conditions in which the proprioceptive response is greatly increased are the prerequisite for the appearance of synchrony. This may be the cause of synchrony in spasticity and rigidity as well as in decerebrate rigidity during proprioceptive stimulation, and it may account for this phenomenon in the acute state of poliomyelitis, in which the proprioceptive reflex is intensified.

If it is conceded that the gradation of muscular contraction in voluntary effort and on stimulation of the motor cortex involves the proprioceptive reflex in a similar manner, there is good reason to assume that the increase in synchronization seen in the normal muscle with maximal voluntary effort is likewise due to the great contribution to tension which the proprioceptive reflex makes under these conditions (10). The reason is as follows: It has been found in experiments with stimulation of the motor cortex at various intensities that in the deafferented muscle the maximal tension is greatly curtailed (721) but the muscle tension at threshold is not altered. The gradation of the muscle response to near-threshold stimuli is unchanged by deafferentation, but the further increase in response to cortical stimuli of suprathreshold intensity is less than in control muscles. This observation shows that the increase in muscle tension at greater intensities of stimulation depends to an important extent on proprioceptive reflexes. The lesser amplitude of the EMG in the deafferented than

* In recent studies Buchthal and Madsen (171) give new evidence for the increased degree of synchrony of discharges which occurs in muscular atrophy of central origin in spite of moderate effort.

in the normal muscle indicates that fewer neurons are activated in the former than in the latter. From these experiments it seems to follow that proprioceptive reflexes play a minimal role when cortical stimulation is near threshold. However, with increased cortical stimulation, and presumably with growing voluntary effort, this reflex gains in importance as it calls an increasing number of units into action.

The Electromyogram as an Indicator of Peripheral Nerve Conduction in Man

Although the physiology of the peripheral nerve is not treated in this book, it appears to be desirable to review briefly the usefulness of the electromyographic method for the study of the physiology and pathology of the peripheral nerve in man. Helmholtz in his classical experiments calculated the velocity of the conduction of the nerve impulse in the frog by determining the latent period of the muscular contraction after the nerve had been stimulated with a single shock at two different distances from the muscle. This principle can be utilized in the human being by applying supramaximal shocks through the skin on a peripheral nerve and by recording action potentials from the small muscles of the hand and foot through surface electrodes. The values thus obtained indicate the velocity of conduction of the fastest nerve fibers* and lie between 46 and 67 meters per second (682). As has been found in animal experiments, the conduction velocity increases during recovery following nerve suture, but even after one year only 60 per cent of the physiological maximum of conduction velocity is reached. Since nervous conduction increases with the diameter of the axon during normal growth and also with advancing regeneration after nerve suture, the experiments indicate that the diameter of the regenerated nerve fibers remains subnormal for a long period. With progressing regeneration the amplitude of the muscle action potentials † is augmented, since more muscle fibers are re-innervated. This is seen not only with electrical stimulation of the nerve but also under conditions of voluntary innervation (1103).

Even several years after a nerve had been sutured, certain differences in the pattern of innervation persist. Thus spontaneous action potentials are said to occur in the muscle at rest. More important is the finding that with concentric needle electrodes unit potentials of

* That a peripheral nerve is composed of fibers of different diameters and that velocity of conduction depends on the diameter were shown in the classical studies of Erlanger and Gasser (323).

† The amplitude of the action potential is an indicator of the number of activated neurons (Loofbourrow, 862).

very large amplitude appear (up to 14 millivolts; i.e., two to four times that of the homologous control muscle). They indicate that nerve branching occurs during regeneration. Consequently more muscle fibers are innervated by a single motor unit than in the intact muscle (1252).

An application of these methods to patients with chronic poliomyelitis showed that the fastest rates of conduction of nerve fibers are much reduced in this disease (679). Furthermore the amplitude of the EMG * is progressively diminished with increased reduction in the speed of conduction. This effect suggests that the virus attacks preferentially the motoneurons with the largest diameters. Such an interpretation is in agreement with certain clinical and experimental data. Poliomyelitis less affects distal than proximal muscles, and the latter are supplied with nerve fibers of larger diameters. During the acute stage of the disease the nerve fibers of large diameter are more affected than those of small. Before the former degenerate, they seem to pass through a stage of increased excitability and more rapid rate of conduction (982). This increased excitability accounts for the augmented stretch reflex in the acute stage of infantile paralysis. The careful counting of motoneurons and the determination of their distribution according to size indicate that with increases in the severity of the infection the large motoneurons decrease in number so that the small neurons predominate. Only in the more severe forms of the disease are the small neurons likewise destroyed. It is of interest to point out that this vulnerability of the large motoneuron has also been found in amyotrophic lateral sclerosis (1237) and in experimental thiamine deficiency (1143).

Electromyographic Studies of Nervous Discharges in Ischemia and Hypocalcemia and Their Relation to Tetany

The excitability of the peripheral nerve is greatly dependent on its physicochemical environment. In the absence of ions the nerve (and muscle) lose rapidly but reversibly their excitability, and changes in the ionic composition of the immersion fluid alter fundamentally their reactivity to electrical stimulation.† The effects of ions as well as of numerous drugs are similar to the polarizing effects of the constant current (364). The excitability of the nerve is lessened at the anode, and the nerve membrane appears to be in a state of diminished

* The amplitude of the EMG is also reduced during volitional contraction at the diseased side but in this case it is not certain that the impulses initiating the willed movements in homologous normal and paretic muscles are strictly comparable.

† See bibliographical entries 427, 429, and 676 for literature.

permeability (427, 429), whereas cathodic polarization lowers the threshold, increases the permeability of the cell membrane, and favors the potassium-sodium exchange which is the basis of the excitatory process and its transmission over the whole nerve (686). Calcium salts have an effect similar to anodic polarization, whereas potassium salts exert an action similar to cathodic polarization. Apparently the potassium/calcium balance is the decisive factor since, lowering of the calcium and increase in the potassium concentration cause similar effects. The addition of sodium-oxalate or sodium-citrate, which diminish the ionization of calcium, is a commonly used procedure to produce excitation. Excitation appears in the form of spontaneous discharges. The frequency of these also increases with alkalinity and decreases with acidity, just as the nerve muscle preparation shows similar changes in excitability with a changing *p*H (434).

Kugelberg (809, 810) applied this fact to human nerves and showed that hyperventilation and also ischemia of the arm lead to spontaneous discharges of the motor and sensory nerves. Hypocalcemia, in cases of hypoparathyroidism, is particularly suited to show unit discharges of the nerves under these conditions, but ischemia, especially in combination with hyperventilation, is effective in normal persons as well. As to the mechanisms involved, it may be said that hyperventilation reduces the concentration of ionized calcium in the blood through increased alkalinity. Apparently the excitatory action of ischemia (asphyxia) on neurons is augmented under these conditions, although it would seem to counteract the *p*H changes.

The spontaneous discharges which are evoked in hypoparathyroidism through ischemia are most effective if the proximal parts of the arm nerves are subjected to it. Reflex effects play no part, since the unit discharges of the motor nerves which are recorded in the form of EMG's persist after the nerve central to the ischemic region has been blocked by procaine. Likewise, the Trousseau spasm of the hand is not diminished by the blocking of the nerve.

This activity of the peripheral nerve is based on single-unit discharges at a rate of about 20 per second; not infrequently groups of double spikes due to repetitive discharges of the same nerve fiber are recorded. As the excitation continues, more units are called into action, but the frequency of individual units remains rather constant. It is interesting to note that under these conditions of abnormal discharges of peripheral origin, the neuron behaves very much as under strictly physiological conditions when cortical or reflex excitation initiates impulses in the peripheral nerve, since in both instances recruitment accounts more for the magnitude of the contraction than

do varying rates of discharge. This is also shown by the fact that voluntary contraction and ischemic discharge can be duplicated by the stimulation of peripheral nerves with slowly rising, constant currents.

The study of nerve discharges has shown that after the cessation of ischemia, a strong repetitive burst of potentials occurs which is much stronger than during the ischemia (808). Here again the peripheral nerve acts as the ganglion cell. It was pointed out earlier that the readmission of air after a period of asphyxia leads to a greatly increased central excitability (490), which may culminate in generalized convulsions (1100).

Electromyographic Studies of the Function of the Neuromuscular Junction

Before the pathological physiology of the myoneural junction is discussed, its physiological function may be briefly surveyed.* Since there is a discontinuity between the somatic nerve endings and the muscle, the transfer of impulses from nerve to muscle involves a problem similar to that of synaptic transmission. As in the latter problem, two theories are involved, one emphasizing the role of electrical potentials, the other that of a neurohumor (acetylcholine).

The former theory has been briefly mentioned. It may suffice to repeat that systematic studies with increasing amounts of curare have shown that the end-plate potential consists of a local electrotonic potential on which is superimposed the propagated potential leading to the contraction of the muscle. The nerve impulse arriving at the end plate sets up a catelectrotonic potential, which results from depolarization, and gives rise to the action potential as soon as the former reaches a critical level. Curare depresses the local potential gradually, and the transmission of impulses and indirect contraction of the muscle cease.

That acetylcholine is liberated at the neuromuscular junction was shown in experiments with indirect stimulation of the muscle in which the perfusate was assayed for this substance. It was found that the stimulation of somatic nerves caused the appearance of acetylcholine, although the autonomic fibers had been previously eliminated through degeneration (250, 336, 337). The somatic nerves are consequently cholinergic, in Dale's terminology. The interpretation that acetylcholine plays a physiological role in neuromuscular transmission is supported by the following data. If acetylcholine is injected into the artery close to the muscle, a contraction is evoked which is equal

* See Rosenblueth (1067), Koelle (794), and Gelfan (421) for references.

in tension to that resulting from a maximal shock applied to the nerve. Physostigmine, which inhibits cholinesterase, potentiates the effect of a single shock, so that a tetanus results instead of a single twitch; and cholinesterase has been found to be present in high concentrations at the myoneural juncture (962), so that the acetylcholine liberated can be destroyed quickly. Apparently this substance plays an important role in the depolarization of the end plate, since physostigmine increases the end-plate potential of the curarized muscle. The essential role of acetylcholine in neuromuscular transmission has now been recognized by Eccles, who for a long time sponsored the electrical theory.*

Electromyographic studies on myasthenia gravis (610–612) have enlarged the basis for the neurohumoral theory. This disease seems to involve a partial blocking of the myoneural junction. Harvey *et al.* stress the similarity between myasthenia gravis and partial curarization. That this partial block involves some abnormality in the acetylcholine metabolism is suggested by several facts. Whereas in the normal person prostigmine reduces the amplitude of the EMG during maximal voluntary contraction, the opposite effect occurs under these conditions in the myasthenic patient. In both instances the power of contraction parallels the amplitude of the action potentials. Intra-arterial injection of acetylcholine likewise produces opposite effects in normals and myasthenic cases; in the former the contractions become weaker, in the latter, very powerful, leading to sustained flexion of the wrist, hand, and fingers, as in tetany. Finally, it could be shown that maximal stimulation of the motor nerve is characteristically modified by prostigmine. In the normal person repetitive discharges follow a single maximal shock. If several shocks are applied at brief intervals, it is found that, whereas before the injection of the drug the action potentials remain maximal, there is a marked decline of the second and of all following electric responses after prostigmine. These changes appear to be the result of the persistence of acetylcholine, which in too high concentrations blocks the myoneural junction. On the other hand, in myasthenia gravis a few maximal shocks lead to a progressive decline in the amplitude of the action potential, and prostigmine lessens this effect and apparently improves neuromuscular transmission. Other inhibitors of cholinesterase (580) act in a similar manner (but with differences in duration). Apparently an inadequate amount of acetylcholine reaches the end plate in myasthenia gravis, and consequently drugs which increase

* On the other hand, Nachmansohn (963) concedes that the release of acetylcholine is intimately associated with the action potential.

the persistence of this substance reduce the block and improve voluntary muscular contraction.

The application of these methods to chronic cases of poliomyelitis yielded similar results (679). Whereas twitches resulting from single repetitive shocks given at brief intervals or a tetanus elicited by a rate of stimulation of 20 to 40 per second for a few seconds produces action potentials of constant amplitude in normal persons, a progressive decline occurs in the clinical cases. The interpretation that a partial blocking of the myoneural junction is involved is supported by the favorable effect of neostigmine* under these conditions.

Since the method of evoking muscle potentials by maximal electric shocks applied to a peripheral nerve indicates through the amplitude of these potentials the relative number of muscle fibers which react to the stimulus, it can be used to decide rather objectively the difficult question of the therapeutic efficacy of neurotripsy in infantile paralysis. Hodes (680) showed that a moderate increase in the amplitude occurs, a fact suggesting that nerve-crushing slightly increases the number of innervated muscle fibers. It is interesting to note that neuromuscular transmission also improves, although the mechanism involved is not known.

Fibrillation

The denervation of a striated muscle resulting from peripheral injury or destruction of the motor horn cells leads to the "spontaneous" activity of single muscle fibers. This phenomenon is designated as fibrillation. It is not visible through the skin, but may be seen in the tongue in the form of small twitches (421). The insertion of electrodes into a degenerating muscle reveals fibrillation through small potentials of short duration (Fig. 39). Denny-Brown (281) states that they last 1 to 2 milliseconds and have an amplitude up to 100 microvolts and a frequency of 2 to 10 per second. Recent studies (816) show that the frequency may vary within wider limits (between less than 1 per second and 30 per second). Moreover, particularly following mechanical or electrical stimulation, repeated bursts of high frequency (100 per second) may appear. These spikes are synchronized potentials due to the nearly simultaneous discharge of several muscle fibers. This is indicated by the analysis of a "spike" when an oscillographic record is taken on fast-moving paper and also by the fact that the amplitude of a potential may suddenly decrease and recover later.

Landau points out that only a small fraction of the whole muscle shows fibrillation. The intensity and onset vary considerably between

* This drug also inhibits cholinesterase.

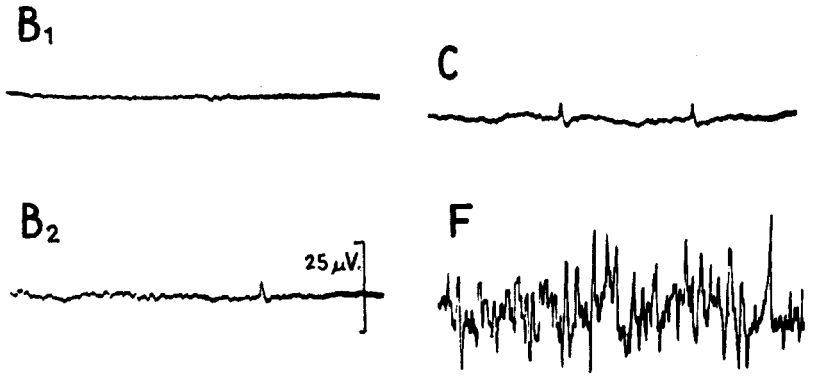

FIGURE 39. Fibrillation potentials of a striated muscle following sectioning of the motor nerve. *Record* B_1: 4 days after sectioning; no spontaneous activity. *Record* B_2: same day as in B_1; potential evoked by pricking the muscle. *Record C*: spontaneous fibrillation 5 days after sectioning. *Record F*: spontaneous fibrillation 10 days after sectioning. (De Smedt, 282.)

different species and even between different muscles of the same animal. The twitches are easily evoked by mechanical or electrical stimulation, and fibrillation becomes maximal when Wallerian degeneration of the nerve is complete (335, 1214).

As briefly discussed elsewhere,* the denervated muscle is greatly sensitized to acetylcholine, and consequently this substance has been thought to be the cause of fibrillary twitches. However, it is likewise known that the denervated muscle is highly responsive to various physical and chemical stimuli, and certain experimental data do not seem to support the acetylcholine hypothesis. Thus it has been found that fibrillation persists after curare, whereas the effect of acetylcholine is blocked by this drug. The study of inhibitors of cholinesterase such as prostigmine has led to conflicting results in the hands of several investigators. Although it remains for future research to determine the nature of the physical or chemical factor which is primarily involved in fibrillation, it should be stressed that the greater sensitivity of the denervated muscle is not the only important factor. Whereas in the normal muscle the response to mechanical stimulation is very brief, the insertion or movement of an electrode may evoke a train of impulses in the denervated structure (811). This lack of accommodation of the denervated muscle has been studied quantitatively by De Smedt, who showed that with decreasing accommodation of the muscle the frequency and amplitude of the fibrillations increase, as indicated by the EMG. Moreover he reports that these spontaneous

* See pp. 266ff.

potentials disappear on regeneration of the nerve before the indirect excitability of the muscle is re-established. Here again the fundamental importance of the accommodation of the muscle is obvious, since it increases distinctly at the time when fibrillation disappears.

Summary

As this brief survey has intended to show, the value of electromyography is considerable:

1. It allows one to obtain a semiquantitative indication of the activity of muscles in health and disease without interference with their physiological interrelations.

2. It gives insight into the factors, such as speed, inertia, and resistance, which modify the innervation patterns under physiological conditions.

3. It reveals the quantitative differences, based to a considerable extent on the magnitude of the myotatic reflex, which exist between normal and pathological conditions and the qualitative differences between innervation patterns in spasticity, tremor, etc.

4. Electromyographic investigations make it possible to follow objectively the changes occurring during regeneration of nerves, to contribute to neurological diagnosis, and to study quantitatively the neuromuscular function in normal and pathological conditions.

5. Finally, an important beginning has been made toward analyzing the function of the human central nervous system in terms of motor unit discharges.

~ 7 ~

Studies on Experimental Convulsions

ALTHOUGH action potentials of the brain were already described in 1875,* it may be said that the modern period of electrophysiological research was inaugurated by Berger's discovery (87) that even with the skull intact, action potentials of the brain can be recorded. The confirmation of this work by Adrian and Matthews and their interpretation of the alpha potentials as synchronous discharges of neurons of the occipital lobes (16) greatly furthered the development of this new field. The knowledge of clinical neurology, particularly as relates to epilepsy, has been increased by the electroencephalographic work of Berger and his followers in the United States, Canada, and England, under the leadership of Gibbs (541), Jasper (733), and Grey Walter (1204b). A natural sequel to these studies was the direct recording of action potentials of the cortex and of subcortical structures in physiological experiments on animals. This method is now being applied by Penfield and Jasper and by others to problems of human brain pathology.

The physiological aspects of convulsions were not neglected by the early investigators of brain physiology in the nineteenth century —Brown-Sequard (165), François-Franck (379), Bubnoff and Heidenhain (168), Heubel (641), Luciani (877), and many others. However, the development of modern techniques brought new information on the nature of the convulsive discharge, the spread of convulsive activity, and many related problems. It has also thrown new light on the normal functions of the neuron. The benefit for physiological research resulting from a consideration of pathological functions and vice versa is well illustrated in a study of experimental convulsions.

* See Gibbs for historical details.

Acetylcholine and Cortical Activity

It is not planned to discuss the chemical changes which accompany neuronal activity at physiological and convulsive levels, but to single out a few chemical factors which are of importance for the maintenance of normal and convulsive activity. Ever since the discovery by Otto Loewi (854) that acetylcholine (AcCh) is a chemical mediator of vagal activity, attempts have been made to extend the range of application of the concept of neurohumoral transmission. This aspect of the problem of the action of AcCh will be discussed elsewhere,* and only the relation of this substance to normal and convulsive neuronal activity will now be considered.

Numerous data are available which point out that AcCh plays an important role in the activity of cells in general and neurons in particular. Not only is AcCh found in measurable quantities in many cells and tissues, but also the enzyme cholinesterase (ChE) seems to be rather ubiquitous. Several authors (339, 795, 960–962) have emphasized that ChE is present in the central nervous system and that its appearance in the early stages of development shows a definite relation to function. The embryos of amphibia show an increase in the ChE concentration with increasing motility. In the human brain it has been found that the concentration of ChE increases *pari passu* with the morphological development (Youngstrom, 1256), and a similar relation between ChE concentration and function has been established for various parts of the central nervous system in foetal and postfoetal life. Of particular importance for our discussion is the fact that the ChE content of the gray matter is greater than that of the white matter (Nachmansohn, 960–962).

That AcCh has a distinct effect on the excitation of ganglion cells was shown by Bronk (142), who by perfusion of a sympathetic ganglion with AcCh elicited a postganglionic discharge, although the preganglionic nerve fibers failed to react. Apparently AcCh is an excitatory substance for ganglion cells in relatively low concentrations, but not for nerve fibers. The validity of this inference was tested for the cortex of the brain. Miller and collaborators (932) showed in a study of brain action-potentials that AcCh alone or in combination with eserine, which inhibits ChE activity, excites the cortex. Moreover it was observed that the excitability of the motor cortex was increased (930) by eserine or eserine plus AcCh applied locally to the motor cortex, and movements may be elicited through this form of chemical stimulation of cortical ganglion cells. Bonnet and Bremer (113) found likewise that AcCh, when applied in minute doses (0.2

* See pp. 251ff.

gamma per rabbit intra-arterially), lowered the threshold of the motor cortex to electrical stimulation, and they also presented evidence for an increased after-discharge in spinal reflexes as a result of small doses of this substance. That the excitatory effect of AcCh is not confined to motor neurons was shown by Bonnet and Bremer, who noted under its influence an increased after-discharge in the action potentials of the acoustic cortical projection area in response to sound stimulation. Moreover, by the topical application of AcCh Kremer (803) elicited autonomic effects such as a rise in the blood pressure from the cerebral cortex. It may therefore be said that AcCh, with or without inhibition of the ChE, increases the excitability and causes excitation of neurons of the somatic and autonomic nervous system.

The stimulation of cortical neurons can result not only in the arousal but also in the suppression of cortical activity. Certain specific suppressor areas* located at the lateral surface of the brain as well as the medial (limbic area) may be activated by electrical stimulation or by strychnine (Dusser de Barenne and McCulloch, 306) and induce a temporary loss or diminution in cortical excitability and cortical potentials. These suppressor functions of the cortex can also be activated by the local application of AcCh (or by the use of the more stable choline derivative, mecholyl) in combination with eserine to the suppressor areas (79). Suppression appears in the form of a gradual decline in and finally a cessation of spontaneous activity, as seen in the electrocorticogram. It may also be demonstrated as a reduction in or loss of excitability of the motor cortex if the latter is stimulated at regular intervals before and after the application of AcCh to one of the suppressor areas. As in Dusser de Barenne's experiments, the effect occurs after a latent period of several minutes and is reversible.

Apparently the specifically different functions of various neurons involving activation and suppression may be called forth by AcCh and/or inhibition of ChE. In addition, cortical electrical activity and responsiveness to afferent stimuli may be reduced by the topical application of ChE (79). Obviously AcCh is a powerful stimulator of the various functions of cortical neurons.

Acetylcholine and Convulsive Activity

The preceding discussion has shown how intimately neuronal activity is associated with AcCh and eserine. The spontaneous activity and

* Sloan and Jasper (1119) suggest that this effect is not confined to specific suppressor areas but is only an expression of the spreading depression which follows the stimulation of any cortical area.

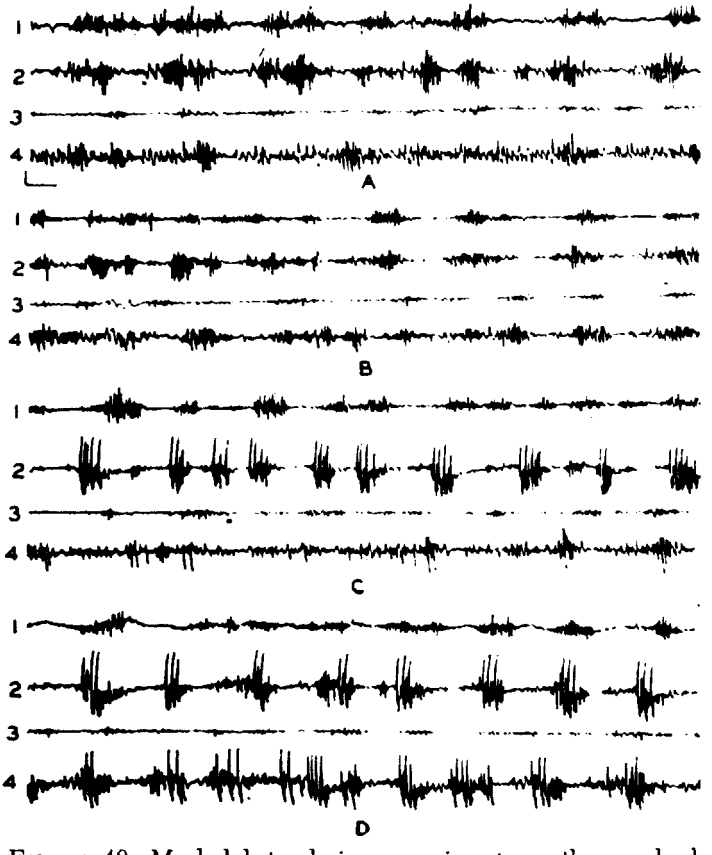

FIGURE 40. Mecholyl-strychnine experiment on the cerebral cortex of a "Dial"-ether cat. *Records A:* control; 0 minutes. *Records B:* 10 minutes later; 9 minutes after the administration of 2.5-per-cent mecholyl to sites 2, 3, and 4. *Records C:* 16 minutes after beginning of experiment; 6 minutes after the administration of 0.5-per-cent strychnine to sites 1, 2, and 4. *Records D:* 23 minutes after beginning of experiment; 6 minutes after rinsing all sites. Convulsive spikes appear as the result of the interaction between mecholyl and strychnine. (Hyde, Beckett, and Gellhorn, 720.)

responsiveness of the neurons to various stimuli seem to be greatly modified by either increasing the AcCh concentration in their external environment (through the topical application of AcCh) or stabilizing the AcCh in the internal environment of the cells (through eserine). This suggests that abnormal activity such as convulsions may likewise depend on AcCh if it can be assumed that pathological activity

involves physiological processes which are altered quantitatively but not qualitatively.

The observation of Miller (932) that the application of AcCh plus eserine to the cortex induces typical convulsive spikes was made the basis of a systematic study of the interaction of AcCh and convulsive drugs. It was shown that convulsive activity induced by various convulsants is greatly enhanced by mecholyl (preferred to AcCh because of its greater stability) or by inhibitors of cholinesterase such as eserine or prostigmine (720). Figure 40 shows the interaction of mecholyl and strychnine, both applied topically to the cortex in subthreshold concentrations. Convulsive activity appears solely in those areas which were subjected to the influence of both drugs. Similarly it can be shown that eserine plus a convulsant applied to the same cortical area evokes strong convulsive spikes, although each of the drugs fails to alter the electrocorticogram. Local convulsions, due to the topical application of a convulsant in a suprathreshold concentration, may be greatly intensified by eserine or mecholyl, although in the concentration used these substances fail to alter normal brain potentials. Finally, convulsive activity which had disappeared through frequent washings of the cortex following the topical application of the convulsant, could be re-evoked by eserine, although this drug did not show such a convulsive effect by itself. These and similar experiments showed conclusively that mecholyl and inhibition of ChE increase convulsive activity initiated by a wide variety of chemically dissimilar substances, including picrotoxin, strychnine, metrazol, mescaline, beta-erythroidin, antibiotic substances (streptomycin), and dyes (acid fuchsin). The experiments suggest that the basic neuronal processes underlying physiological activity and those involved in convulsions are similar as far as the role of AcCh is concerned.

It has been noted clinically that a convulsive focus may be activated by the injection of metrazol in concentrations inadequate to produce generalized convulsions (760). This condition may be imitated in a physiological experiment. The brain can be sensitized to metrazol by the topical application of acetylcholine to the cerebral cortex. A local seizure is thereby produced (375).

Our own experiments with the highly effective anti-cholinesterase DFP (di-isopropylfluorophosphate) were inconclusive, but other studies showed results which are in line with the previously described work. Thus it was found that DFP produced epileptiform changes in the human EEG (582) characterized by large, slow potentials of a

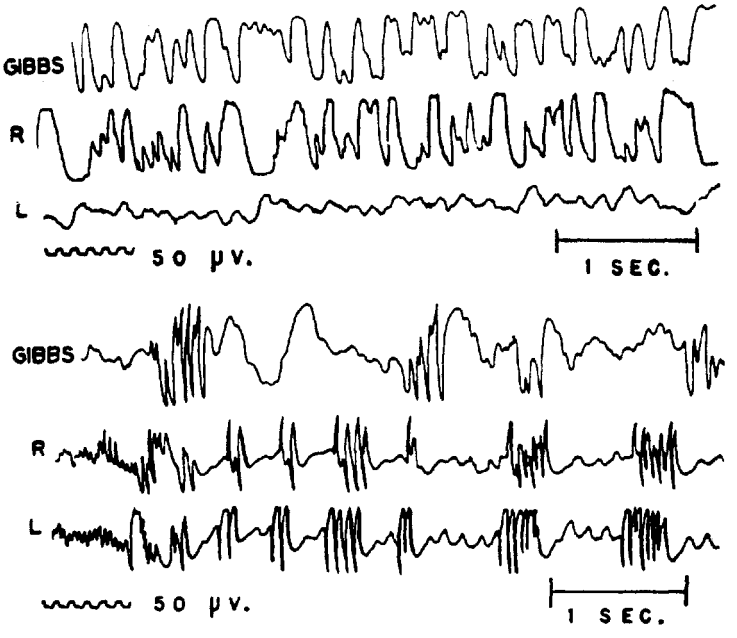

FIGURE 41. *Upper part:* pattern of psychomotor seizure in man (Gibbs) compared with the effects of DFP on the electrocorticogram of a rabbit. The right ECG observed in a rabbit is similar to the tracing in man; the left side lags behind the right. *Lower part:* myoclonic pattern in man (Gibbs) compared with DFP effects on the ECG of a rabbit. (Freedman *et al.*, 381.)

frequency of 3 to 6 per second. In the curarized rabbit this drug elicits on intra-arterial injection typical grand mal seizure patterns and other convulsive changes similar to those seen in man in various forms of epilepsy (381) (Fig. 41). The alteration in nervous activity finally culminating in convulsions is directly related to the decrease in the ChE of the brain (Table 5), but it is worthy of note that a large factor of safety seems to exist, since permanent changes occur in the EEG only with a decrease of the ChE concentration of the brain to 9 per cent of its original value (589). It should also be mentioned that eserine in doses too small to affect the blood pressure and heart rate increases distinctly the susceptibility of rats to electrically induced convulsions.

It may be concluded from these investigations that AcCh plays an important part in the regulation of the activity and excitability of the neuron. In small concentrations it lowers the neuronal threshold and leads to excitation which may produce movements, autonomic

changes, or suppression of cortical activity and movements. In higher concentrations it may elicit convulsive activity either directly (by the administration of AcCh or mecholyl) or indirectly (by DFP or eserine). Both procedures result in typical changes in the EEG or ECG. Moreover it sensitizes to, or aggravates, the action of convulsive drugs on cortical neurons.

TABLE 5. The Relation between Clinical Signs of DFP Toxicity and Brain Cholinesterase Activity (Freedman and Himwich, 382)

Number	DFP Mg/Kg Subcut.	Clinical Signs	Brain ChE CO_2/100 Mg/ Brain/Hr
6	0	None	917
3	0.5	Increased mouth movements, exopthalmos	256–409
7	1.0	Slight trembling, fasciculation, moderate weakness of the hind limbs, some hyperreactivity on tapping spine, "champing"	60–178
8	2.0	Marked salivation, "champing," pronounced weakness of all limbs, inability to crawl, exaggerated trembling, marked hyperreactivity on tapping spine	20–39
6	3.0	Above signs in more severe form, tonic and clonic convulsions, either in extremis or dead	11–16

The mechanism involved in these reactions is not fully understood. The fact that AcCh alters the excitability of neurons suggests its action on the cell membranes, and Beutner and Barnes (98) have shown its depolarizing effect on physicochemical models of the cell membrane. The observations of Feldberg and Fessard (341) that AcCh produces an electrogenic effect on the electrical organ in fish support such an interpretation. To what extent AcCh acts as a transsynaptic transmitter in the somatic nervous system is under debate.*

Although AcCh is by no means a stimulus specific for nervous structures, it greatly enhances the reactivity of the neuron to physiological stimulation (electrical stimuli applied to the motor cortex, sensory stimuli) and under pathological conditions, as indicated by the study of convulsants.

Recent studies by Tower and McEachern (1165) showed the applicability of this work to epilepsy. The analysis of the cerebrospinal fluid for acetylcholine was positive in a high percentage of epileptics and practically negative in other neurological disorders, provided that cases of brain trauma are omitted. Although no significant relation between the type of epilepsy and the occurrence of

* See p. 254ff.

acetylcholine in the cerebrospinal fluid could be established, the frequency of positive findings of acetylcholine was directly correlated with the frequency of convulsions and the severity of electroencephalographic changes. During the convulsions and within the postictal period (6 hours after convulsion) the acetylcholine test was positive in all cases, but only in 70 per cent in the interictal samples. It is noteworthy that cerebral trauma induced experimentally (115) or studied clinically (1164) leads to the appearance of even greater amounts of acetylcholine in the cerebrospinal fluid.

Anoxia and Convulsive Activity

The great sensitivity of the central nervous system and particularly of the cortex of the brain and cerebellum to a reduction in the oxygen supply and its relation to the state of neuronal activity were mentioned earlier. Studies from Bronk's laboratory (142) on sympathetic ganglia indicate that the sensitivity to anoxia is related to the degree of activity. If this finding is applied to the somatic nervous system – and experiments to be discussed subsequently seem to justify such an extension – one would expect the neuron in the convulsive state to be more susceptible to anoxia than when it is within the range of physiological activity.

In a discussion of this problem it is advisable to consider first the action of anoxia on local convulsive activity induced by the application of small pledgets soaked in strychnine and applied to the cortex of the brain (Baglioni, 59; Dusser de Barenne, 303). This simple method can be used for the study of convulsants in general, as we have seen in the preceding section; it also allows one to compare the influence of various factors on normal and convulsive activity at the same time while the neurons are subjected to a certain change in the internal environment.

Experiments with the inhalation of nitrogen or oxygen-nitrogen mixtures (490, 977) for varying periods of time, which were terminated when marked changes in convulsive activity had developed, showed that convulsive neurons are more sensitive to anoxia than normal ganglion cells. By properly timing the exposure of the brain to anoxia or hypoxia or asphyxia, it is easy to demonstrate that at a time when the normal potentials are still unaltered, spike potentials (recorded from a strychninized area) have completely disappeared (Fig. 42). Such changes may occur although the blood pressure remains unchanged or (in asphyxia) rises slightly.

Close study of the convulsive potentials furnishes important clues for the interpretation of these phenomena. Thus it is seen that as the

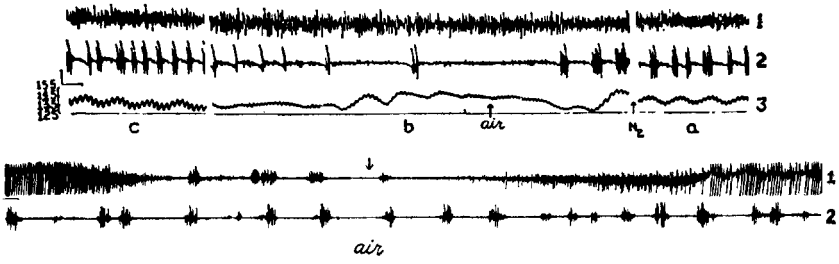

FIGURE 42. Anoxia and asphyxia on normal and convulsive potentials. *Read this figure from right to left.* Calibration in both parts of figure: 300 microvolts. *Upper part:* the effect of inhalation of nitrogen on: RECORD 1—normal potentials (left sensory cortex); RECORD 2—convulsive potentials (right sensory cortex, picrotoxin 0.1 per cent); RECORD 3—blood pressure (mm. Hg) in a dog anesthetized with chloralosane: *a,* control; *b,* 55 seconds after the onset of nitrogen inhalation; *c,* 115 seconds after readmission of air. Time calibration equals 2 seconds. *Lower part:* the effect of asphyxia on: RECORD 1—convulsive potentials (right sigmoid gyrus, picrotoxin 0.05 per cent); RECORD 2—normal potentials (right gyrus suprasylvius). Cat anesthetized with Dial. The record starts 1 minute after the onset of asphyxia. The arrow marks the point of the readmission of air. (Gellhorn and Heymans, 490.)

spike potentials disappear from the convulsive cortex they are replaced by normal potentials. This observation is particularly characteristic for experiments performed on animals anesthetized with Dial, in which the cortical potentials appear in a grouped form ("Dial" potentials; see Figure 42, lower figure). In experiments with chloralosane showing some small background activity between the convulsive discharges, it is noted that the background activity persists at a time when the convulsive discharges have disappeared. Similarly it is seen that on the readmission of air the normal potentials reappear long before spike discharges are restored. These observations suggest that convulsive activity requires a higher degree of oxygenation of the brain than normal activity. As the oxygen supply is diminished by a marked fall in the blood pressure (Dusser de Barenne, 303), convulsive activity also disappears and may be replaced by normal activity. Only with further extension of the period of hypoxia are the normal potentials affected and finally eliminated.

What is happening to the neurons in the convulsive area during anoxia and asphyxia? The records show not only a diminution in the frequency of the convulsive discharges but also a reduction in the amplitude of the individual spikes under these conditions. Such spikes are generally considered to be the result of synchronous discharges of many neurons (Adrian, 7a; Bremer, 128, 130; Jasper, 733). Conse-

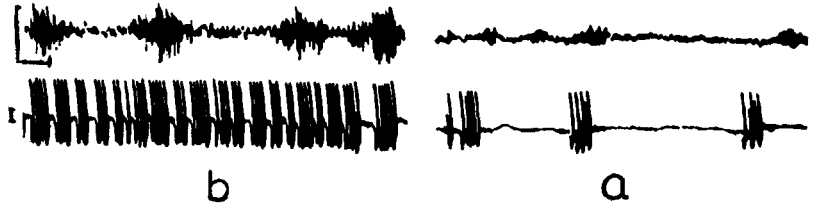

FIGURE 43. Rebound in normal (*upper record*) and convulsive (*lower record*) potentials of the cortex following asphyxia in a "Dial" cat. Calibration: 50 microvolts. *Read this figure from right to left: a,* control; *b,* 30 seconds after the readmission of air. (Gellhorn and Heymans, 490.)

quently their reduction in size may be due to a loss of responsiveness of some neurons, so that the total number of neurons contributing to the spike is diminished (decruitment). However, it is not unlikely that the abnormally high frequency of convulsive neuron discharge is also lowered by anoxia. Since the height of the spike depends on both the number of active neurons and their rate of discharge, the relative importance of the two factors could be determined by an analysis of spikes recorded through cortical microelectrodes or from single fibers of the pyramidal tracts.

On the readmission of air, changes occur in the cortex which indicate not simply a return to the preanoxic level of activity but a temporary increase in the rate of convulsive discharges (Fig. 43). Such a "rebound" is particularly interesting if studied in a previously strychninized cortical area in which, owing to frequent "washings" of the cortex, the convulsive activity had completely disappeared from the electrocorticogram. Following a brief period of anoxia and asphyxia convulsive spikes may appear on the readmission of air. A tendency to overt convulsions following anoxia has been noted by Mayer (911) and Schubert. A parallel phenomenon seems to be the increased reactivity of the brain to visual (1100) and auditory (514) stimuli noted on the readmission of air following a period of hypoxia.

Anoxia and Electroshock

Although it may be stated that the observations reported in the preceding section have unequivocally established the fact that the convulsive neuron is more sensitive to anoxia and asphyxia than the normal neuron, the relation of the oxygen supply to convulsive activity requires still further comment. It is well known that anoxia leads to generalized convulsions in unanesthetized animals. Is not this finding contradictory to the conclusions which have just been made?

The answer to this question lies in the fact that the central nervous

system cannot be considered an organ consisting of uniform parts. As was mentioned earlier, the neurons and their metabolism show definite gradients at different levels of phylogenetic development. Metabolism and susceptibility to anoxia run parallel. Consequently the cortex of the brain is more sensitive to changes in the internal environment, and particularly to anoxia, than the brain stem (671, 949, 976). Moreover the gray mantle of the cerebral cortex is known to hold the brain stem in abeyance, and release phenomena are to be expected whenever the cortex of the brain is surgically or functionally eliminated. These facts must be taken into consideration in order to understand the effect of varying degrees of anoxia on the susceptibility of the organism to generalized convulsions.

Experiments on electrically induced convulsions involving a technique similar to that used in the human being in electroshock treatment indicate that moderate anoxia greatly increases the responsiveness to this shock (470). Table 6 shows that the number of animals which did not convulse was diminished, and the severity of the convulsions was increased. Generalized clonic-tonic convulsions appear at a barometric pressure of 280 mm. Hg in response to a shock which under control conditions (at normal barometric pressure) produces either no reactions or slight clonic twitches often restricted to the head or forelegs. If unanesthetized animals are used, a reduction in the barometric pressure, leading to a temporary loss of righting reflexes and probably eliminating, at least in part, the metencephalon, is likewise accompanied by an increased convulsive response to

TABLE 6. The Influence of a Lowered Barometric Pressure on the Convulsive Reactivity of Rats to Electroshock (Gellhorn and Ballin, 470)

	Percentage of Rats Having		
	Light Clonic Convulsions	Severe Clonic-Tonic Convulsions	No Convulsions
Barometric Pressure 280 Mm. Hg			
Control	77	3	20
Anoxia	15	82	3
Control	68	0	32
Barometric Pressure 120–155 Mm. Hg*			
Control	55	17	28
Anoxia	19	55	26
Barometric Pressure 90–120 Mm. Hg†			
Control	54	18	28
Anoxia	19	0	81

* Until loss of righting reflex occurred.
† Until two gasping movements were observed.

electroshock. However, more severe degrees of anoxia, affecting the medulla oblongata, as indicated by gasping, result in a great reduction in convulsive reactivity.

These experiments suggest that release of the brain stem from cortical inhibition is the cause of the greatly increased convulsive response to electroshock seen in moderate degrees of anoxia. If, however, the anoxia is severe enough to eliminate brain-stem functions or to interfere even with medullary activity, this action is reversed. The lower parts of the brain stem are no longer released, and the depressant effect of anoxia on convulsive activity becomes as evident for the whole organism as when its action on the cortex is studied in experiments with the topical application of a convulsive drug.

Convulsions and Release from Cortical Inhibition

This interpretation of the action of anoxia on convulsive activity is supported by the observation that temporary depression or suppression of cortical activity may so release the brain stem that either subthreshold convulsive discharges become manifest or convulsive activity confined to the brain stem may be activated and spread over the whole central nervous system (455, 471).

A few figures may illustrate this startling phenomenon. First, strychnine is administered intravenously so that spikes appear in the cortex and subcortical areas. Then asphyxia is produced, leading to a reduction in the amplitude of normal and convulsive potentials and frequently to their complete elimination. At this moment a resurgence of convulsive activity appears which lasts about 10 seconds and consists of synchronous spikes in both hemispheres. These spikes increase in frequency and diminish in amplitude and are noted in cortical and subcortical areas. (See Figure 44.) Even the cerebellum was found to participate in this general convulsive pattern. If recorded with monopolar and bipolar electrodes, it is seen that the monopolar potentials are larger, suggesting a subcortical origin for these discharges.* Such discharges never occur in asphyxia when convulsive potentials are restricted to a cortical area by the topical application of the convulsive drug.

That a sensitization to convulsive discharges occurs in anoxia is inferred from the fact that even after the intravenous injection of strychnine in subconvulsive concentrations so that no spikes appear during the control period, a generalized convulsive discharge occurs

* If each of the poles of a bipolar cortical electrode is placed in perfect symmetry to a subcortical convulsive focus, the arrival of the convulsive discharge would alter the cortex under each pole similarly, and no potential difference would be recorded.

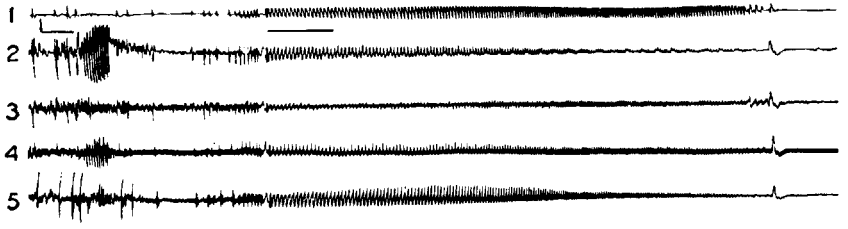

FIGURE 44. Generalized synchronous convulsive discharge induced by asphyxia. Strychnine, 2 mg. intravenously. Calibration: 100 microvolts and 1 second. At the beginning of the discharge the tape speed is doubled. The records start 70 seconds after the beginning of asphyxia. *Record 1:* left hypothalamus. *Record 2:* left gyrus marginalis. *Record 3:* left sensorimotor cortex. *Record 4:* left auditory cortex. *Record 5:* right motor cortex. (Gellhorn, Ballin, and Riggle, 471.)

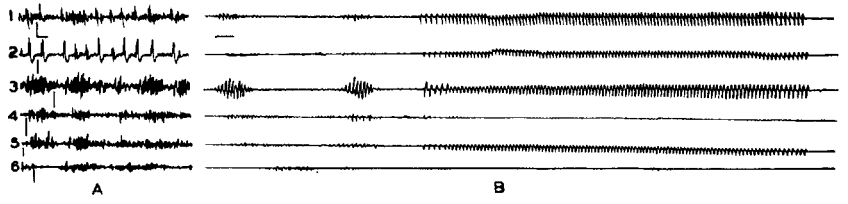

FIGURE 45. Generalized synchronous convulsive discharge induced by asphyxia following the injection of strychnine into the posterior hypothalamus. Calibration: 300 microvolts and 1 second. *Records A:* control. *Records B:* in asphyxia; synchronous spikes appear 100 seconds after the onset of asphyxia. Recordings from (1) ventrolateral thalamus (monopolar); (2) hypothalamus (monopolar); (3) ventrolateral thalamus (bipolar); (4) sigmoid gyrus (bipolar); (5) sigmoid gyrus (monopolar); (6) ectosylvian gyrus (bipolar). (Gellhorn, Ballin, and Riggle, 471.)

in asphyxia. Here again it is seen that under the influence of asphyxia the potentials decrease progressively in amplitude, the effect being greater on the cortical areas than on the hypothalamus. When the cortical activity is abolished, a synchronous discharge of spikes appears in all records with the same characteristics as in the preceding figure.

It was suggested that this synchronous bilateral convulsive discharge which occurs in asphyxia or anoxia in animals which have been strychninized by the intravenous route is of subcortical origin. An example of an experiment in which this assumption was tested is seen in Figure 45. In this experiment strychnine was injected into the right hypothalamus. As a result strychnine spikes appear in this area. It should be noted that during the control period as well as at the

beginning of the asphyxia, cortical activity, thalamic activity, and hypothalamic activity, as disclosed by the potentials of these areas, are completely asynchronous. With progressing asphyxia the hypothalamic spikes and the normal potentials of the cortex and thalamus are reduced in amplitude or disappear. Then suddenly in all leads a synchronous spike discharge occurs which corresponds in its essential features to the convulsive discharge seen in systemically strychninized animals in asphyxia. This type of experiment seems to indicate that the synchronous convulsive discharge is of subcortical origin. Its appearance in asphyxia or anoxia at a time when cortical potentials are greatly reduced or absent suggests that the release of subcortical structures from cortical inhibition represents the trigger mechanism which inaugurates the convulsions. Whether the hypothalamus or the reticular substance plays a specific role has not yet been determined, but it was found that the injection of strychnine into several subcortical areas, such as the thalamus or the caudate nucleus, may likewise elicit bilateral synchronous convulsive discharges in anoxia and asphyxia. This discharge involved in each case the hypothalamus. Until it is determined through lesions which parts of the brain stem are essential for this phenomenon, it may suffice at present to emphasize that subcortical areas, including the hypothalamus, may become the pacemakers of bilateral synchronous convulsive activity when as a result of reduced oxygenation the inhibitory action of the cortex is diminished or abolished.

The chief reason for presenting these experiments in somewhat greater detail is the belief that they resolve the apparent discrepancy existing between the experiments showing that convulsive potentials are more readily abolished by hypoxia than are normal potentials and those observations which give evidence for increased convulsive reactivity of the whole organism under these conditions. In addition this subcortical discharge may also be used to illustrate some general rules concerning convulsive activity and chemical environment. It was noted that the subcortical discharge occurring in asphyxia after previous strychninization of the hypothalamus may be demonstrated repeatedly, although progressively decreasing, in the same animal at proper intervals. At times a reinjection of strychnine is necessary. Since it was shown previously that eserine increases convulsive activity under conditions of topical application of the convulsant to the cortex, the validity of these observations for the subcortical discharge was tested. It was found that after this discharge could no longer be evoked by asphyxia, an intervening injection of eserine was adequate to sensitize the hypothalamus to such a degree that subse-

quent asphyxia experiments evoked a generalized convulsive discharge. This striking effect of eserine in enhancing the subcortical convulsive discharge was seen with small amounts of this drug which did not lower the blood pressure. Apparently the activation of convulsive activity by eserine is not confined to local convulsive discharges of the cortex, but may be demonstrated in generalized convulsions. Their threshold is lowered and the frequency and duration of the discharge are enhanced by the inhibition of the cholinesterase.

Application to Epilepsy

That certain forms of epilepsy (petit mal) are of subcortical origin has been emphasized by Penfield, Jasper (733), and their collaborators for a number of years. The idea was suggested by the occurrence of synchronous bilateral convulsive discharges (3 per second, spike and dome pattern) which spread rapidly over the whole cortex. This discharge "appears suddenly and disappears as suddenly, as though controlled from some centrally-placed switching mechanism capable of controlling the rhythmic discharge of large cortical areas of both hemispheres" (Jasper). Moreover section of the corpus callosum does not abolish this bilateral synchronous discharge, and convulsive activity has also been recorded from the diencephalon.

The conception of the petit mal discharge as being of subcortical origin was supported by the beautiful experimental studies of Jasper and Droogleever-Fortuyn (736). These authors succeeded in eliciting bilateral discharges of the petit mal type by stimulating a small part of the massa intermedia of the thalamus. Low-frequency stimulation of 3 or 8 per second was particularly effective. The discharge occurred after a latent period up to 50 milliseconds, indicating multiple synaptic delays. It persisted after the main commissural systems, such as the corpus callosum, the anterior and posterior commissure, and the fornix, had been sectioned. Although stimulation of the hypothalamus failed to produce the petit mal-like discharges, Jasper concluded that "the massa intermedia, and perhaps a portion of the hypothalamus, seem to be the structures without which the bilateral effects from unilateral thalamic stimulation could not be produced." *

Apparently, bilateral synchronous convulsive activity is achieved through the activation of the intralaminar thalamic system (Dempsey and Morison, 274–276). Whether this system is likewise involved in the convulsive subcortical discharge seen in anoxia and asphyxia after

* Hayne *et al.* (619) find no support for the subcortical origin of the petit mal discharge in EEG records from cortical and subcortical parts of the human brain, but positive evidence was presented by Spiegel (1132a).

systemic strychninization or on injection of a convulsant into the hypothalamus has not yet been determined but appears to be very likely. If this work is applied to the problem of subcortical discharge produced experimentally by Jasper and occurring clinically in the form of petit mal epilepsy, it may be suggested that it depends not only on physiological stimulation or pathological excitation of a sub-

TABLE 7. The Influence of Electroshock on Rats after 4 and 24 Hours of Fasting*

Number of Rats	Current	Number (and Percentage) of Convulsant Rats	
		After 4 Hours of Fasting	After 24 Hours of Fasting
62	27 ma†	10 (16%)	
62	27 ma		19 (31%)
55	24 ma	4 (7%)	
55	24 ma		10 (18%)

* Unpublished observations. – The effect of fasting on the blood sugar was found in another experiment to be as follows:
In 42 rats, after fasting 4 hours, blood sugar, mg. % = 105 ± 4.7
In 70 rats, after fasting 24 hours, blood sugar, mg. % = 90 ± 2.9
† Milliamperes, alternating current, 60/sec, applied for 0.4 seconds.

cortical area but also on the degree of inhibition which the cortex exerts on the brain stem. The degree of this inhibition seems to be directly related to the degree of cortical activity. Consequently any condition which diminishes cortical activity is bound to increase subcortical discharges.

The tendency of hypoglycemia to promote convulsions is supported by clinical and experimental evidence. Petit mal discharges in patients (542) and seizure in epileptic monkeys (798) are enhanced through hypoglycemia. Even a relatively slight diminution of the blood sugar through fasting increases the frequency and severity of electrically induced convulsions (Table 7). The data suggest that this increased susceptibility to convulsions is related to the release of subcortical structures resulting from the diminished cortical control.

Since hyperventilation precipitates petit mal discharges with great regularity, it might be inferred that it likewise reduces cortical activity. However, the literature is controversial on this point, since Dusser de Barenne (307) and collaborators found that cortical reactions, as measured by the response of the gray matter to electrical stimulation, were increased in hyperventilation and decreased when the *p*H of the brain and blood was shifted in an acid direction.

On the other hand, sensory functions (visual and acoustic) (514, 515) and mental activity (496, 501) were found to be diminished in hyperventilation, whereas subcortical reflexes (vestibular nystagmus) (516, 518) were increased. As a possible solution of the apparently contradictory observation that grand mal discharges are more likely to occur when the carbon dioxide content of the blood is high (Gibbs, 540) whereas petit mal attacks are precipitated by hyperventilation (i.e., when the carbon dioxide content of the blood is lowered), it is suggested that the origins of these two forms of epilepsy are different and that variations in the carbon dioxide content of the blood act differently on the cortex and on subcortical structures.*

The Brain Stem in Anoxic and Hypoglycemic Convulsions

That severe anoxia leads to generalized convulsions was clearly established by numerous physiologists, including Paul Bert (95), who noted that the rate at which the barometric pressure or the oxygen tension at normal barometric pressure is reduced is decisive for the effect, since in gradually progressing anoxia death may ensue without any excitatory phenomena while in rapid deoxygenation severe convulsions precede death. Similar phenomena occur in asphyxia or in severe hemorrhage. It is generally assumed that a release of subcortical centers takes place under these conditions, since, as discussed earlier, the brain stem and particularly the medulla oblongata are much less sensitive to anoxia than the gray mantle of the brain.† Strong support for the release hypothesis of anoxic convulsions comes from the experiments of Noell and Dombrowski (976), who recorded cortical and brain-stem potentials during nitrogen inhalation in the rabbit. They found that at a time when the cortical potentials had been greatly diminished, the activity of the brain stem, particularly in the reticular formation, was increased.

There are other forms of convulsions which appear to be closely related to anoxic convulsions. Schubert cites the older literature according to which convulsions may follow the recovery from prolonged asphyxia or exposure to high concentrations of carbon dioxide. Richet (1046) and Schubert (1100) studied convulsions occurring on recompression after severe decompression (lowering of the barometric pressure). Most favorable for the induction of these convul-

* See Chapter 19.

† Noell (975) believes that there are no essential differences in the resistance between cortical and subcortical neurons to anoxia and that the disappearance of cortical activity slightly before that of subcortical neurons is due to the lesser circulation of blood in the former.

sions is rapid recompression at a time when convulsive and other excitatory phenomena seen at low barometric pressure have diminished or disappeared. The study of the blood pressure reveals two phases during decompression: in the first phase the blood pressure rises; in the second, it falls. The latter, also characterized by a cessation or a diminution of somatic excitability, may indicate beginning medullary paralysis. Recompression alters and reverses this process and generalized convulsions occur, during which the blood pressure rises above the control level. Schubert thinks that these recompression convulsions illustrate a general law of neuronal activity, first enunciated by S. Mayer (911), according to which excitation occurs on restoration of the normal blood supply provided that the normal nutritive conditions of the neuron have been greatly interfered with. It should, however, be borne in mind that the release of the brain stem from cortical control may again be the decisive factor. The rapid rise in the blood pressure indicates that medullary and possibly pontine centers recover, while the cortex is still severely depressed. This uninhibited activity of part of the brain stem is probably as essential for decompression as for recompression convulsions. To what extent sino-aortic reflexes contribute to these phenomena has not yet been determined.

These considerations apply to hypoglycemic convulsions induced by insulin. Clinical observations (Himwich, Frostig, *et al.*, 660) illustrate the release of brain-stem functions as cortical responsiveness progressively declines. Studies of Hoagland *et al.* (671) on the action potentials of the cortex and hypothalamus disclose not only the greater stability of the latter but also the fact that a phase of hyperactivity of the hypothalamus may occur at a time when cortical potentials disappear. Finally, convulsions were noted to occur when the cortex had become electrically silent (Moruzzi, 949).

The Relation of Anoxic to Hypoglycemic Convulsions

The similarity of anoxic and hypoglycemic convulsions as well as the resemblance between anoxia and hypoglycemia in their action on somatic and autonomic functions raises the question of their mutual relations. Does anoxia aggravate insulin convulsions? What is the effect of a lowered blood sugar on anoxic convulsions?.

Studies on rats showed that a mild degree of anoxia, which under control conditions does not evoke any abnormal symptoms, precipitates convulsions in hypoglycemic animals (552). Whether anoxia is produced by a lowering of the barometric pressure or by the inhalation of oxygen-nitrogen mixtures does not alter the result. In each

case convulsions occur earlier, and with a greater fatality, than in the corresponding control experiments in which the animals were subjected to insulin alone. If at the onset of the convulsions occurring in rats injected with insulin and inhaling 7-per-cent oxygen the oxygen-nitrogen mixture is replaced by pure oxygen, the animals cease to convulse and recover. These data show clearly that hypoglycemia sensitizes rats to anoxia to such a degree that mild or moderate degrees of anoxia lead to fatal anoxic convulsions unless pure oxygen is immediately administered. This conclusion is borne out by observation of the character of the convulsions. Insulin con-

TABLE 8. The Relation between Hypoglycemia, Anoxia, and Convulsions (Gellhorn, Packer, and Feldman, 509)

I. Effect of 10 Units of Insulin/Kg (Intraperitoneally) on Normal Rats

Number	Latent Period of Hypoglycemic Convulsions, in Minutes	Remarks
1	223	Recover on injection of glucose.
2	228	
3	∞	
4	∞	
5	152	Recover on injection of glucose.
6	217	
7	188	
8	∞	
9	159	Recover on injection of glucose.
10	141	
11	153	
12	∞	

II. Effect of 10 Units of Insulin/Kg (Intraperitoneally) on Rats Subjected for 2 Hours to Inhalation of 7-per-cent Oxygen

Number	Latent Period of Anoxic Convulsions, in Minutes	Remarks
1	28	All died in spite of injection of glucose.
2	51	
3	107	
4	∞	
5	37	All died in spite of injection of glucose.
6	48	
7	63	
8	∞	
9	27	All died in spite of injection of glucose.
10	22	
11	23	
12	61	

TABLE 8 continued.

III. Effect of 10 Units of Insulin/Kg (Intraperitoneally) on Rats Subjected for 2 Hours to Inhalation of 7-per-cent Oxygen, and Effect of Immediate Treatment with Pure Oxygen at the Onset of Convulsions

Number	Latent Period of Anoxic Convulsions, in Minutes	Effect of Immediate Treatment with Pure Oxygen	Number of Minutes before Appearance of Hypoglycemic Convulsions*
1	47	Recover	179
2	46	Died	
3	31	Recover	
4	58	Recover	
5	46	Recover	
6	26	Recover	190
7	30	Recover	143
8	51	Died	
9	60	Died	
10	94	Recover	

* The number of minutes is counted from the time of the discontinuance of the treatment with pure oxygen. — All the rats showing these hypoglycemic convulsions recovered on injection of glucose.

vulsions are characterized by clonic-tonic discharges. Convulsions observed after the administration of oxygen-nitrogen mixtures or in hypoglycemic-anoxic rats do not show the tonic phase at all. On the contrary, the animals show a few clonic movements and then die unless they are saved by the administration of oxygen.

That fundamental differences exist between anoxic and hypoglycemic convulsions is supported by the following observations:

1. Insulin-injected rats develop typical hypoglycemic convulsions and recover on the injection of glucose.

2. Insulin-injected rats subjected to 7-per-cent oxygen show anoxic convulsions and fail to recover on the administration of glucose.

3. Insulin-injected rats subjected to 7-per-cent oxygen which show anoxic convulsions and recover on treatment with 100-per-cent oxygen show later (in air) typical hypoglycemic convulsions (Table 8).

The clinical symptoms of convulsions depend on the oxygenation of the blood. When the latter is very low, anoxic convulsions occur which show only the clonic phase. Such convulsions occur in severe anoxia or are precipitated by moderate anoxia in animals like the rat, which is very sensitive to anoxia if the oxygen consumption of the brain is reduced by hypoglycemia.

Hypoglycemic convulsions are clonic and tonic. They do not occur in hypoxia, although the blood sugar, following the injection of insulin,

falls to convulsive levels and is actually lower* than in animals which were treated with similar amounts of insulin but inhaled air (509, 920–922). These observations suggest that the tonic phase requires a higher degree of oxygenation than the clonus. This interpretation is apparently correct, since Ruf showed that a weak clonic discharge with which an electrically induced convulsion terminated could be converted into a long-lasting tonic-clonic phase by the administration of oxygen (1075).

The Oxygen Consumption of the Convulsive Neuron

Against this background the fundamental question concerning the magnitude of the oxygen consumption of the convulsant as compared with the normal neuron needs to be considered.

That convulsive activity is accompanied by a decrease in the oxygen tension of the brain tissue was convincingly shown by Davies and Remond (260), who developed suitable procedures through which dissolved oxygen could be determined in the brain by means of an electrolytic method. A micro-oxygen electrode applied to the outer wall of an arteriole shows no variations in the oxygen tension during convulsive discharges, whereas a distinct fall in the oxygen tension appears under these conditions when the electrode is placed near a venule or some distance away from any blood vessel. Apparently the oxygen tension of the arterial blood remained constant in these animals, which were studied under curare and artificial respiration, but the oxygen tension in the tissues decreased shortly after the onset of convulsive activity. These authors showed also that when a minute blood vessel was occluded, the oxygen tension fell more rapidly in the vicinity of a convulsive focus than under control conditions.

An interpretation of these data must take into consideration the circulatory changes in the area. If vasoconstriction accompanied convulsive activity, the decline in oxygen tension in Davies' experiments would be fully accounted for on a circulatory basis. However, direct experiments showed that during focal convulsive activity the cerebral blood flow increases in the convulsive area (1003). Such an increase in local brain perfusion is not simply the result of increased blood pressure but may occur while the latter is constant or actually falls. It appears to be related to increased neuronal activity, since the augmented blood flow occurs several seconds after the onset of the seizure.

* The greater fall in the blood sugar is due to the failure of secreted adrenalin to mobilize glucose under these conditions (508).

Here again is an interesting example illustrating that only quantitative differences exist between normal and convulsive activity. If the normal activity of the cortical hand area is increased by electrical stimulation leading to a contralateral movement, the blood supply to this and not to the leg area is augmented (Penfield, 1003). Similarly, unilateral convulsions elicited by electrical stimulation of the left cortex are accompanied by an increased blood flow in the left, but not in the right, hemisphere. Apparently metabolites of neuronal activity account for these circulatory changes. If the oxygen tension falls in the convulsive area, as Davies showed, it indicates clearly that the oxygen consumption of the brain is so large that the compensatory increased blood flow is inadequate to maintain a normal oxygen tension in the brain. These findings are of importance not only for physiological considerations but also as evidence against the vasospasm theory of epilepsy, particularly since a study of focal convulsions in the human being reveals similar restricted areas of vasodilatation.

Temperature and Convulsions

It is an established fact that the metabolism and activity of organs and tissues increase with increasing temperature (754). Hoagland (667) showed for the mammalian brain that the activity of this organ as measured by the frequency of the alpha potentials increases with rising temperature. From these data one may infer that these changes would continue until the oxygen supply became deficient. Such a limitation is bound to occur earlier in convulsions. These conclusions are supported by experimental studies in which the cortex of the brain was heated, its temperature measured by thermocouples, and the effect of increased brain temperature studied comparatively on the normal brain and on topically induced convulsions (1152, 1153).

Figure 46 illustrates the disappearance of convulsive potentials during heating at a temperature of the brain which only slightly reduces the amplitude of normal potentials. It is characteristic that with cooling, normal potentials but not convulsive activity reappear. If convulsants are reapplied, they re-evoke convulsive activity; but the spikes are smaller than those recorded before heating. These investigations show further that before the convulsive potentials disappear, their frequency and amplitude are diminished. Since there is no evidence of a change in synchrony of the potentials, the results appear to indicate that with increasing temperature the number of excitable neurons which contribute to normal and convulsive poten-

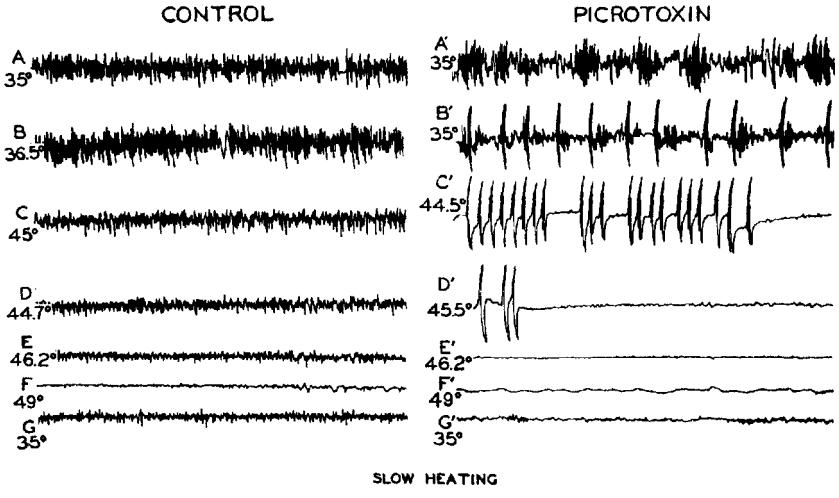

FIGURE 46. The effect of gradual local heating on normal and convulsive cortical potentials. Note the disappearance of convulsive potentials at 45 degrees while normal potentials persist; also the greater damage in the convulsive than in the normal area (compare G with G'). (Teschan and Gellhorn, 1153.)

tials decreases. This decrease accounts for the decline in the amplitude of spikes and of normal potentials with increasing temperature.

The greater oxygen demand of the convulsive neuron, combined with the increased metabolism of any neuron at a rising temperature, seems to be responsible for the greater sensitivity of convulsive neurons to heating. This is indicated not only by the upper temperature limits compatible with convulsive activity but also by a comparison of the reactivity, with and without the action of a convulsant, of cortical areas heated to a similar degree. On cooling one recognizes a lesser activity in the previously convulsive area than in the control. Moreover the greater reduction in the number of excitable neurons in the former is seen on the reapplication of a convulsive drug to both areas. The amplitude and frequency of the spikes are much less in the previously convulsive area than in the control area, although the exposure to heat was the same in both.

The selective action of increased temperature on convulsive activity is probably another illustration of the greater sensitivity of the convulsive neuron to hypoxia. Before the oxygen supply becomes the limiting factor, convulsive as well as normal activity increases with rising temperature. If the cortex is repeatedly heated to a moderate degree

for short periods, the frequency of the convulsive discharges increases with each heating.

The effect of alterations in body temperature on convulsions is less well understood than the action of local changes in brain temperature on normal and convulsive activity. A lowering of the temperature of the body is accompanied by an increased susceptibility to convulsions. The physiology involved is still incompletely understood, but Noell's investigations (974) suggest that anoxia is not a factor and that again the release of the brain stem may be decisive. Impulses which originate in the brain stem and activate the cortex would then account for the fact that at lowered temperatures brain potentials show an increased degree of synchrony, but more work is needed to establish this mechanism.

The increased temperature of the body and also of the brain in fever would be expected to cause greater damage to the cortex than to subcortical structures. The symptoms seen in fever may be due in part to the impairment of cortical function resulting from increased temperature as such, in part also to the additional inadequate oxygenation, but these questions likewise need further study.

The Role of Afferent, Particularly Nociceptive, Impulses in the Precipitation and Inhibition of Convulsions

It has been well recognized since the times of Hughlings Jackson that afferent impulses have some effect on the precipitation and inhibition of convulsions, and experiments showing that such procedures may alter convulsive activity were reported by François-Franck in the last century (379). Further work was done by the Italian school (Amantea, 30, and Clementi, 232), using strychnine topically on various cortical areas. It showed that afferent stimuli may activate the cortex to such a degree that overt convulsions are induced.* This work has been confirmed in more recent studies in which, through the recording of the potentials in various parts of the central nervous system some insight has been gained in addition into the mechanism involved (468).

In view of the fact that an emotional disturbance not infrequently precedes the first epileptic attack, it is noteworthy that direct stimulation of the hypothalamus may precipitate convulsions. The frequency and amplitude of convulsive discharges greatly increase and lead to a condition similar to that seen in status epilepticus (Fig. 47). Such a discharge is often followed by an almost complete electrical silence.

* Forster (374) showed recently that acoustic stimulation precipitates generalized convulsions after the application of AcCh to the auditory cortex.

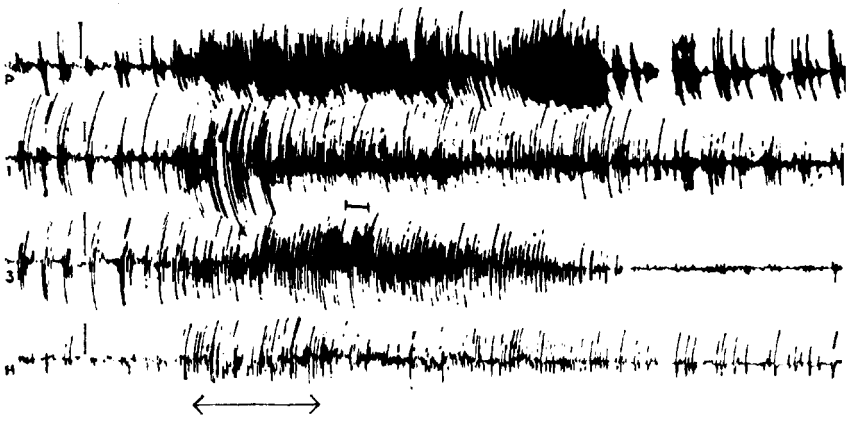

FIGURE 47. The effect of stimulation (indicated by opposing arrows) of the contralateral hypothalamus on the posterior suppressor area (P), auditory projection area (1), motor area (3), and the posterior hypothalamus (H) of the cat. Stimulus: 1.9 volts for 10 seconds. Calibration: 100 microvolts. 0.2 mg of picrotoxin per kilogram of body weight injected intravenously. (Gellhorn and Ballin, 468.)

The mechanism by which hypothalamic excitation aggravates convulsive activity may be discussed at this time because it seems certain that hypothalamic-cortical discharges are involved. The changes in cortical potentials following hypothalamic stimulation are independent of the hypothalamic "downward" discharge,* since they persist after cervical sympathectomy and also after high cervical transection of the spinal cord. On the other hand, stimuli arising in the hypothalamus directly or, indirectly, through the stimulation of peripheral sense organs furnish afferent impulses to the cortex of the brain which may aggravate or precipitate convulsions.

Among the afferent stimuli which have been found effective in precipitating generalized convulsive discharges, nociceptive impulses (stimulation or ligation of the sciatic nerve) should be mentioned first. In animals treated with subconvulsive doses of picrotoxin the frequency and amplitude of the potentials increase gradually until nearly maximal convulsive discharges are recorded (Fig. 48). Such experiments suggest that one of the important factors in aggravating or eliciting convulsions as a result of afferent (including hypothalamic)† stimulation is brought about by the recruitment of additional neurons previously not participating in the convulsive discharge.

* See Chapter 14.

† It will be shown later that nociceptive stimuli act on the hypothalamus.

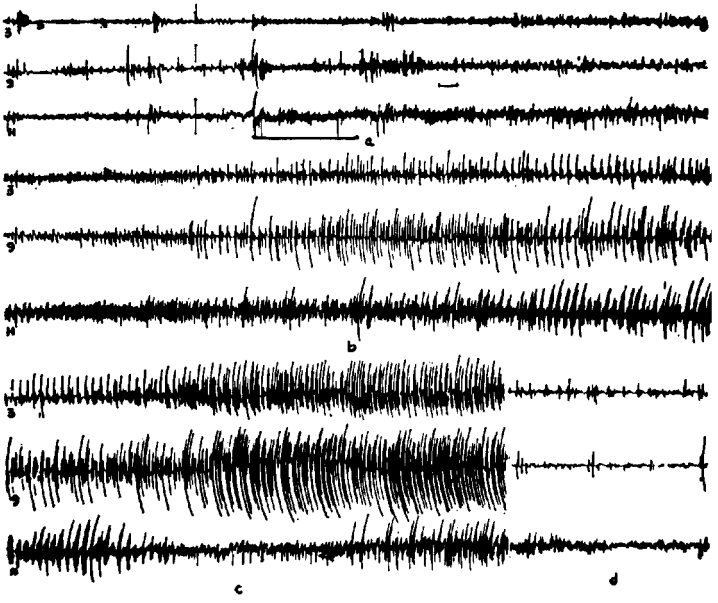

FIGURE 48. The effect of stimulation (indicated by the horizontal line near the letter "a") of the contralateral sciatic nerve on the motor area (*records* 3), the optical projection area (*records* 9), and the posterior hypothalamus (*records* H) of an etherized cat which had been given "intocostrin." Stimulus: 1.9 volts for 5 seconds. Records a, b, and c are continuous; records d, a few minutes later. (Gellhorn and Ballin, 468.)

Further Studies on the Mechanism Involved in the Precipitation of Convulsions

Like the alpha potentials of the resting cortex which are seen in the human electroencephalogram, the spikes representing convulsive activity result from the synchrony or near synchrony of normal potentials. Since many more neurons contribute to a convulsive spike than to an alpha potential, the spike has been interpreted as a sign of hypersynchrony (7, 130).

The action of afferent stimuli on the normal brain is similar in principle to that on the convulsive. Stimulation of moderate intensity increases asynchrony because the various neurons tend to discharge at different frequencies (Adrian) to near-threshold stimuli, and thresholds vary widely in a neuron population. Consequently the normal brain shows potentials of lesser amplitude and greater frequency, whereas the spike may be reduced in amplitude or disappear under these conditions. Strong stimuli, however, cause nearly maximal

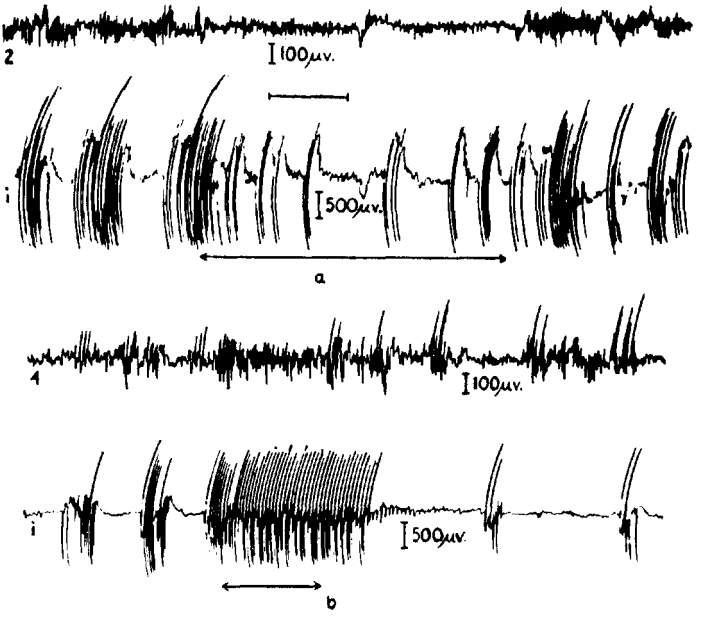

FIGURE 49. The effect of stimulation of the contralateral sciatic nerve on a nonstrychninized sensory area (records 2 and 4) and on a strychninized suppressor area (records i). *Records a:* taken during stimulation with 3.6 volts, at 40.4 per second, for 20 seconds. *Records b:* showing stimulation with 9.8 volts, at 40.4 per second, for 6 seconds. (Gellhorn and Ballin, 468.)

rates of discharge, so that individual differences between neurons become minimal. Furthermore, many additional neurons are "recruited." These two processes combined result in more frequent and possibly larger spikes than were recorded before the stimulation.

This interpretation is supported by experiments, such as that illustrated in Figure 49, in which the effect of stimulation of the sciatic nerve with different intensities is recorded on a normal and on a strychninized cortical area. Stimulation with 3.6 volts decreases greatly the number of spikes, whereas the spikes increase in frequency under the influence of stimulation with 9.8 volts. The nonstrychninized areas show somewhat larger potentials of high frequency during the period of stimulation with 9.8 volts (recruitment), whereas the potentials are reduced in size on stimulation with 3.6 volts (asynchrony).*

However, the intensity of stimulation is not the only important factor, since functional differences may exist in different parts of the cortex. One would expect that the more excitable area would undergo

* The large "Dial" potentials are absent in either case during stimulation.

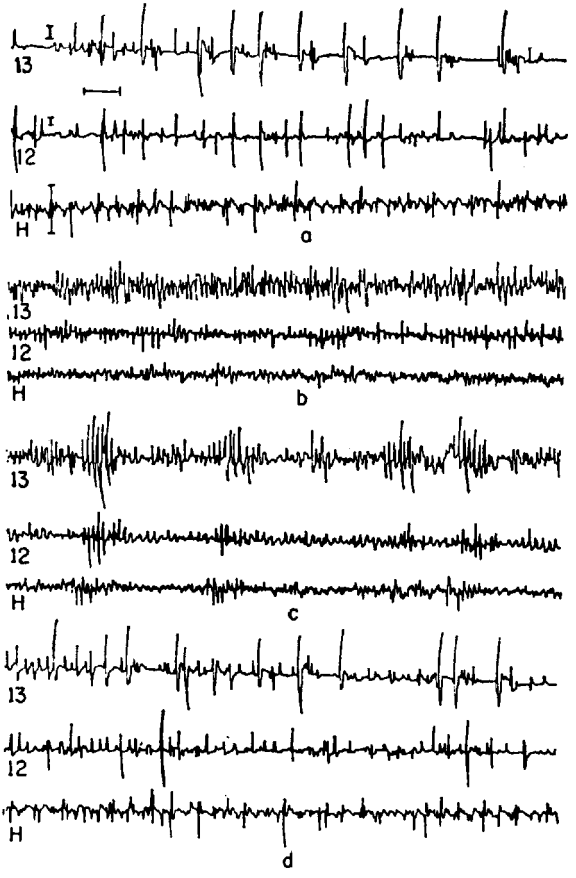

FIGURE 50. The effect of hypothalamic stimulation on the posterior sigmoid gyrus (*records 13*), the suprasylvian gyrus (*records 12*), and the hypothalamus (*records* H) of a cat which had been given an injection of "Dial" 36 hours and an injection of picrotoxin 24 hours before the records were taken. The hypothalamus was stimulated with 11 volts for 10 seconds between records a and b. Records c and d were taken after intervals of 1 minute. Calibration: 100 microvolts. (Gellhorn and Ballin, 468.)

recruitment whereas the less excitable part of the cortex would only show signs of asynchrony. This interpretation is suggested by the variations in the degree of convulsive response to a given stimulus that exist between different cortical areas of animals in which all parts of the cortex are presumably in a similar state of picrotoxinization, the convulsive drug having been given intravenously. Such differences may also be observed in the reactions of two strychninized areas (local application of strychnine) under the influence of the

same afferent stimulus. Under these conditions, and also in systemically induced convulsions, it was not infrequently seen that an afferent stimulus increases convulsive potentials in one area but suppresses them in another.

The fundamental relation between synchrony and convulsive discharges is illustrated in a particularly interesting manner in Figure 50, in which the various phases of excitation could be separated because they followed each other rather slowly. Before hypothalamic stimulation the picrotoxinized cat showed spike potentials in the cortex and hypothalamus (a). Immediately after stimulation the large spike potentials disappeared and were replaced by small, frequent background potentials (b). At a later stage (c) grouped "Dial" potentials, which were separated from each other by small, and often frequent background potentials, were seen in their place. Finally the "Dial" potentials passed away, and the spikes returned (d). This experiment illustrates the principle that stimulation involves decreased synchrony and that during recovery the original state is attained through stages of increasing synchronization. The highest asynchrony appears in the form of small, frequent potentials. A moderate degree of synchronization is indicated by the appearance of "Dial" potentials, and the highest one, by spikes.

It is of great interest to point out that according to this observation the period of spikes (hypersynchrony) is preceded by one showing relatively large grouped potentials. These "Dial" potentials, based on a moderate degree of synchrony, are similar to the delta potentials seen in sleep. Similar slow, large potentials occur in anoxia, hypoglycemia, and hyperventilation. It was mentioned earlier that the disposition to convulsive discharges in these conditions may be due to the release of the hypothalamus and reticular substance from cortical control. However, such an interpretation is hardly applicable to the phenomenon of sleep, and the question of the relation of convulsions to sleep must be raised.

Convulsions and Sleep

It is known from long clinical experience that convulsions frequently occur during sleep, and the systematic studies of Gibbs have shown that convulsive discharges are more often detected in the electroencephalogram (EEG) during sleep than in the state of wakefulness (537). There are several reasons why these findings cannot be explained on the basis of a subcortical release as in anoxia, hypoglycemia, and related conditions. First, Gibbs noted that sleep increased the percentage of convulsive discharges occurring in cases of cortical

focal epilepsy (particularly of the psychomotor type with a focus in the temporal lobes) more than it did in cases of petit mal epilepsy with a presumably subcortical origin. Second, there is no indication that the depression of cortical activity will release the hypothalamus in sleep. On the contrary, it is generally assumed that diminished hypothalamic activity and particularly a diminished hypothalamic-cortical discharge play a prominent role in the causation of sleep. Moreover, as discussed elsewhere,* sleep has been looked upon as a state of functional deafferentation (Bremer, 126, 129; Kleitman, 780) in which the effectiveness of afferent stimuli on the brain is unquestionably diminished. Consequently we are confronted with the paradox that afferent stimuli may precipitate convulsions but also that sleep may predispose to them, although afferent stimuli are then less effective. The resolution of this difficulty seems to lie in the fact that, as the slow, large delta waves indicate, there is a tendency toward synchrony in sleep. Consequently, in this state, hypersynchrony may be more easily elicited than under conditions of wakefulness.†

Proprioceptive Impulses and Convulsive Activity

The close relation of normal to convulsive activity has been repeatedly emphasized. Experiments with electrical stimulation of the motor cortex furnish appropriate illustrations. Proprioceptive reflexes intensified by the fixation of a joint in a position in which the reacting muscles are lengthened not only increase the normal response of the motor cortex as indicated by the amplitude of the EEG, but determine the appearance and duration of the after-discharge (491) (Fig. 51). The latter is a convulsive or nearly convulsive phenomenon.

The importance of proprioceptive impulses for the after-discharge is further illustrated by observations on the effect of deafferentation. Whereas in the normal leg the after-discharge increases in intensity and duration with increasing stimulation of the motor cortex, it remains weak and appears to be unaltered by the intensity of the stimulus after deafferentation (721). Moreover the character of the after-discharge is altered: it is tonic in the normal, but clonic in the deafferented, extremity.

Proprioceptive impulses may also alter strychnine convulsions

* See p. 185.

† Grey Walter (1204a) concurs in this view as he writes that "sleep too, with its slower rhythms . . . should act as a convulsant." Note also the appearance of positive bilateral spikes of 14 and 6 per second during sleep in persons in whom autonomic symptoms, personality disturbances, and a high incidence of precipitation of convulsions through emotional excitement suggest an epileptic focus in the diencephalon (539).

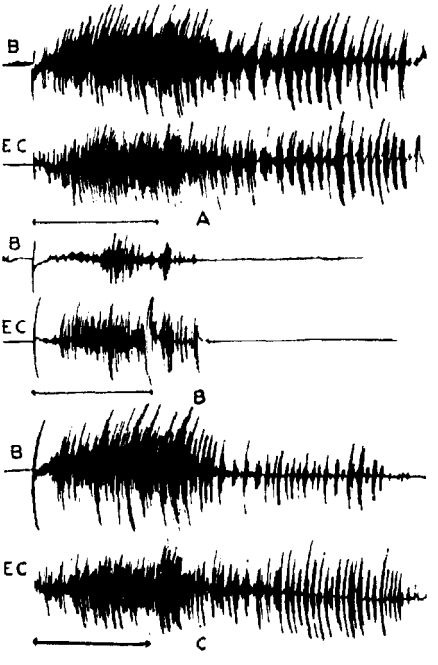

FIGURE 51. The facilitatory action of proprioception on the after-discharges of a monkey under "Dial" anesthesia, as shown by stimulation of a biceps point in area 4. The stimulation is indicated by the horizontal lines below the records. Stimulus: 2.9 volts, at 90 per second. Muscle: B, biceps; EC, extensor carpi radialis. *Records A and C:* elbow fixated at 150 degrees. *Records B:* elbow fixated at 30 degrees. (Gellhorn, Hyde, and Gay, 491.)

induced by the topical application of this drug to the cerebral cortex. Nociceptive and proprioceptive impulses act in a similar manner: they either increase convulsive activity (augmentation in the frequency of strychnine spikes) or cause inhibition (i.e., a decrease in the frequency or a disappearance) of the spikes. The former appears to be the result of increased recruitment, the latter, of increased asynchrony.

The relative importance of cutaneous and proprioceptive impulses for the maintenance of convulsive activity of the spinal cord is illustrated in Table 9, in which the frequency of convulsive spikes induced by strychninization of the posterior columns of the lumbar part of the spinal cord is shown. It is seen that "skinning" has no decisive effect on the convulsions, whereas deafferentation abolishes them. It appears that of the various afferent impulses thus far investigated, nociceptive and, to a lesser degree, proprioceptive impulses have the greatest effect in precipitating and propagating convulsions. The action of the distance receptors and of cutaneous sense organs is definitely less. The relation of this peculiar order to the activation of the hypothalamus and its cortical projection system is pointed out elsewhere.*

* See p. 199.

TABLE 9. The Number of Convulsive Movements Following Strychninization of the Posterior Columns in the Cat (Gellhorn, Hyde, and Gay, 491) *

	Movements per Minute	
	Right Tibialis	Left Tibialis
Control	15	15
Skinned	20	11
Deafferented	1	0

* A 2 mm.^{2} piece of filter paper soaked in 3 per cent strychnine was placed at L 4 in a "Dial" cat. Skinning and deafferentation of the right hind leg preceded similar procedures with the left. The convulsive movements were recorded by means of electromyograms.

The Behavior of the Motor Unit in Convulsions

Changes in synchrony and recruitment are undoubtedly important factors in the causation of convulsive discharges, but the behavior of the individual neuron should not be neglected. By recording potentials from individual fibers of the pyramidal tracts, Adrian and Moruzzi (17) were able to study single neurons in convulsive activity induced either by the local application of a convulsant to the motor cortex or by adequate electrical stimulation leading to an after-discharge. In both conditions a marked increase in the frequency of the discharge was noted, which may be as high as 500 to 1,000 impulses per second. Afferent stimuli* increase the discharge rate of a normal neuron and may also precipitate a convulsive discharge in the neuron previously treated with a convulsive drug. Accordingly it may be said that fundamental changes in the individual neuron which greatly increase the frequency of discharge, together with alterations in synchrony and recruitment of groups of neurons, are the determining factors in the development of convulsions. The individual activity of a single neuron as well as the interaction of groups of neurons is altered under the influence of sensory stimulation. This alteration causes excitation of the normal brain and the precipitation or inhibition of convulsions in the convulsive brain.

Carotid Sinus Reflexes and Convulsions

There is evidence in the literature that afferent impulses which affect brain activity are not restricted to those originating in the somatic nervous system. Koch (788) showed that variations in the ca-

* See also Bremer's experiments (130) on the effect of afferent impulses on strychninized neurons in the spinal cord.

rotid sinus pressure are accompanied by dramatic changes in the excitability of unanesthetized dogs. A fall in the pressure induced increased excitability, leading to convulsions, whereas a rise in the blood pressure induced sleeplike conditions. The application of these findings to the field of experimental convulsions showed that convulsive activity may be varied within wide limits through carotid sinus reflexes (522, 523).

It was noted that in animals in which a convulsive drug had been injected in subthreshold doses, a decrease in the carotid sinus pressure evoked temporary convulsions. This result was obtained independently of the procedure by which the pressure in the carotid sinus was reduced. Thus clamping the carotids below the bifurcation, raising the head, or the application of amylnitrit increased convulsions. On the other hand, tilting an animal into the "head-down" position or raising the blood pressure by small doses of adrenalin reduced convulsions.

In order to interpret these changes in convulsive activity in terms of carotid sinus reflexes, it was necessary to determine the effect of altered brain circulation on the convulsions under the conditions of tilting. This was done by repeating the experiment in the same manner after the carotid sinuses had been denervated and the vagi cut. Such "denervated" animals then showed effects in the opposite direction – that is, a slight increase in the convulsions on tilting in the "head-down" position and on the injection of adrenalin, and a decrease in intensity when the animal was placed in the "feet-down" position. Animals in which either the carotid sinus nerves or the vagi were intact behaved like normal animals with respect to the action of adrenalin and alterations of the posture of the head on convulsive activity.

From these observations it seems to follow that variations in the carotid pressure and convulsive activity undergo parallel changes in sino-aortic denervated animals. Contrariwise, in the normal animal convulsions are diminished in the "head-down" position and are increased in the "feet-down" position. This shows plainly the importance of the sino-aortic reflexes in relation to convulsions, since they completely offset and overcompensate the effect of marked alterations in circulation brought about by alterations in posture and other procedures.

It is interesting to note that the effect of adrenalin in decreasing somatic excitability can be demonstrated not only in convulsions resulting from the injection of convulsants such as metrazol, but also in hypoglycemic convulsions. If unanesthetized rabbits show hypo-

glycemic convulsions after insulin, the injection of adrenalin in minute quantities (0.006 and 0.02 mg/Kg) is sufficient to abolish the convulsions. The animal relaxes and shows normally coordinated movements. A determination of the blood sugar reveals that the amount of adrenalin injected was insufficient to raise the blood sugar. Some time later, hypoglycemic convulsions start again and may be stopped a second or even a third time by the repeated injection of small amounts of adrenalin (Gellhorn, Darrow, and Yesinick, 479). Similarly it is found that the strychnine-like effects seen in chloralosane anesthesia disappear on the injection of minute doses of adrenalin. The activation of the sino-aortic pressure receptors seems to be responsible for these effects.*

The sino-aortic area appears to be one of the important regulators of excitability of the somatic nervous system. Its powerful influence can be demonstrated in simple reflexes such as the knee jerk (Spychala, 1133) as well as by the study of convulsions. To what extent the chemoreceptors of this region alter nervous activity in general and convulsive discharges in particular outside of the region of the medulla oblongata, where their effects on respiratory and vasomotor centers are well established, is still unknown.†

Age and Convulsions

That certain forms of convulsive disorders, particularly epilepsy of the petit mal type, are more common in children than in adults may indicate changes in extracerebral and/or intracerebral factors with increasing age. It is conceivable that the greater convulsive reactivity in childhood has its cause in such extracerebral factors as the lesser constancy of the internal environment. It is common knowledge, to mention only one example, that temperature regulation is less precise in early childhood; and Barcroft (65) has emphasized that changes in the internal environment may lead to convulsions. Variations in the permeability of the blood-brain barrier may also be

* However, repetition of this work under conditions of controlled circulation is needed before the suggested interpretation can be accepted.

† Experiments showed that the effect of anoxia and the inhalation of carbon dioxide on convulsions is greatly modified by sino-aortic reflexes. Brief periods of inhalation of 8-per-cent oxygen reduce or abolish convulsions after sino-aortic denervation, although no effect of this mild anoxia was seen in the normal animal. On the contrary, the inhalation of 15-per-cent carbon dioxide abolished rapidly convulsions in the normal animal, whereas such effects were absent after the elimination of sino-aortic reflexes. This change in the effects of anoxia and hypercapnia through the elimination of sino-aortic receptors is difficult to explain. It is probably related to the fact that carbon dioxide increases and anoxia diminishes the sino-aortic pressor reflexes. For further details see Yesinick and Gellhorn (522).

a factor, since experiments by Behnsen (81) on the mouse, based on the permeation of dyes, and by Dölter and Kruse (289) on bromide determination in the blood and cerebrospinal fluid gave evidence for a greater permeability of this barrier at an earlier than at a later age. These factors seem to explain why 75 to 100 per cent of seven- to seventeen-day-old rats convulse when injected with 0.5 to 1.0 mg/Gm acid fuchsin, although adult rats do not show convulsions after injection with 3 mg/Gm. Treatment with drugs which increase the permeability of the blood-brain barrier augments the incidence of convulsions in adult rats (Fröhlich and Mirsky, 396).

Important as these findings are, they are probably not pertinent to the problem concerning the cause of the high incidence of petit mal epilepsy in childhood. This convulsive disorder, which seems to be of subcortical origin (see Jasper), raises the question whether the susceptibility to generalized convulsions originating in or involving the diencephalon is related to age. Whether the stimulation of the massa intermedia, which may cause an appearance of the petit mal type of discharge, is more apt to produce convulsions in younger than in older animals is not known. However, experiments on rats subjected to electroshock indicate that their susceptibility to generalized convulsions decreases with increasing age (469) (Table 10). This

TABLE 10. Age in Relation to Convulsive Reaction to Electroshock (Gellhorn and Ballin, 468)

Number of Rats	Average Weight, Grams	Average Age, Weeks	Number of Convulsant Rats*					Percentage of Convulsant Rats
			++++	+++	++	+	±	
Current of 24 Milliamperes for 0.8 Seconds								
10	52	4	10	0	0	0	0	100
27	72	7	26	1	0	0	0	100
29	120	10	15	8	4	2	0	100
9	164	18	1	0	3	1	4	44
30	244	24	0	0	1	5	24	20
18	282	50	0	0	0	1	17	6
Current of 27 Milliamperes for 0.8 Seconds								
37	250	37	5	4	0	3	25	32
24	342	58	1	0	0	1	22	8
15	360	76	0	0	0	1	14	7
Current of 29 Milliamperes for 0.8 Seconds								
12	228	25	3	3	2	3	1	92
11	233	68	1	2	1	1	6	46

*++++ = tonic-clonic convulsions; +++ = clonic convulsions, 10 sec.; ++ = clonic convulsions, 6–10 sec.; + = clonic convulsions, 2–5 sec.; ± = no convulsions.

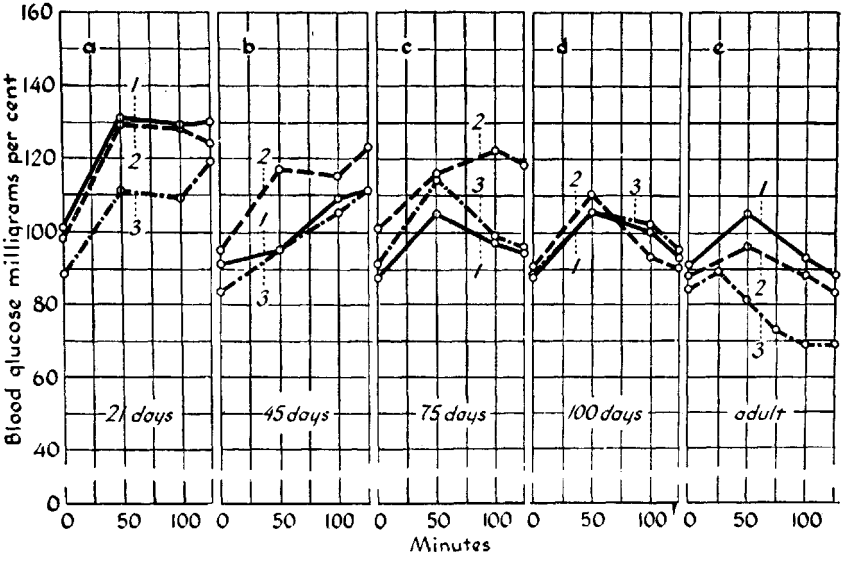

FIGURE 52. The relation between age and the reactivity of sympathetic centers, as indicated by the degree of hyperglycemia in response to hypoxia. Rats of different ages were exposed for 125 minutes to an atmospheric pressure of 280 mm. Hg. The hyperglycemic response decreases with increasing age. (Safford and Gellhorn, 1078.)

effect does not seem to be due to differences in weight, since adult rats of similar weights but different age show a significant difference in their convulsive reactivity. It should, however, be mentioned that Davenport found convincing evidence that weight (at least in rats) also influences the threshold reaction to electroshock (258).

The explanation of the observations that convulsive reactivity decreases with increasing age is still uncertain. It may be related to differences in the AcCh metabolism of the growing organism (Nachmansohn; Welsh and Hyde; and others), and Freedman and Himwich found, as mentioned earlier, a decreasing sensitivity of rats to poisoning with DFP as their age increased.* Since numerous data related to generalized convulsions point to the hypothalamus as an important structure in these reactions, it is of interest to mention that the excitability of sympathetic centers declines with increasing age (1078). There is reason to assume that the hypothalamic "downward" discharge and the hypothalamic-cortical discharge are similarly altered in several conditions. This may possibly contribute to the

* In these experiments, however, possible changes in the blood-brain barrier are not excluded.

greater susceptibility to electroshock of young rats, which show increased reactivity of sympathetic centers, and may play a role in the predominance of petit discharge in childhood and adolescence. (See Figure 52.)

Concluding Remarks

The field of experimental convulsions is obviously too large to be dealt with adequately in this chapter. Numerous topics, such as the spreading of convulsive activity (Erickson, 322; Hoefer, 690), the chemistry of the brain in convulsions (779, 1139), the relation of the endocrines to convulsive activity, and the action of anticonvulsants (Toman, 1161), have not been mentioned. However, it was not the intention of the writer to cover the available factual material as completely as possible, but to develop significant ideas which may inspire the reader to delve further into the literature and to amplify, complete, and correct the data which have been presented.

That convulsive activity is not a qualitative but a quantitative alteration of normal activity was illustrated particularly by the study of the action of AcCh and ChE. The effects of anoxia and increased temperature on local convulsions showed the availability of oxygen as a limiting factor in convulsive activity. The work of Adrian and Moruzzi gives a deeper insight into the fundamental cellular basis of the problems of convulsions, and Davies' studies illustrate the modern methods by which the metabolic processes can be linked to convulsive activity.

The relation of the circulation to convulsive activity has been discussed from two different angles. The association of convulsions with an increased blood supply to the convulsant area appears to be due to the increased metabolism of the convulsant neurons and the inability of the circulation to remove completely the excess of acid metabolites. The profound changes resulting from carotid sinus reflexes, although still incompletely understood, call attention to the importance of general circulatory reflexes for brain activity in general and convulsive activity in particular.

Afferent impulses conveyed to the brain through the spinothalamic system as well as through the hypothalamus modify convulsive discharges just as the normal activity of the cortex is altered under these conditions. The physiological changes are in both instances similar in principle and based on changes in synchrony and recruitment. The milder changes, consisting of increasing asynchrony only, resulting from afferent stimuli of lesser intensity or from lesser responsiveness of a cortical area, cause inhibition of focal or generalized convulsions;

the greater effects based on increased recruitment of previously inactive neurons account for the precipitation or aggravation of convulsive discharges. Finally, the study of convulsions under various conditions demonstrates the complex interrelation between the cortex and subcortical structures. The conversion of moderate cortical convulsive activity into a status epilepticus as a result of direct or indirect (through afferent impulses) excitation of the hypothalamus illustrates on a larger scale the important role which continued hypothalamic discharges and probably impulses from the reticular substance play in maintaining normal cortical activity. On the other hand, the occurrence of convulsions in anoxia and hypoglycemia is based on the principle that a release of the brain stem takes place when there is a progressive decrease in cortical excitability. Under such conditions the hypothalamus seems to become the pacemaker of all brain activity.

The experimental data discussed and the interpretation given are admittedly incomplete. They furnish merely a sketch of the problems involved in an understanding of convulsive activity, but they illustrate, it is hoped, the fruitfulness of the physiological method for the study of pathological phenomena and the rewards for physiology itself of this type of research.

PART III

The Physiological Basis of Consciousness

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~ 8 ~

An Approach to the Problem

Nichts ist drinnen, nichts ist draussen,
Denn was innen, das ist aussen.
Goethe, *Epirrhema**

"Mind and body are not to be conceived as two disparate entities between which we have to make, or find, some sort of amphibious bridge, but . . . talking about minds and talking about bodies are different ways of classifying and interpreting our experiences." A. J. Ayer (48)

"In the nervous system we are looking at the threads while with the mind we perceive the patterns, and . . . one day we shall discover how the patterns are made out of threads." W. R. Brain (123)

THESE three quotations – from a poet, from a philosopher, and from a neurologist – remarking how closely interwoven are mind and body, raise the question whether it is possible to lay the groundwork for a physiological interpretation of mental processes. Attempts in this direction have been made not infrequently in the past. Verworn (1187) hypothesized that memory and the growth of the neuron are related, E. Hering (626) dealt in a famous oration with memory as a characteristic of living systems, and von Kries (805), the author of the duplicity theory of vision, spoke on one occasion on the material basis of consciousness. Pavlov (995, 996) attempted through his conditioned reflex studies not only to give psychology an objective basis but also to create an understanding of the physiological mechanisms underlying mental disease. The master of neurophysiological research of the present age, however, C. S. Sherrington (1109), in his Rede

* It is interesting that a century later Herman Hesse in his *Fabulierbuch* expresses this idea in almost the same words: "Nichts ist aussen, nichts ist innen, denn was aussen ist, ist innen."

lecture discussed with considerable skepticism the possibilities of physiological research into the basis of psychic phenomena.

But in spite of Sherrington's warning, work will go on in this direction, particularly at a time when procedures such as lobotomies and lobectomies are rather frequently performed and surgeons, psychologists, and physiologists unite in an endeavor to evaluate the results of these operations in their physiological, psychological, and psychiatric aspects. Penfield's interesting observations, moreover (999, 1000), that dreamy states, hallucinations, and illusions may be evoked by electrical stimulation of the cortex of the temporal lobe in the unanesthetized human being furnish another approach to a physiological psychology.

The investigation of the complex processes of the central nervous system has greatly profited by, and is still learning from, experiments on conduction of the nervous impulse in the peripheral nerve. Similarly the study of the physiological basis of the most primitive mental states may be a logical beginning for an understanding of the mind from a physiological point of view. Perhaps some pseudophilosophical problems are still keeping scientists away from investigations of this kind. The writer does not agree with Riese and Hoff (1054) in thinking it "wise to renounce in experimental physiology terms such as consciousness, volition, or any other term implying functions accessible only to self-experience." On this ground that part of the study of sense organs concerned with the relation of the objectively defined sensory stimulus to the subjectively experienced sensation could no longer be considered a proper object of physiological investigations.

It seems more advisable to follow the lead given by clinical neurology, which, on the basis of careful observation and unhampered by philosophical bias, laid the foundation for a physiology of consciousness. According to Martin (902) there are several states of awareness or degrees of consciousness: "(1) the normal condition, in which the person is responsive and reacts to psychological stimuli and indicates by his behaviour and conversation that he has the same awareness of himself and his environment as ourselves; (2) sleep, a condition of inactivity from which he can be roused and resumes his normal state; (3) a state of unconsciousness in which he appears to be deeply asleep but cannot be roused to normal consciousness; and (4) a much less common state, or group of states, in which the patient is awake and active but gives evidence that he is not completely, if at all, aware of himself and his doings, and of which he has no recollection afterwards; such are the states presented by certain epileptic equivalents, post-epileptic automatism, and post-traumatic excitement; probably delirium belongs also to this group."

The task of the following discussion will be to characterize the state of activity of the cortex and subcortical structures in different states of awareness. In view of the complexity of the problem the chief topics to be presented in this part of the book are here first briefly outlined.

The physiology of sleep will be considered on the basis of observations on man, with emphasis on changes in the EEG and on the factors contributing to them. Studies on experimental animals involving stimulation and lesions in the brain stem will reveal the fundamental diencephalic-cortical mechanism underlying functional alterations in the degree of awareness within physiological limits. The concepts thus obtained are tested in experiments in which the overt symptoms of arousal are correlated not only with changes in cortical potentials but also with hypothalamic-cortical discharges.

The well-known fact that a patient may become conscious of a limb previously amputated furnishes a unique opportunity to analyze the factors which contribute to the awareness of one's own body. These factors are in essence similar to those that are indispensable for the awareness of one's environment and again illustrate the fundamental role of hypothalamic-cortical interrelations.

The state of consciousness is diminished physiologically in sleep and experimentally in anesthesia or during changes in the internal environment (anoxia, hypoglycemia, etc.). The mechanisms underlying these different states of awareness will be shown to be different. The primary event leading to sleep is subcortical, whereas a reduction in cortical activity and a subsequent release of the brain stem seem to accompany and probably initiate states of reduced awareness in anesthesia, anoxia, and similar conditions.

One of the main conclusions arrived at from these investigations will be the recognition of the fact that the cortical activity which mirrors the state of awareness depends on several afferent systems. Their significance can be demonstrated through excitation and focal destruction in the diencephalon. But the story is incomplete unless the influence of the lower brain stem is taken into account. Therefore the relation of the reticular substance and particularly of Magoun's activating system to the diencephalon and cortex will be discussed. This analysis will explain why lesions in the brain stem and increased pressure in the area of the posterior fossa cause deep coma in man.

~ 9 ~

The Physiology of Consciousness

The Electroencephalogram in Sleep

THE state of consciousness in which a person is aware of himself and his environment depends on the complexity of the nervous organization. Its range varies between different individuals, the intelligent and the stupid, the newborn and the adult. There are also different levels of consciousness in the same person depending on the degree of his alertness. Electroencephalography has confirmed and expanded these common experiences. With the eyes closed a person may show well-developed alpha potentials of a frequency of 8 to 12 per second and an amplitude of about 50 microvolts; when he is in a state of greater alertness or attention, owing either to outside stimuli or internal conditions, the potentials are of the beta type – i.e., of smaller amplitude and greater frequency. They are indicative of a greater cortical excitation, resulting in discharges less synchronous than those responsible for the occurrence of alpha potentials.

Again it is common experience that transitory states exist between wakefulness and sleep and that the latter passes through different phases, known to older investigators (Kohlschütter, 796) from the changes in threshold of the stimulus for awakening. These phases have been related to brain activity through electroencephalographic research. As Loomis (865, 866), Davis (263, 264), Blake and Gerard (103, 104), and their collaborators have shown, the EEG changes as a person becomes drowsy in that the alpha potentials become temporarily interrupted and their amplitude diminishes. With light sleep delta potentials, of slower frequency and greater amplitude, replace in part the alpha potentials, and in addition groups of waves of a frequency of 14 per second (spindles) appear. As the sleep deepens, more spindles are recorded and the delta potentials increase in ampli-

tude and duration. Finally the spindles become minimal, the delta potentials, which started with a frequency of about 5 per second, slow down to 0.5 per second, and their amplitude increases still further (up to about 200 microvolts). These changes occur in records taken from different parts of the skull, but quantitative differences exist. Thus the spindles are more distinct in the parietal cortex than in the frontal and occipital leads.

Of particular interest for our problem are observations in which an attempt was made to correlate various levels of awareness with changes in the EEG. This was accomplished by asking the experimental subject to signal any change in the state of consciousness which might occur as he was going to sleep. Thus it was observed that when a subject indicated he had "drifted off" for a moment, the alpha potentials were lost or depressed for at least 1.5 seconds and that during this time small delta potentials appeared (263). Blake confirmed these results and showed that the disappearance of alpha potentials was very brief in "dozing" (average duration 6 seconds). If the absence of alpha potentials was recorded for a somewhat longer period (averaging 9 seconds), it was accompanied by a dream which could be remembered, whereas a still longer absence of these potentials (average 55 seconds) indicated a dream which could not be recalled (103).

The progressive changes in the EEG, from the disappearance of alpha potentials to their replacement by large, slow delta waves at various stages of sleep, indicate that sleep involves increasing degrees of synchrony in the discharge of cortical neurons. Since afferent stimuli have been shown to produce increased degrees of asynchrony and such stimuli may induce awakening, with a return of alpha potentials, the study of electroencephalographic sleep records supports the interpretation of sleep as a state of physiological deafferentation. That visual and acoustic stimuli are not of particular importance may be concluded from the findings that persons who are both blind and deaf do not show any deviations in the sleep-wakefulness cycle (802). The claim of Galkin that the elimination of olfactory impulses leads to somnolence could not be confirmed (517). Galkin's results (408) were probably due to inadvertent encephalitic changes following the operations. On the other hand, considerable evidence exists for the importance of muscle tone and the significance of proprioceptive impulses for the maintenance of wakefulness.

In experiments in which an attempt was made greatly to prolong the period of wakefulness, it was found that wakefulness could not be maintained in a reclining position, whereas apparently during

sitting or standing the tone of the muscles successfully prevented the onset of sleep (780). It seems that the afferent impulses originating in the muscle spindles and quantitatively related to the intensity of the muscle tone determine to a great extent the excitability of the nervous system and thereby the state of wakefulness.

Changes in the muscle tone are reflected in the human EEG (103). Alpha potentials disappear at the onset of sleep before consciousness is lost, at a time when the tone of the muscles decreases markedly. Most important in this respect are the experiments of Bremer (126, 127, 129). Unanesthetized animals with low medullary transection, a procedure excluding proprioception from limbs and trunk, were observed to have spontaneous, alternate phases of sleep and wakefulness. Acoustic stimuli arouse these animals, and movements of the eyeballs and pupillary dilatation occur. The cortical potentials during the sleeplike condition differ in a characteristic way from those recorded when the animal is aroused. In sleep the animals show relatively slow and very regular potentials, whereas during the period of wakefulness the action potentials are more frequent and irregular. When practically all afferent impulses are eliminated, as in animals in which the brain stem has been sectioned behind the nuclei of the oculomotor nerves, the animals remain permanently in a sleeplike state and cannot be aroused by sensory stimuli.

The Central Control of Sleep

These investigations raise the question, From what part of the central nervous system is the sleep cycle regulated? The reduction of cortical excitability through the elimination of the action of afferent impulses does not alone explain sleep and wakefulness, since this cycle persists in decorticate animals (Goltz, 557; Rothmann, 1071). Even in the human being the absence of the telencephalon does not abolish the sleep cycle (Gamper, 409).* Moreover, numerous clinical cases with disturbances in the sleep mechanism showed the diencephalon and midbrain to be involved (Mauthner, 910; others). Extensive studies by von Economo and observations by Fulton and Bailey (399), Rowe (1072), and many others suggested that the regulation of sleep is associated with the hypothalamus. These clinical findings were extended by animal experimentation. Of the earlier work, that of Demole (273) and Cloetta (233) should be mentioned, who showed that the injection of calcium chloride into the hypothalamus results in a sleeplike condition, whereas the injection of potassium

* No sleep cycle exists in anencephaly, in which only the myelencephalon is intact (941).

chloride calls forth a general excitation. More significant is the work of Ranson (1032) and his collaborators Ingram (725) and Harrison (605), who showed that bilateral lesions in the lateral hypothalamic area produce in cats and monkeys a profound somnolence which may last for days or weeks. Similar lesions placed in the anterior part of the hypothalamus had no such effects, and thalamic lesions produced somnolence only in a few cases in which the destroyed areas were very large and damage to the adjacent hypothalamic area was not completely excluded. From the location of the lesions, particularly from the failure to produce somnolence in cats with thalamic lesions, these authors conclude that sleep results from the elimination of the "downward discharge" of sympathetic impulses originating in the hypothalamus rather than from the influence these impulses may have on the thalamus and cortex.

It is difficult to explain why the diminution of the sympathetic "downward discharge" may lead to somnolence unless we take into consideration that the sympathetic tone and the reactivity of the somatic nervous system show frequent parallel changes. It has been shown by Hess (634, 636, 637) that on stimulation of the diencephalon in unanesthetized cats "ergotropic" effects are obtained which consist of increased sympathetic responses and are accompanied by an increased excitability of the somatic nervous system. In contradistinction to these responses recorded upon stimulation of the posterior parts of the diencephalon, excitation of its anterior section results predominantly in parasympathetic effects which are associated with a diminished responsiveness of the somatic nervous system (see Figure 80, p. 342). A reduction in respiratory volume, sleeplike conditions, and "hypothalamic adynamy" (loss in muscle tone) occur at the same time (635).

Changes in the balance of the autonomic centers are accompanied by alterations in the reactivity of the somatic nervous system not only when diencephalic centers are directly stimulated but also as a result of sino-aortic reflexes which modify sympathetic discharges. Koch (788) showed that an increase in the intrasinusal pressure leads to a marked decrease in general somatic excitability; the striated muscles relax, and the animals seem to fall asleep. On the other hand, when the pressure in the carotid sinus is lowered, the general excitability of the animal is greatly increased, a result that is also evident in the greater intensity of spontaneous movements. These observations seem to indicate that the tone of the striated muscles depends, at least partially, on reflexes mediated by the receptors of the carotid sinus. In addition Spychala (1133) observed that variations in the intra-

sinusal pressure alter the response of the knee jerk to a standard stimulus. When the pressure in the carotid sinus is increased, the action potentials of the quadriceps muscle are decreased. Muscle activity increases, however, when the pressure in the sinus falls below the normal level. Apparently the carotid sinus reflexes exert an important influence not only on the autonomic but also on the somatic nervous system. The tone and the excitability of spinal somatic neurons are inhibited by the pressure receptors under physiological conditions, and the degree of inhibition is directly related to the pressure in the carotid sinuses.

The mechanism by which parallel alterations in the sympathetic and somatic nervous systems are effected is not well understood. Some authors have assumed a direct action of sympathetic impulses on striated muscles (Ken Kuré, 814a) or on the anterior horn cells of the spinal cord. But it seems more likely that direct or reflex excitation of sympathetic centers such as the hypothalamus influences the somatic (extrapyramidal) neurons (664) as well. This interpretation is strongly supported by the phenomena occurring as a result of a release of brain-stem activity from cortical control, seen, for example, in anoxia and asphyxia. As pointed out elsewhere,* under these conditions sympathetic and somatic reactivity are greatly increased, and consequently generalized convulsions take place which are accompanied by sympathetic discharges.†

The significance of these changes in somatic excitability, and particularly in the muscle tone, for sleep and wakefulness is evident from the earlier discussed work of Kleitman on the relation between the muscle tone and wakefulness. It may be assumed that extrapyramidal impulses originating in the hypothalamus induce a certain degree of muscle tone which is reinforced by spinal reflexes. However, the afferent impulses originating in the muscles do not remain confined to the spinal cord but influence hypothalamic as well as cortical activity. They illustrate the feed-back mechanism so characteristic of the central nervous system.

Before we enter into a critique of Ranson's idea that the "center" ‡ of wakefulness in the posterior hypothalamus influences the state of awareness solely by its "downward discharge," some experimental

* See pp. 151ff.

† There are apparently some quantitative differences between the release of autonomic and of somatic centers from cortical control which appear when the cortical control is only partially inactivated. In mild anoxia sympathetic hypothalamic reactivity may be increased whereas somatic reactions elicited from this area are decreased (475).

‡ See p. 216.

work remains to be discussed which indicates that not only wakefulness but sleep too is actively regulated by the diencephalon.

Hess claimed for many years that the stimulation of various parts of the diencephalon, and particularly of the inferior part of the massa intermedia, with low frequency currents induces sleep. The sleep resembles natural sleep in its gradual onset. The cat curls up in a corner, the striated muscles and the nictitating membranes relax, and the pupils constrict. The animal falls asleep and shows a gradual development of spindles and delta potentials in the cortex and thalamus which are comparable to the human EEG at different stages of sleep (19, 640a) (see Figure 53). The cat remains in this condition for some time after the cessation of the stimulus. Following spontaneous awakening the reapplication of the stimulus induces sleep again. As in normal sleep, appropriate stimuli, particularly the smell of meat, arouse the animal.*

In contradistinction to Ranson's experiments, sleep is induced in Hess's work not by lesions but through stimulation. The assumption of Harrison (604) that Hess's stimulation produced lesions is unconvincing (636). Moreover, that even mechanical stimulation of the diencephalon produces sleep had been found earlier (88). It should be emphasized that the diencephalic areas which on stimulation induce sleep (19, 636, 718) are not identical with those which elicit similar symptoms through lesions. The former are located in the intralaminar nuclei belonging to the dorsal medial thalamus, the latter in the posterior hypothalamus (Ranson, 1031; Ranström, 1036; and others).

Ranson assumed that the posterior hypothalamus is a center of wakefulness and that its elimination results in sleep and somnolence. Hess, on the other hand, believes that sleep is an active process as suggested by the fact that it results from the stimulation and not from the elimination of a certain diencephalic area. An important contribution which seems to clarify, at least to a certain extent, this disagreement has been made by Nauta (968). This investigator placed transverse incisions in various parts of the diencephalon of the rat and noted that the normal sleep cycle was unaltered as long as the hypothalamus was left intact. However, incisions either just in front of or posterior to the mammillary bodies led to prolonged sleep. It was initiated by yawning and stretching; then the animals curled up,

* Kaada (743) observed that a sleeplike condition was induced by stimulation from "two zones within the anterior 'rhinencephalon' – one around the genu of the corpus callosum on the medial surface, and a second centering around the olfactory tubercle in the postorbital, anterior insular, anterior hippocampal gyral and part of adjacent temporal cortex."

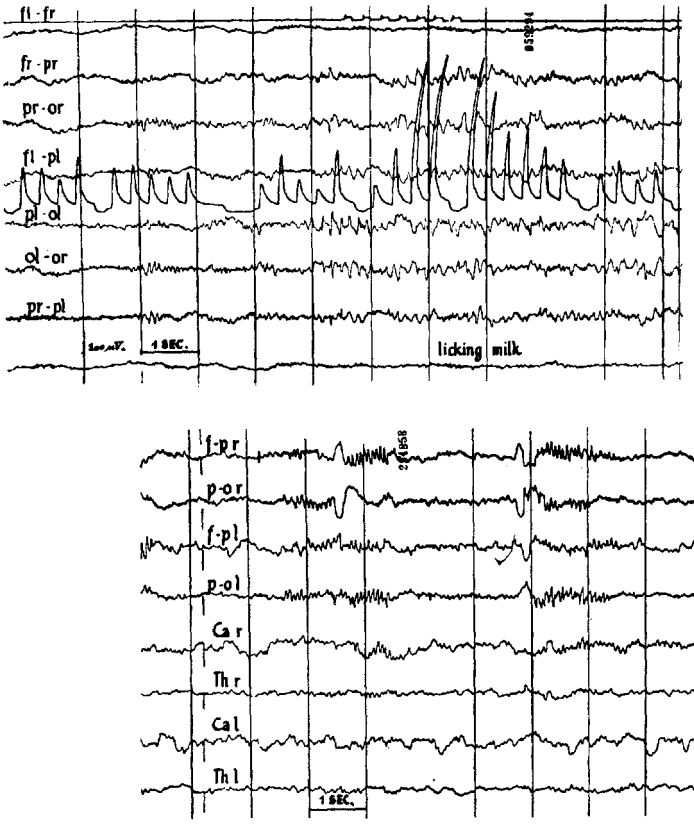

FIGURE 53. The effect of electric stimulation of the intralaminar nuclei (the hypnogenic area of Hess) on the electrocorticogram, thalamogram, and caudatogram of a cat. Bipolar recording, from cortex and subcortex. Abbreviations: r, right side; l, left side; f, frontal; p, parietal; o, occipital; Ca, caudate nucleus; Th, thalamus. *Top records:* relaxed, waking animal before stimulation. *Middle records:* drowsy animal shortly after thalamic stimulation. *Bottom records:* animal in deep sleep about 20 minutes after stimulation. (Akert, Koella, and R. Hess, Jr., 19, 640a.)

lay on their side, and showed a slow, regular respiration. The condition of sleep was accompanied by hypothermia, but was not caused by it, since sleep persisted after these operations even in animals placed in an incubator which prevented the fall in body temperature. Appropriate stimuli led to temporary awakening. If the transverse incision was confined to the medial part of the mammillary bodies, no permanent disturbance of the sleep mechanism resulted. The experiments confirm Ranson's work according to which the center of wakefulness is located predominantly in the lateral part of the posterior hypothalamus. In view of the fact that incisions just posterior to the mammillary bodies likewise induce sleep, Nauta concludes that this part of the hypothalamus receives from the tegmentum of the midbrain impulses which are important for hypothalamic activity and thereby for the maintenance of the state of wakefulness.

Evidence for the existence of a sleep center was obtained by extending the transverse incisions to the rostral part of the diencephalon. If the infundibular and mammillary areas are separated from the preoptic region, a state of sleeplessness results which finally leads to exhaustion and death. Unfortunately no objective records confirming the more or less complete absence of sleep until death supervenes are thus far available. Nauta's observations, however, are of such great interest that part of his description of these animals may be quoted.

"The animals showed a normal interest in their environment. Their general condition was excellent at first and they spontaneously took food and drink. Soon, however, their state deteriorated, which is not surprising considering the large amount of sleep to which the rat is accustomed. After a period of 24 hours the sleepless rats usually began to show symptoms of fatigue. They did not eat or drink of their own accord and their interest in the surroundings decreased. Symptoms of sham rage, if present, persisted. In spite of the fatigue and even of the succeeding exhaustion, during which the gait became unsteady, sleep was not forthcoming, the opened eyes and the spontaneous activity proving that the animals were awake. After a period averaging three days the exhausted animals fell into a state of coma* which soon ended in death. A return of the sleeping capacity was never observed in any of the animals."

The relation between the anterior sleep center and the posterior waking center of the diencephalon is illustrated by an experiment in which the two operations were combined. Such animals showed per-

* These observations show clearly the fundamental difference between the neurological basis of sleep and of coma.

manent sleep, as if only the posterior operation had been performed. Apparently the rostral procedure was ineffective, since the sleep center could no longer act on the center of wakefulness. It seems to follow from these important observations, the extension of which to higher animals is urgently needed, that the anterior hypothalamic sleep center produces sleep by inhibiting the posterior center of wakefulness. It is interesting to note that von Economo, on the basis of clinical observations, had already postulated such a rostral center of sleep in the human being. He failed to recognize, however, the dependence of the action of this center on the hypothalamic center of wakefulness and thought that sleeplessness resulting from anterior hypothalamic lesions was due to the direct action of this area on the cerebral cortex.

The relation of this sleep center to the observations of Hess, Akert, *et al.*, according to which sleep may be induced from the intralaminar nuclei of the thalamus, is still problematic. It remains to be seen whether the active inducement of sleep by electrical stimulation is influenced by the elimination of Nauta's rostral sleep center.

It is of interest to mention that inhibitory influences on the posterior hypothalamus may be exerted from other parts of the diencephalon. Wheatley (1230) has shown that destruction of the ventromedial nuclei of the hypothalamus leads to rage responses, which are apparently due to a release of the posterior hypothalamus, but no disturbances in the sleep cycle were observed in these animals. As Drs. Ingram and Wheatley pointed out to me, cats thus operated on survive for years, and, as I saw for myself, they are perfectly quiet in the cage as long as they remain unprovoked.

Although many data need to be filled in before a reasonably complete theory of sleep can be established, sufficient experimental observations are available to sketch in outline the sleep mechanism. As was mentioned earlier, Ranson emphasized the importance of the sympathetic "downward discharge." That such sympathetic discharges alone are of little significance is evident from the fact that neither nearly complete extirpation of the sympathetic nervous system by Cannon nor extirpation of the spinal cord below the exit of the phrenics (Hermann, 628) interferes with the sleep cycle. It is also known that cases with high transection of the spinal cord in man show a normal alternation of sleep and wakefulness. These last two observations indicate that even the elimination of the assumed sympathetic-somatic (extrapyramidal) "downward discharge" does not result in sleep. It seems to follow that this discharge plays only an

auxiliary role in the regulation of sleep. Its nature will be discussed below.

This leaves us with the necessity of explaining the sleep cycle and its most important symptoms – i.e., changes in the degree of awareness – by the actions of the hypothalamic sleep and waking centers on other central nervous structures. Since the parallelism between changes in cortical potentials and the state of awareness is well established, there arises the question of the extent to which these cortical changes are related to different degrees of activity of hypothalamic centers.

The evidence for a hypothalamic-cortical "upward discharge," presented elsewhere,* may be briefly summarized. Bilateral hypothalamic lesions cause a reduction in cortical activity, indicated by large, slow potentials or by the almost complete disappearance of brain waves. This suggests that hypothalamic discharges exert widespread effects on cortical activity, whereas thalamocortical connections affect specific projection centers of the cortex. Similarly, stimulation of the hypothalamus, and particularly of the area of the mammillary bodies, with condenser discharges abolishes "Dial" potentials in the cortex of both hemispheres, and the injection of strychnine into the same part of the hypothalamus results in the appearance of strychnine spikes in both cortices. Finally, the diminution of cortical activity in asphyxia leads to activation of a strychnine focus in the hypothalamus and the appearance of synchronous strychnine spikes in all parts of the cortex (Gellhorn, Ballin, and Riggle).†

The Role of the Diffuse Thalamic Systems

These observations showing that the hypothalamus influences the activity of the whole cerebral cortex raise the question of the part played by thalamic nuclei in the maintenance of wakefulness and arousal as well as in the production of sleep. Is sleep simply an act of inhibition of the posterior hypothalamic center of wakefulness, or does it also result in discharges to the cortex which lead to a reduction in cortical activity through a specific mechanism and not alone through a diminution of the hypothalamic-cortical discharge? This

* The dependence of cortical activity on the hypothalamus is amplified by anatomical studies. LeGros Clark (230b) presented evidence for the role of the dorsomedial nucleus (cf. also Murphy and Gellhorn's strychnine studies) of the thalamus as a link between hypothalamus and cortex, and Meyer and Beck (928) inferred from their studies on human material that this nucleus relates impulses from the hypothalamus to the frontal lobe and particularly to its orbital surface.

† See p. 152.

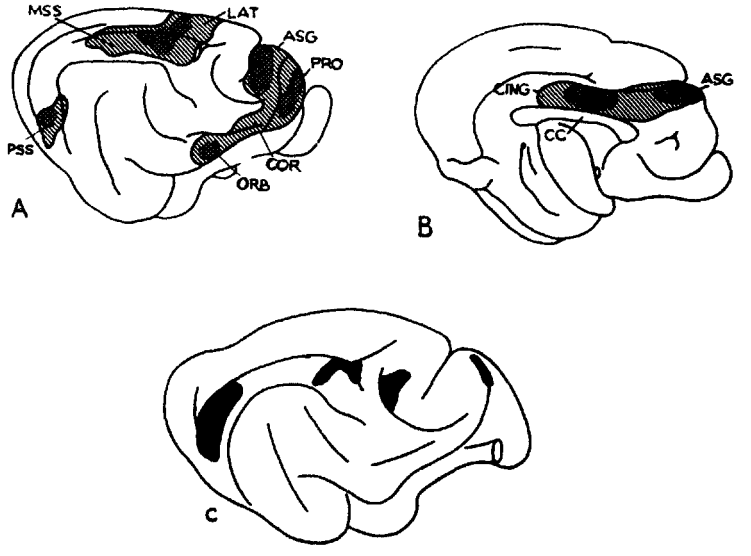

FIGURE 54. Views of the lateral (Fig. A) and medial (Fig. B) aspects of a hemisphere of the cat, with the cortical regions from which recruiting responses may be recorded shown by cross-lining. The darker-shaded zones indicate the most responsive areas. ASG, anterior sigmoid gyrus; CC, corpus callosum; CING, cingulate gyrus; COR, coronal gyrus; LAT, lateral gyrus; MSS, middle suprasylvian gyrus; ORB, orbital gyrus; PRO, gyrus proreus; PSS, posterior suprasylvian gyrus. (Starzl and Magoun, 1134.)

The bottom figure (C) shows the cortical suppressor areas of the cat's brain. (Garol, 413.)

question cannot be answered with certainty at present, but attention is called to the fact that two types of diffuse cortical discharges can be initiated from the thalamus. The first is the recruiting response of Dempsey (274, 275) and Morison (945, 946) which causes a gradual increase in the amplitude and a "waxing and waning" of potentials in both cortices. It is evoked by low-frequency stimulation of the medial and dorsal nuclei of the diffuse thalamic system.* This system projects to the gyrus cinguli at the mesial side of the brain and to those parts of the lateral surface which are not occupied by the visual, auditory, and somatic projection areas. As a comparison of A, B, and C in Figure 54 indicates, *this thalamic system projects to all cortical suppressor areas* and their immediate vicinity.

The second type of diffuse cortical response is induced by stimula-

* Center median, intralaminar, anterior, ventralis anterior, and anterior reticular nuclei (Starzl and Magoun, 1134).

tion of the ventromedial part of the thalamus,* with an extension to the internal capsule and the reticular nucleus. It results in diffuse asynchrony of cortical potentials like that seen on stimulation of the sciatic nerve. This system is activated by the hypothalamus and subthalamus and by afferent nerve impulses which through their collaterals excite the reticular substance in the brain stem (1135b). The excitation is conducted from the reticular substance to subthalamus and hypothalamus and from there to the cortex.†

The importance of the second diffuse projection system for the maintenance of wakefulness will be shown in the following section by the study of arousal reactions. The relation of the first system to sleep is still problematic, but it appears significant that stimulation of the intralaminar thalamus produces sleep, calls forth the recruiting response of the cortex, and sends impulses to the cortical suppressor areas. Hunter and Jasper (718) claim that stimulation of these nuclei elicits the "arrest reaction," which closely resembles the symptoms of the petit mal attack, and typical spike and dome patterns in the cortex and thalamus. Although recent work (1134) does not quite confirm the identity of the sites responsible for the recruiting response and the petit mal potentials, it is not unlikely that these adjacent thalamic nuclei are functionally interrelated ‡ and involved in physiological and pathological changes in the state of consciousness.

Many details are still unknown concerning the interaction of the thalamus, hypothalamus, and cortex and their relation to various states of consciousness, but it may be assumed that variations in the activity of the posterior hypothalamus determine the cycle of sleep and wakefulness. The importance of afferent and particularly proprioceptive impulses for the level of awareness has been emphasized (129, 780); their relation to hypothalamic activity will now be discussed.

The Arousal Reaction

It will be shown that different degrees of awareness and the level of activity of the cortex and diencephalon are correlated. These

* "Ventromedial portion of the thalamus including ventromedial and most of the ventrolateral nuclei" and more anteriorly the reticular nucleus (1135a).

† Starzl, Taylor, and Magoun (1135a) present evidence that discharges from the reticular activating system in the brain stem may reach the cortex from the subthalamus and hypothalamus directly, through the internal capsule – i.e., without intervention of the thalamus. Such a direct hypothalamic-cortical path was shown to be in part responsible for hypothalamic-cortical discharges in the earlier work of Murphy and Gellhorn (958).

‡ According to Rose and Woolsey (1063) the midline nuclei do not project to the neocortex directly but affect it through a series of intrathalamic delays (see also McLardy, 917a).

experimental observations seem to provide a physiological basis for an understanding of the material basis of consciousness.

Berger (87) was the first to note that attention, mental activity, or afferent stimuli – for instance, those involved in the fixation of a visual object – lead to a decrease in cortical alpha potentials in man. The synchronous activity of numerous cortical neurons maintained by thalamocortical impulses and reinforced by corticothalamic excitation (Dusser de Barenne and McCulloch, 304) is interfered with by afferent stimuli, which increase the discharge rate of cortical neurons without inducing a uniform pattern of discharge. As a result, alpha potentials are blocked and smaller and faster "beta" potentials, which are most prominent in the frontomotor leads, are recorded (253). If the attention is specifically directed toward certain sensory stimuli, this blocking effect may be relatively localized. Thus Adrian (11) showed that listening to the ticking of a watch does not alter the alpha potentials in the occipital part of the skull, which is not concerned with acoustic perception, but visual attention leads to their replacement by beta waves. In general, however, changes in attention cause a blocking of alpha potentials in wide areas of both cortices.

Rheinberger and Jasper (1044) made pertinent observations in unanesthetized or lightly anesthetized animals in which previously several electrodes had been inserted between the skull and dura. They noted that the extent and degree of cortical activation increase with the general responsiveness of the animal. In addition they presented good evidence for the fact that acoustic stimulation may abolish the relatively slow and large cortical potentials which are seen in the resting animal and induce small, fast potentials; this cortical response is comparable to the blocking of the alpha and the appearance of beta potentials in the human EEG.

In the human being the application of stimuli at various stages of sleep leads to an "arousal reaction" which is characterized by a relatively long latent period (100 milliseconds or more) and is composed of slow and fast waves, the latter being superimposed on the former. This response (264) is recordable from all parts of the skull, a fact indicating a generalized reaction, but it is more pronounced in frontal and central than in temporal and occipital areas. The fast components appear frequently in the form of 14-per-second spindles, as in normal sleep. In the light of previous discussions this generalized discharge suggests the activation of the hypothalamic center of wakefulness which, via the second diffuse thalamic system discussed earlier, stimulates the whole cortex.

This excitation may appear in two different degrees in man, indi-

cated by the absence or presence of palmar sweating,* which is known to originate in cortical frontal sympathetic centers. If the arousal reaction is not accompanied by the galvanic reflex, a lesser degree of awareness, characterized by a lack of orientation, exists (Darrow, 253). Similar observations can be made in animals. In the waking state the cat responds to slight stimuli with an orientation reaction and an apparently cortically induced sympathetic discharge leading to a contraction of the nictitating membrane. This reaction is abolished by light anesthesia.† We conclude with Darrow that in the normal organism subcortical discharges induced through afferent stimuli lead to such a degree of activation of the frontal cortex that cortical sympathetic centers are excited. Under these conditions a high degree of awareness exists.

Further Studies on the Arousal Reaction and Its Relation to the Activity of Subcortical Structures

The action of afferent impulses on the cortex of the brain has been studied by many investigators and particularly, to mention only the foremost, by Adrian (8, 9), Bard (68), Bremer (128), and Woolsey (1247, 1248). In most instances the animals were deeply anesthetized so that the spontaneous activity of the cortex was minimal. Under these conditions even very slight stimuli, such as touch or pressure applied to a hair of the skin, elicited cortical potentials in a small part of the specific projection area of the medial lemniscus and the spinothalamic systems. This is the basis of the delimitation of these areas and that of their numerous smaller subdivisions. On the other hand, studies of the arousal reaction in man and animals revealed widespread cortical effects. Localized reactions occurred in deeply anesthetized and apparently unconscious animals, while diffuse cortical changes, observed in unanesthetized animals, were accompanied by the well-known signs of increased attention (turning of the head, pupillary dilatation, etc.). To explain the basic difference between these reactions, a systematic investigation was carried out in which the action of optical, acoustic, proprioceptive, and nociceptive impulses was studied at different levels of anesthesia on the cortical potentials in monkeys and cats and correlated with the state of awareness noted in the experimental animals (93, 473).

It was first observed that in the state of light pentothal anesthesia the nature of the afferent impulses determines to a large extent the

* The so-called psychogalvanic reflex.

† In this condition signs of sympathetico-adrenal discharge which are of subcortical origin may appear as the result of afferent stimulation (511).

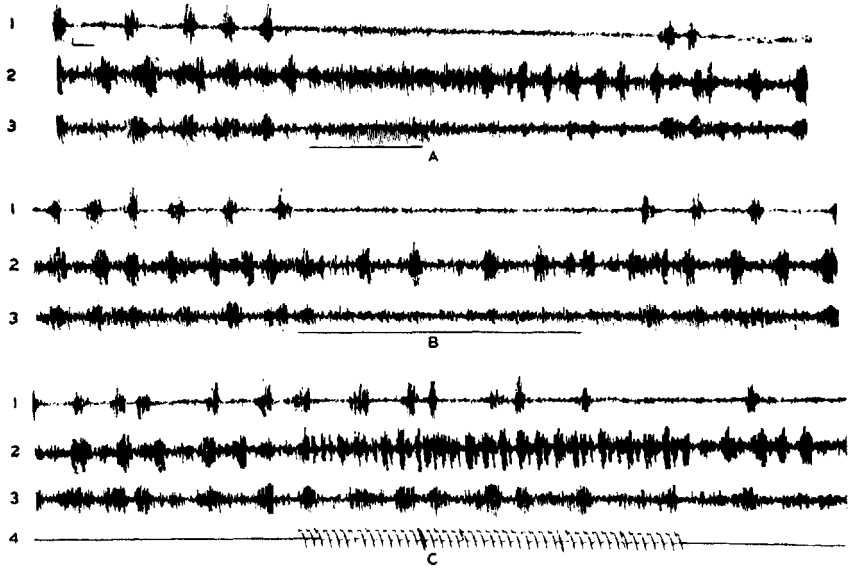

FIGURE 55. Records showing the specific cortical auditory response to acoustic stimuli and the generalized cortical activation through nociceptive and proprioceptive impulses. Record 1 of each series is from the left sensorimotor area; record 2, the left primary auditory area; record 3, the left optic area. *Records A:* generalized cortical response to nociceptive stimulation. *Records B:* partially generalized cortical response to proprioceptive stimulation. *Records C:* specific cortical response to auditory stimulation. Line 4 under series C indicates the acoustic stimuli. (Gellhorn and Bernhaut, 473.)

type of cortical response. Figure 55A shows that nociceptive stimulation eliminates barbiturate potentials, characterized by grouped outbursts of activity in all cortical areas. The excitation appears in the form of potentials of greater frequency and amplitude than the background potentials recorded before the application of this stimulus. They are therefore interpreted to be the result of increased asynchrony in the cortical discharges *and* of the recruitment of additional neurons. The effect greatly outlasts the duration of the stimulus in most cortical areas, the most profound alteration of potentials appearing in the sensorimotor cortex.

Proprioceptive stimulation induced by passive movements results in this experiment in an incompletely generalized response, since the excitation appears in some specific projection areas (the sensorimotor cortex and occipital lobe) while other areas (e.g., the auditory cortex) remain unchanged (Fig. 55B). Finally (Fig. 55C), acoustic stimuli cause a typical response in the auditory cortical area, but no changes

in other parts of the cerebral cortex. From this and similar experiments it is concluded that the effectiveness of afferent impulses in producing a generalized cortical reaction increases according to the following series: optic, < acoustic, < proprioceptive, < nociceptive. Even in animals which had been anesthetized 24 hours before the observation and thus were relatively "light," optical stimuli hardly ever elicited a reaction outside the optical projection area. On the other hand, nociceptive stimuli failed to cause general reactions only in very deeply anesthetized animals.

Generalized cortical reactions were accompanied by signs of arousal. Thus in a monkey anesthetized with "Dial" 24 hours before the experiment, proprioceptive stimulation* caused the disappearance of "Dial" potentials in all cortical areas and evoked movements of one or more limbs, whereas acoustic stimuli elicited only a specific cortical reaction in the auditory projection area, but no movements. Similar results were obtained in other experiments, although the signs of awareness were variable, and not infrequently opening of the eyelids, movements of the eyes, and pupillary dilatation appeared instead of or in combination with movements of the extremities.

The relation between cortical reactions to various stimuli and the state of consciousness is well illustrated by comparing potentials and behavior in different states of anesthesia. Figure 56 shows the response to proprioceptive stimulation a few hours after the induction of pentothal anesthesia and 24 hours later. In the former condition

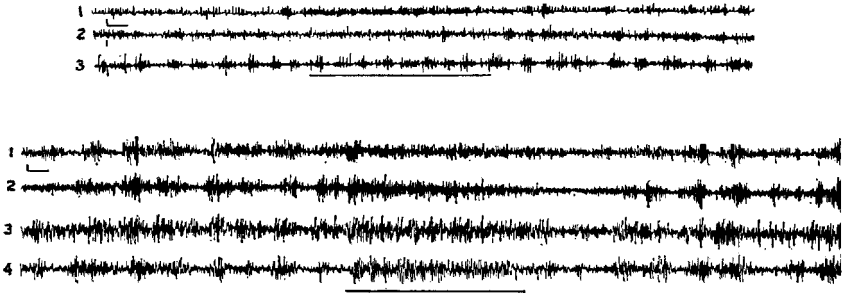

FIGURE 56. The effect of proprioceptive stimulation on the cortex of a cat a few hours after being anesthetized with pentothal (top records) and 24 hours later (bottom records). *Top records:* 1, left sensorimotor area; 2, left auditory area; 3, left visual area. Proprioceptive stimulation of both hind legs for 18.5 seconds. Excitation is confined to the sensorimotor cortex. *Bottom records:* 1, left sigmoid gyrus; 2, left gyrus proreus; 3, left auditory area; 4, left suprasylvian gyrus. Proprioceptive stimulation of one hind leg for 14 seconds. Excitation is generalized. (Gellhorn and Bernhaut, 473.)

* Induced by passive movement of one extremity.

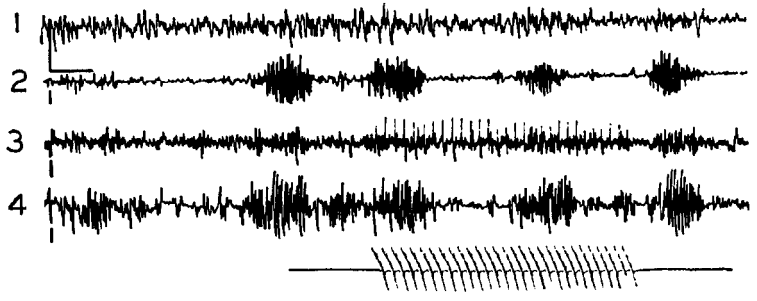

FIGURE 57. Records showing the effect of acoustic stimulation on the hypothalamus and cortex of a "Dial" cat. The response is specific for the auditory area. *Record 1:* left lateral mammillary nucleus. *Record 2:* left sensorimotor area. *Record 3:* left primary auditory area. *Record 4:* left visual area. (Gellhorn and Bernhaut, 473.)

the response is specific (excitation in the sensorimotor cortex only) and not accompanied by any signs of increased awareness; in the latter the reaction is present in all cortical areas, outlasts the duration of stimulation, and is accompanied by spontaneous movements during and after the stimulation period. Conversely it was found that with increasing degrees of anesthesia the generalized cortical reaction passes over into a specific one and the signs of awareness diminish or disappear. Similar observations were made in the monkey and showed a parallelism between general cortical reactions and signs of awareness (blinking, eye or leg movements).

These experiments show that afferent impulses may affect cortical activity in two different ways, depending on the nature of the sense organs involved* and the state of anesthesia. The specific cortical response, in contradistinction to the generalized cortical reaction, is not accompanied by ocular or other signs of arousal. Since it was noted earlier that nociceptive stimuli cause bilateral cortical excitation and the disappearance of "Dial" potentials in the hypothalamus (Gellhorn and Ballin, 466) it was thought that hypothalamic excitation, arousal, and generalized cortical excitation were interrelated. This is indeed the case in both monkey and cat. Figure 57 shows that acoustic stimulation eliciting only a specific cortical reaction leaves hypothalamic potentials as well as cortical activity outside the acous-

* The intensity of the acoustic stimulation plays a minor role in the type of cortical reaction produced; increasing the loudness of a sound did not change a specific cortical reaction to a generalized one under the same conditions of anesthesia. However, nociceptive stimuli of near-threshold intensity may be less effective than strong proprioceptive stimuli.

tic projection area unchanged. Proprioceptive and nociceptive stimuli (Fig. 58), however, induce excitation in the hypothalamus and large parts of the cortex. The degree of generalized cortical excitation seems to parallel that of the hypothalamus. Recent studies in collaboration with Dr. W. P. Koella show that hypothalamic lesions interfere with the generalized response without abolishing the specific cortical reaction (790).

By systematically investigating various parts of the diencephalon, it was found that the generalized response to nociceptive stimuli is abolished by foci in the posterior hypothalamus. Extensive lesions in the anterior hypothalamus, however, do not alter the generalized cortical excitation to nociception. Lesions in the ventral medial thalamic nuclei and the subthalamus (above the posterior hypothalamus) are as effective as destruction of the posterior hypothalamus. If the lesions are unilateral, their effect is confined to the ipsilateral side. Thus Figure 59 illustrates that before the lesion nociception causes a generalized cortical excitation characterized by disappearance of the "Dial" potentials and increased frequency and amplitude of the "background" potentials. After a lesion in the left ventral medial thalamus extending partially into the subthalamus and posterior hypothalamus, the action of nociception is confined to the cortex contralateral to the side of the lesion.

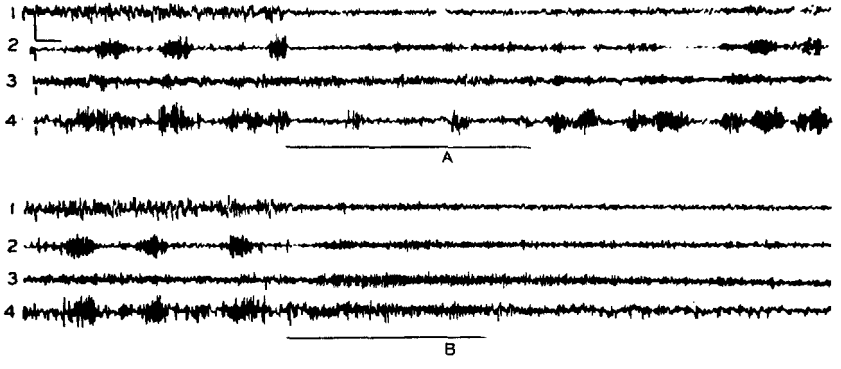

FIGURE 58. Records showing the effect of proprioceptive (series A) and nociceptive (series B) stimulation on the hypothalamus and cortex of a "Dial" cat (same animal, same experiment as in Figure 57; records 1–4 from same areas). *Records A:* partially generalized cortical response, with activation of the posterior hypothalamus; excitation in the lateral mammillary nucleus (record 1), sensorimotor and optic areas (records 2 and 4); no excitation in the auditory area (record 3). *Records B:* generalized cortical response, with activation of the posterior hypothalamus. (Gellhorn and Bernhaut, 473.)

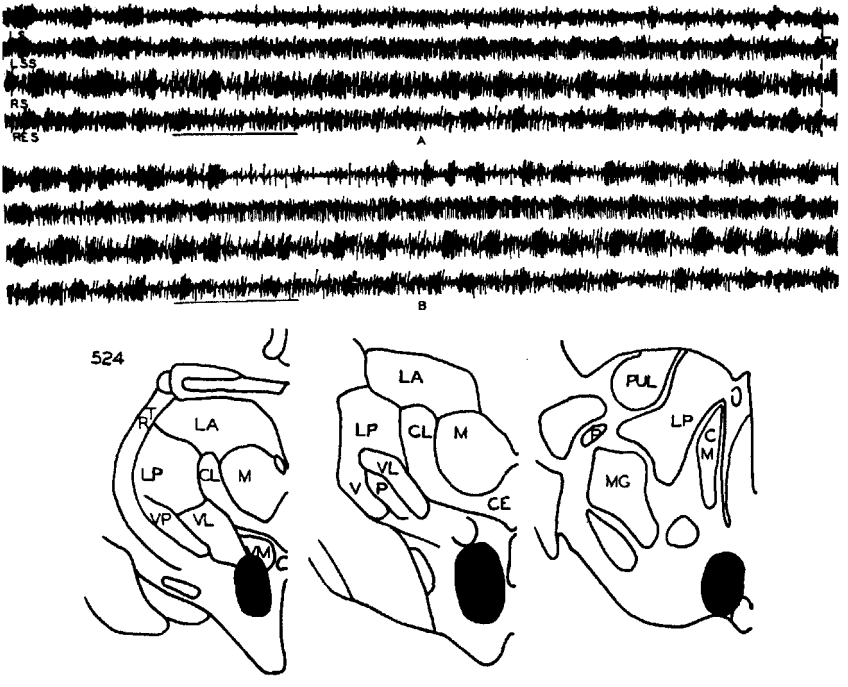

FIGURE 59. *Top:* The effect of nociceptive stimulation (right hind leg immersed in water of 60 degrees centigrade for 15 seconds) on the electrocortigram of a cat. Calibration: 30 microvolts. Time: 1 second. LS, left sigmoid gyrus; LSS, left suprasylvian gyrus; RS, right sigmoid gyrus; RES, right suprasylvian gyrus. *Records A:* before coagulation in the right hypothalamus. *Records B:* after coagulation in the right hypothalamus.

Bottom: Localization of a lesion involving the right posterior hypothalamus and extending to the ventral thalamus. CL, n. centralis lateralis; LA, n. lateralis anterior; LP, n. lateralis posterior; M, n. dorso-medialis; RT, n. reticularis; VL, n. ventralis lateralis; VM, n. ventralis medialis; VP, n. ventralis posterior. (Koella and Gellhorn, 791.)

It may be concluded from these investigations that afferent impulses of nociceptive (or proprioceptive) origin which cause arousal reactions activate the hypothalamic-cortical system. The ventromedial part of the thalamus seems to be the chief thalamic relay in the transmission from the hypothalamus to the cortex. Apparently, cortical activity is influenced by afferent impulses not only via the spinothalamic system but also through the hypothalamic-cortical system.*

* It should be added that a diffuse cortical excitation results from stimulation of certain cortical areas such as the anterior limbic area and parts of the "rhinencephalic" cortex (postorbital and piriform gyri). According to Kaada (743) the thalamic reticular system and the hypothalamus are involved in this reaction.

The latter involves the diffuse thalamic system (1135a). If both systems are activated, a high degree of cortical excitation and awareness ensues. Anesthesia diminishes the reactivity of the hypothalamic-cortical system more than that of the spinothalamic system. Consequently, specific responses due to activation of the spinothalamic system remain in deep anesthesia in which consciousness is completely abolished.*

The responsiveness of the hypothalamic center of wakefulness as well as the nature of the afferent impulses seems to determine whether afferent stimuli will cause changes in consciousness. Those stimuli which induce arousal activate the hypothalamic-cortical system, and the degree of arousal is paralleled by the degree of activation of this system. If it is permissible to assume a correspondence between the degree of subjective consciousness and the intensity and duration of the objective signs of awareness (eye movements, pupillary dilatation, blinking, movements of the extremities), it may be said that consciousness is a function of the activity and responsiveness of the hypothalamic-cortical system. This statement is in agreement with the fact that somnolence results and cortical activity disappears almost completely if through large hypothalamic lesions the hypothalamic-cortical impulses are eliminated (Obrador, Kennard, and others).

It is of considerable interest that unilateral lesions affecting the hypothalamus or the hypothalamic-cortical projection via the ventromedial part of the thalamus change the cortical potentials on the ipsilateral side. The excitatory pattern (frequent, small potentials) forming the "background" activity is greatly reduced, and the grouped "Dial" potentials become more marked † and appear in shorter intervals than before the lesion. The effect of such a lesion is similar to that produced by the administration of added amounts of barbiturates.‡

Application to Problems of Epilepsy: The Hypothalamus and the Spread of Convulsive Activity

The investigations reported in the previous section are also of interest for questions which lie outside the problem of consciousness. Their significance for the physiology of convulsions seems to warrant a brief discussion. If the spread of cortical excitation in response to

* Sectioning of the thalamic projection to the cortex abolishes cortical potentials in deeply nembutalized cats in which the hypothalamic-cortical system is functionally eliminated (840). This illustrates the dual mechanisms on which cortical potentials (and the maintenance of consciousness) depend.

† See Ingram *et al.* (726).

‡ See p. 481.

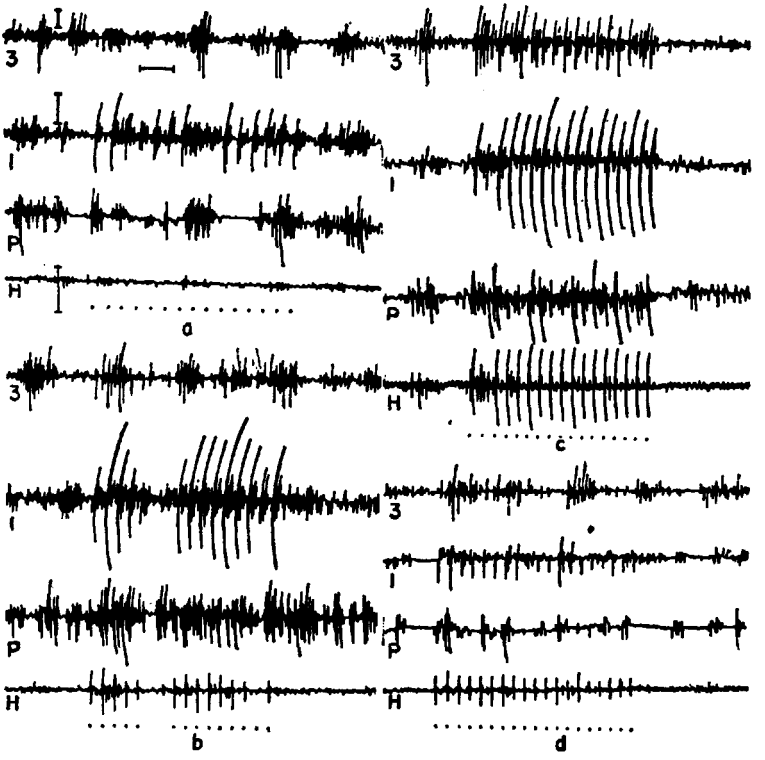

FIGURE 60. The effect of a convulsant on the hypothalamic-cortical response to acoustic stimulation. The stimulation is indicated for each series by a row of dots. The record labeled 3 of each series is from the motor area; record 1, from the auditory cortex; record P, from the occipital suppressor area; and record H, from the posterior hypothalamus. *Records a:* control. *Records b:* 31 minutes after the intravenous injection of picrotoxin, 0.7 mg/Kg, in a cat. *Records c:* 71 minutes after. *Records d:* 95 minutes after. (Gellhorn and Ballin, 467.)

afferent stimuli depends on the excitation of the hypothalamus and its state of reactivity, the hypothalamic-cortical mechanism may be of great import for the transmission of convulsive discharges, particularly under the influence of afferent impulses. This is confirmed by the following observations. In deep barbiturate anesthesia, acoustic or optic stimuli affect, as we have seen previously, only the specific cortical projection areas and do not alter hypothalamic potentials. However, on continuous intravenous injection of a convulsive drug such as picrotoxin, leading to progressive degrees of picrotoxinization, the cortical responsiveness to afferent stimuli increases *and a general-*

ized cortical excitation develops at the time at which the hypothalamus reacts to the afferent impulses (Fig. 60). Similarly it is seen that as the effect of picrotoxin recedes with the lapse of time, hypothalamic and generalized cortical reactivity to afferent stimulation decline *pari passu* (467, 468).

These experiments indicate that generalized convulsive activity induced by afferent stimulation occurs only when the hypothalamus is involved. Convulsive potentials as such have no tendency to spread beyond the activated specific projection areas when the hypothalamus is not sufficiently reactive to the afferent impulses employed. This appears to be the explanation of the fact that local strychninization of the acoustic projection area in deeply anesthetized cats does not produce a convulsive response of the cortex to acoustic stimulation outside the temporal lobe. The same mechanism which accounts for increased awareness in the normal organism is, in an animal predisposed to convulsions by the systemic injection of a convulsant, responsible for the spread of convulsive activity over the cortex of both hemispheres: in both conditions the excitation of the hypothalamic-cortical system is the causative factor.

~ 10 ~

The Pathology of Consciousness

The Physiology of the Phantom Limb

One of the conclusions reached from the experimental work described in the preceding chapter, namely, that characteristic differences in arousal value exist between various sensory modalities and that arousal reactions are related to the phenomenon of consciousness, is supported by clinical experiences of an entirely different kind – the study of the factors which determine the appearance of a phantom limb in patients with an amputated extremity. Such an investigation illuminates solely one sector of the problem of consciousness – the role of afferent impulses – but it supplements the work on experimental animals in which the state of awareness can only be *inferred* (from certain movements). In contradistinction to other clinical conditions which have been used for the neurological analysis of the basis of consciousness, the causes of a phantom limb can be analyzed in patients whose subjective reports are reliable, since there is neither brain pathology nor cloudiness of perception.*

The fact that after the loss of a leg an interval of varying duration occurs during which no phantom limb appears – and in a small percentage of cases a phantom limb may never be felt – suggests that it takes time until peripheral irritating factors develop. That the latter are responsible is inferred from the temporary loss of the phantom limb after infiltration with novocaine. Surgical procedures (tight ligature around the nerve trunk) above the injury which minimize scar formation and inflammation at the nerve endings are said to reduce the occurrence of a phantom limb.

It is not surprising that local excitation of the trunk of a peripheral

* For further details see Ebbecke (309) and Riddoch (1053).

nerve is subjectively interpreted as a sensory experience originating in the peripheral parts of the body. As a matter of fact, this projection and objectivation of our sensations has been known for more than a hundred years. Pressure on a peripheral nerve when an "arm goes to sleep" is felt particularly in the fingers and hand. Stimulation of such an arm nerve with the galvanic current gives similar results and illustrates under strictly controlled experimental conditions that this type of unphysiological stimulation is accompanied by sensations which are projected into the fingers and hand.

There is a peculiar parallelism with respect to consciousness between a patient with an amputated leg who shows no irritation of the nerves in the stump and consequently has no phantom limb, and a person or animal with a deafferented extremity. There is no phantom limb in the one case and no awareness of the existing extremity in the other. If no afferent impulses reach the cortex of the brain from the stump or the existing but deafferented limb, the extremity and particularly its distal parts do not appear in consciousness. This loss of awareness of a part of the body is well illustrated by the fact that animals chew on a deafferented extremity.

The observations indicating that the awareness of a real or phantom limb depends on afferent impulses raise two important questions: (1) Do all afferent impulses contribute equally to the conscious appearance of a part of the body? (2) To what extent do observations on patients with a phantom limb reveal the central action of these afferent impulses?

That nociceptive impulses are chiefly involved in the causation of a phantom limb is illustrated by the parallelism between the frequency of pain originating in the stump and the appearance and vividness of the phantom limb. Local anesthesia and particularly operative procedures leading to the interruption of the transmission of nociceptive impulses arising in the stump may eliminate the phantom limb as long as the pain is held in abeyance. Moreover a weak phantom limb may become intensified by mechanical and electrical stimulation of the stump (309). Under such conditions the patient is able to distinguish between the sensation of touch which appears in the stump and the paresthesia or sensation of pain appearing in the toes of the phantom limb.

Proprioceptive impulses also contribute to the phantom limb, since it is commonly felt to be in a certain position, but touch and temperature sensations do not play any role in this respect. Since the latter are exteroceptive and the former interoceptive in origin, it may be said that the body scheme is primarily built on the basis of interocep-

tive sensations.* The failure of a hemiplegic to be aware of a paralyzed arm or leg is due to the absence of proprioceptive impulses, while the absence of a phantom limb in cases of amputation is accounted for by the lack of irritation affecting proprioceptive and/or nociceptive nerve fibers in the stump. This differentiation between exteroceptors and interoceptors in relation to consciousness, inferred from the study of patients with a phantom limb, is interesting in the light of the previously reported experiments showing that the excitation of interoceptors produces signs of general cortical excitation and arousal reactions in lightly anesthetized animals, whereas mere pressure on a limb or exposure to cold and warm temperatures rarely if ever elicits these phenomena but results solely in a cortical excitation restricted to the specific projection area. It seems to follow that not only the transition from sleep to the waking state but also the appearance of a phantom limb involves the activation of the hypothalamic center of wakefulness, since the afferent impulses leading to awareness of a nonexisting limb are those which pre-eminently activate the hypothalamic-cortical system. Moreover the nociceptive system is in this respect more effective than the proprioceptive, and the former is the one largely responsible for the appearance of the phantom limb.

Under strictly physiological conditions proprioceptive impulses seem to contribute primarily to the maintenance of consciousness. This is evident from their role in wakefulness and the loss of awareness of a limb following deafferentation. These impulses provide a sufficient background of cortical activity to make the various parts of the gray mantle responsive to messages reaching the brain via specific afferent systems, including those of the distance receptors, and thereby enable the individual to react appropriately to environmental stimuli. However, the proprioceptive system does not represent anything unique as far as the creation and maintenance of consciousness are concerned. If this interpretation is correct, any interoceptive system † capable of exciting the brain as a whole should be able to produce a similar effect. The nociceptive system, which is activated from the surface of the body and from the muscles and viscera, fulfills these requirements particularly well. Its great effect on the cortex of the brain, indicated by the prolonged action on the hypothalamic-cortical system of a stimulation of nociceptive nerves, makes understandable the fact that it may create a pathological state of awareness, illustrated in the phantom limb, which persists in the consciousness of the patient in

* Pain belongs to exteroceptive and interoceptive sensations.

† The relation of the vestibular apparatus to the hypothalamic-cortical system has not been adequately investigated, but investigations by Gerebtzoff (528) suggest that it may likewise affect the hypothalamus.

spite of the fact that visual perception and reason flatly deny its existence.

The observations on patients with a phantom limb give no direct evidence of the activation of the hypothalamic-cortical system, but furnish certain data about the organization of the sensory cortex in man that supplement those based on recordings of the electrical potentials in the hypothalamus and cortex of experimental animals and are important for the analysis of consciousness. The projection of proprioceptive impulses to the sensorimotor cortex (416) has been discussed, and although details remain to be worked out, the general topography of the cortical projection area seems to follow that established for touch and pressure. Thus, stimulation of the peripheral end of the motor root S_1 activates, through afferent impulses which reach the brain via the ipsilateral spinal cord (464), mainly the medial section of area 4. Similarly, passive movements of the arm affect the cortical portion of the arm area more than those parts of the motor cortex from which movement of the leg or face can be elicited. The validity of these findings for the human brain is suggested by the work of Dawson (266), who recently presented evidence for changes in the EEG recorded from the central section of the skull as a result of proprioceptive impulses. It should also be mentioned that a painless phantom leg disappears after the removal of the contralateral parietal lobe and that at the same time postural sensations in the stump are lost (Head and Holmes, cited by Riddoch, 1053).

Turning now to nociceptive sensations, it may be said that they represent the common cause of the phantom limb, through the stimulation of nociceptive fibers of the stump. The distal parts (fingers or toes) appear more prominent in the phantom limb than the proximal parts, or the latter (for instance, the knee) may not be perceived at all. The observations suggest that the proximal parts have a lesser thalamic or cortical representation than the distal parts. This conclusion is in line with the cortical organization of the touch and pressure sensations based on electrical stimulation of the postcentral gyrus in man (Penfield and Rasmussen, 1002) and with the topography of this area as disclosed by animal experiments in which cortical action potentials are recorded in response to touch stimulation applied to various parts of the skin (1248).

However, it is problematical whether nociceptive impulses are directly or indirectly involved in the production of the phantom limb. The subjective experience that a phantom limb (or a normal extremity) occupies a certain posture, such as flexion of the fingers or toes, seems to be based on impulses of proprioceptive (and of cutaneous)

origin. Nociceptive impulses could also contribute to the perception of the posture, since mild pain stimuli applied to the skin without contact with the latter (radiant heat) can be localized with a high degree of accuracy (504). Yet such a mechanism is not likely, since the phantom leg is associated with intensive pain sensations which tend to irradiate. It is more probable, therefore, that nociception causing a widespread cortical excitation provides the proper background for the specific but intensified perception resulting primarily from proprioceptive impulses, and thus is indirectly responsible for the appearance of a phantom limb.*

It appears to be justifiable to assume that the awareness of a part of the body is in principle due to the same mechanisms which ultimately lead to the awareness of oneself and one's relation to the environment. Observations on patients with a phantom limb show that its production is due to impulses transmitted by proprioceptive and, to an even greater degree, nociceptive nerves. The preponderance of distal as compared to proximal parts in the subjective appearance of the phantom limb seems to indicate that cortical projection areas are excited. The parietal lobe and particularly the postcentral gyrus (269, 1138) are involved, since their removal may abolish the phantom leg.

In comparing these data with the experimental work in which sensory stimuli, hypothalamic and cortical excitation, and motor signs of awareness were correlated, it is noted that cutaneous receptors for touch, pressure, and temperature neither play a role in the production of the phantom limb nor elicit signs of awareness in the lightly anesthetized experimental animal. However, in this state proprioceptive and particularly nociceptive impulses evoke manifestations of arousal, and the same impulses are thought to be responsible for the phantom limb. Since cutaneous stimuli, such as a light touch, cold, and warmth, undoubtedly excite the cortex, the results indicate that the two groups

* Since pain perception persists after cortical ablation and severe pain may be induced by thalamic stimuli, as shown in Dusser de Barenne's strychnine experiments (302) or seen clinically in thalamic lesion (Déjérine and Roussy), and since stimulation of sensory cortical areas with weak electrical stimuli fails to elicit pain (Penfield and Boldrey, 1001), the contribution of the cortex to the perception of pain is still under dispute. However, Dusser de Barenne noted that the pain reaction caused by injecting strychnine into the thalamus and indicated by the motor behavior of the animal was less well localized after removal of the ipsilateral cortex. Since precise localization is generally considered to be a function of the cortex – it is greatly impaired by cortical lesions – it may be suggested that nociceptive impulses have definite cortical projections. The recent observation that frontal lobotomy diminishes the reactivity to pain does not indicate that pain impulses are projected to the frontal cortex, but rather that the affective responsiveness of the patient has been diminished (334).

of impulses activate the cortex through different mechanisms. Since even in deep anesthesia the sensitivity of the postcentral gyrus to minimal cutaneous stimuli or the responsiveness of the auditory and visual projection areas to acoustic and optic stimuli of low intensity is very great, it follows that awareness is not simply a function of the specific sensory projection system. Previous work showed the importance of the hypothalamic-cortical system in this respect and the great affinity of proprioceptive and nociceptive impulses to this system.

The appearance of the phantom limb is in most instances due to the stimulation of nociceptive fibers, whereas the loss of consciousness of an existing part of the body is caused by the fact that proprioceptive impulses can no longer reach the cortex of the brain. Physiologically it is the proprioceptive sense which is primarily involved in our being conscious of the various parts of our body, whereas under pathological conditions proprioceptive excitation leads only infrequently to the phantom limb. It is not surprising that the phantom limb and its persistence in consciousness are commonly associated with the excitation of pain nerves which activate the hypothalamic-cortical system to the highest degree. This system provides the background on which specific sensory patterns activated by proprioceptive and other impulses are superimposed. The result of this interaction is the phantom limb.

On the Difference between Sleep, Anesthesia, and Experimental Coma

For the present let us exclude from our consideration the coma resulting from cerebral trauma or lesions in various parts of the brain and restrict the discussion to a comparison between natural sleep and those sleeplike conditions which, occurring in anesthesia and experimentally induced coma, elicit reversible functional changes in the central nervous system, with concomitant alterations in consciousness.

Briefly stated, natural sleep is the result of diminished activity of the posterior hypothalamic center of wakefulness, probably induced by increased discharges from the anterior hypothalamic sleep center. Diminished "downward discharges" of extrapyramidal origin lessen the muscle tone and thereby reduce the feed-back to the waking center. The diminution of sympathetic "downward discharges" from the lateral hypothalamic area and the mammillary bodies leads to a shift in the autonomic balance maintained by the hypothalamus and medulla oblongata. Patterns of parasympathetic innervation become more prominent, as indicated by the narrowing of the pupils. The disappearance in the early phases of sleep of sympathetic impulses of

cortical origin (Darrow) may also contribute to the alteration in the autonomic equilibrium. According to this interpretation, there are parallel changes in hypothalamic and cortical activity, and the functional changes in the latter appear to be due primarily to diminished discharges from the diencephalon.

Other conditions prevail in anesthesia and in certain forms of coma. If the loss of consciousness is induced by anesthesia, the changes in the EEG and ECG are somewhat similar to those seen in sleep. This holds true particularly for the barbiturates, but the cortical potentials in ether or chloralose narcosis are different. Cortical excitability is decreased in all forms of anesthesia, as indicated by a diminished responsiveness to arousal stimuli and an increased tendency to synchronous potential discharges. The brain stem, however, seems to behave quite differently, as indicated by certain autonomic reactions. The increased blood-sugar level seen in ether and barbiturate anesthesia is due to a sympathetico-adrenal discharge, since it is absent after adrenalectomy (446). Although such a rise in the blood sugar is not found in chloralose anesthesia, the centers of the sympathetico-adrenal system are in a state of heightened reflex excitability and show increased discharges. This is indicated by the chronically denervated nictitating membrane and pupil, which are highly sensitive to adrenalin and contract and dilate respectively with progressing narcosis (511).

Similar mechanisms seem to underlie the loss of consciousness and coma in anoxia and hypoglycemia. If the coma does not progress too far and is not maintained for too long a period of time, the cortical electrical changes are similar to those observed in deep sleep and are characterized by the appearance of large delta potentials. The autonomic centers in the brain stem are released, as indicated by signs of increased sympathetico-adrenal discharges.* There is also direct evidence of an increased reactivity of the brain stem to direct stimulation in hypoglycemic and anoxic coma. The appearance of increased potentials in the brain stem in anoxia and of spontaneous involuntary movements in hypoglycemia must be interpreted in a similar manner.

In anesthesia and in coma induced by changes in the internal environment (decrease in the oxygen tension or in the blood sugar level) the cortex and brain stem suffer opposite changes in excitability, the reason being twofold: first, the greater sensitivity of cortical as compared to subcortical centers to pharmacological agents such as anesthetics and to alterations in the physiological constituents of the blood; second, the release of the subcortex as the result of diminished

* See pp. 295ff.

cortical activity. In spite of the similar action of sleep, anesthesia, and coma on cortical functions, the mechanism by which these changes are brought about is quite different in the two groups, since the control of sleep lies in the diencephalon, whereas the loss of consciousness in anesthesia and experimental coma is the result of the primary attack of these conditions on the cortex of the brain. This fundamental difference between the behavior of subcortical structures in sleep and in anesthesia is also reflected in the cortical potentials. Very light degrees of pentothal anesthesia (hypnotic stage) in which the patient is euphoric and talkative are accompanied by signs of cortical excitation, since the potentials show high frequency and increased amplitude (1172). Such excitation, which is not present in normal sleep, can hardly be of cortical origin, since cortical excitability as measured by reaction-time experiments is decreased. It is suggested that it is due to the increased activity of the hypothalamus which, as pointed out repeatedly, leads not only to an augmentation of the "downward discharge" but to an increased hypothalamic-cortical excitation as well.*

A Tentative Summary

The experimental work on the relation of the brain stem to the cortex – work that is of great significance for an understanding of wakefulness, sleep, and coma – grows so rapidly in volume and complexity that any attempt to summarize its essential features may appear inadequate. Nevertheless such an undertaking may help the reader visualize the chief factors involved.

The electrical activity of the isolated cortex, although not eliminated, is greatly reduced as compared to the cortical potentials in the intact animal. This shows that impulses from the brain stem are largely responsible for normal cortical activity. These afferent impulses may be divided into three groups: (1) the long tract systems, such as the medial lemniscus and spinothalamic systems, which carry impulses from exteroceptors and interoceptors to specific projection areas; (2) the facilitatory system, which originates in the tegmentum of the midbrain and activates the posterior hypothalamus and thence both cortical hemispheres through the ventromedial group of thalamic nuclei; (3) the diffuse afferent system of Morison and Dempsey, involving the dorsal medial (intralaminar) thalamic nuclei, which likewise influences both cortices but affects particularly the areas

* It goes without saying that with a further deepening of anesthesia and the occurrence of slow potentials in the EEG hypothalamic activity is diminished and hypothalamic downward and upward discharges are reduced (see Chapters 19 and 20).

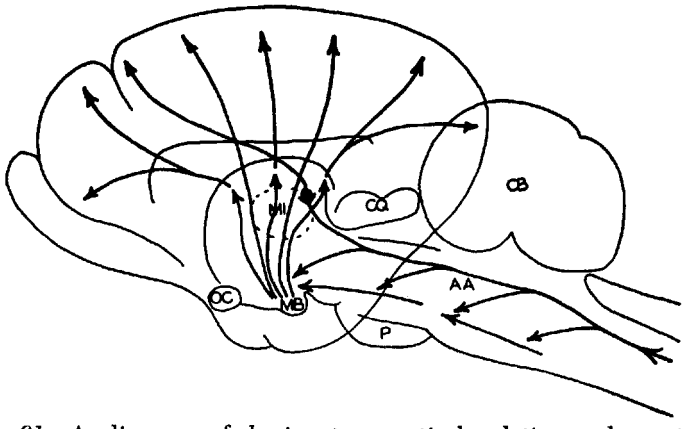

FIGURE 61. A diagram of brain stem–cortical relations: the activating system. AA, Magoun's activating area in the reticular substance; CQ, corpora quadregemina; CB, cerebellum; MB, mammillary body; MI, massa intermedia; OC, optic chiasma; P, pons. The diagram shows the hypothalamic-cortical activation and the dependence of hypothalamic activity on impulses originating in the reticular substance. (W. P. Koella, with utilization of diagrams by Magoun *et al.*)

around the suppressor areas. (See Figures 61–63.) The last system produces on stimulation bursts of slow potentials in the cortex, which are typical of decreased excitability as found in sleep, coma, or surgical anesthesia.

It is noteworthy that stimulation of this intralaminar system produces sleep and arrest reactions, whereas stimulation of the activating reticulo-hypothalamic-cortical system and of any intermediate station, such as the ventromedial group of thalamic nuclei, elicits excitation of the cortex. This appears as arousal and psychomotor excitation following excitation of nociceptive receptors and may lead to the precipitation of convulsions. The electrical equivalent of these excitatory processes is diffuse asynchrony of cortical potentials. There is evidence that centrifugal impulses from the cortex reinforce this facilitatory mechanism.* Judging by the symptoms and the changes in cortical potentials which follow excitation, it is evident that these two diffuse thalamocortical systems influence the gray mantle of the brain in opposite manners.

The diffuse facilitatory system is anatomically sharply separated from the specific-projection system. Nonetheless, it is assumed that

* Bremer (131a) reports in a recent paper that awakening through acoustic stimulation is weakened by extirpation of the auditory projection areas. This suggests that a corticofugal effect reinforces awakening. However, it does not seem necessary to assume with Bremer that this action is exerted on the reticular substance. It appears more probable that the chief effect is on the hypothalamus.

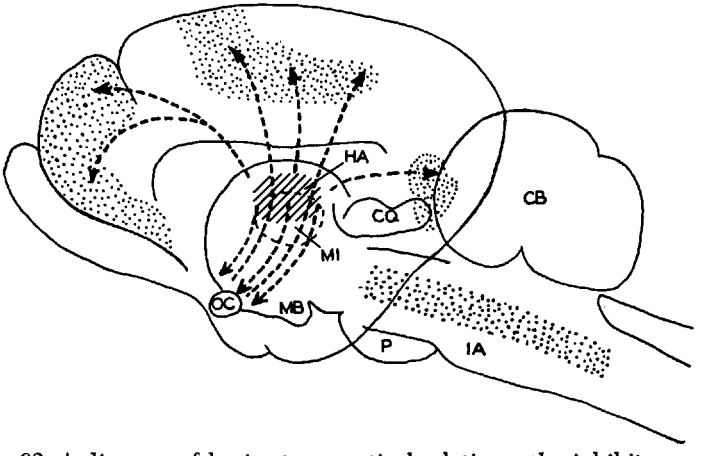

FIGURE 62. A diagram of brain stem–cortical relations: the inhibitory system. CB, cerebellum; CQ, corpora quadregemina; HA, hypnogenic area (Hess); IA, inhibitory area (Magoun); MB, mammillary body; MI, massa intermedia; OC, optic chiasma; P, pons. Stimulation of the hypnogenic area elicits cortical sleep potentials in unanesthetized animals, and excitation of closely related parts of the dorsomedial part of the thalamus calls forth, in anesthetized animals, recruiting responses, particularly from the cortical areas indicated in the diagram. The diagram also indicates that the hypnogenic area may be related to the anterior hypothalamus. (W. P. Koella, with utilization of diagrams by Magoun *et al.*)

both systems are integrated under physiological conditions and make perception possible. The diffuse facilitatory system alone can account for only the lowest degree of awareness because it does not supply the objective content (the sight of an object, etc.) without which consciousness is a philosophic term but not a physiological concept. The specific-projection system cannot work in isolation because without the diffuse facilitatory system the cortex is in too low a state of excitability, marked by large, slow potentials and clinical signs of coma.*

* Although the functional development of the hypothalamic-cortical system relative to that of the long tract systems is not yet known, certain observations which Hill points out are worthy of attention: (1) The blocking response of the alpha potentials in the human EEG through visual stimuli which arouse attention is absent before the third year. (2) The frequencies of the cortical potentials recorded from different parts of the skull show greater differences in the EEG's of children than of adults. (3) Clinical EEG studies on normal and pathological children and young psychopathic adults suggest that a persistence of the slow EEG rhythms of infancy is related to emotional immaturity.

These data suggest that the development of the hypothalamic-cortical system is rather slow. It contributes to the relative uniformity of cortical cerebral rhythms in the adult. It is interesting to note that the prefrontal cortical areas which retain the low frequency of early childhood longest are the first to develop slow rhythms under conditions of anoxia, hypoglycemia, and hyperventilation (Hill, 649a).

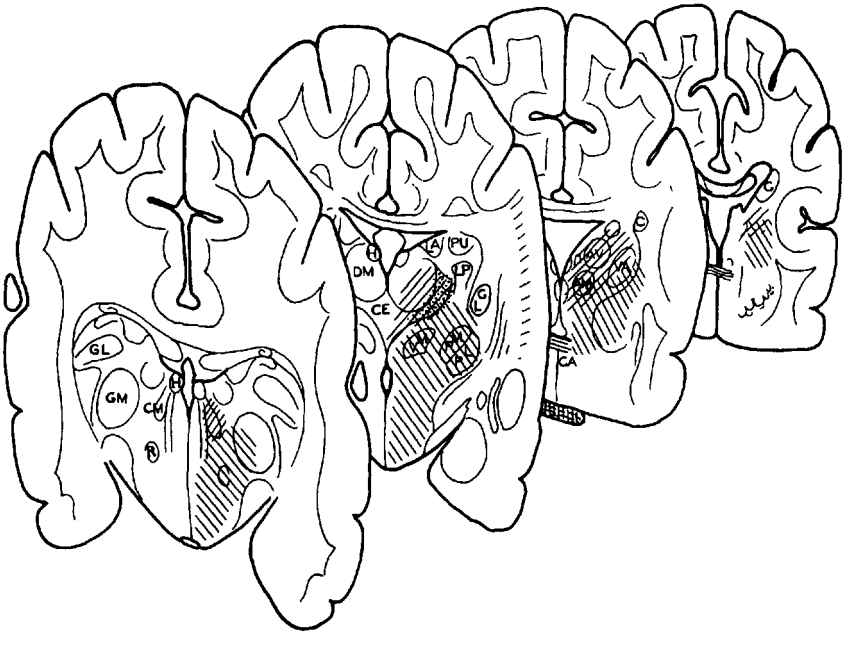

FIGURE 63. A diagrammatic representation of the activating and inhibitory systems on the frontal actions of the cat's brain. The slant lines (//////) indicate the inhibitory zone; the reversed slant lines, the activating zone; the stippled area is the hypnogenic zone. AM, anterior medialis; AV, anterior ventralis; C, caudate nucleus; CA, anterior commissure; CE, centralis medialis; CM, center median; DM, dorsomedialis nucleus; GL, lateral geniculate body; GM, medial geniculate body; H, habenular nuclei; LA, lateralis anterior; LP, lateralis posterior; PL, ventralis postero-lateralis; PM, ventralis postero-medialis; PN, pulvinar nucleus; R, nucleus ruber; VA, ventralis anterior; VM, ventralis medialis. (W. P. Koella.)

The sleep cycle illustrates the intimate interaction between the inhibitory and the facilitatory systems, briefly but inaccurately referred to earlier as centers of sleep and wakefulness. It appears to be probable that from the intralaminar thalamic nuclei the anterior hypothalamus is activated and the posterior hypothalamus is inhibited. Diminished activity of the posterior hypothalamus results in reduced upward and downward discharges and thereby in further enhancement of the state of cortical inhibition.

Sleep and coma are clinically differentiated by different levels of awareness. Physiologically it must be assumed that the transition from wakefulness to sleep involves relatively small changes in the excitability of the posterior hypothalamus, which continues to receive

facilitatory impulses from the activating tegmental system* during the whole diurnal cycle. However, with the loss of the tegmental system the posterior hypothalamus, although still reactive to afferent impulses, is unable to maintain the waking state.

The transition from the waking state to sleep involves a shift in the balance between the inhibitory and the facilitatory thalamocortical systems. At present we cannot point to a single factor as the initiating cause of sleep, but it is quite obvious that many factors tend to alter this delicate equilibrium. The diminution of afferent impulses of proprioceptive and exteroceptive origin weakens the activity of the facilitatory system at the hypothalamic and also at the cortical level. Corticofugal facilitatory impulses, the intensity of which depends on the state of cortical excitation, will be diminished. Consequently the tendency toward sleep will increase.

The evidence of increased reactivity of sympathetic centers in the brain stem in surgical anesthesia and in anoxia and hypoglycemia seems to justify the separation of these conditions of loss of consciousness from natural sleep. As pointed out earlier, the great susceptibility of the cortex to anesthetics, anoxia, and hypoglycemia reduces consciousness in spite of increased subcortical discharges. This phase is followed by one in which hypothalamic reactivity (and consequently hypothalamic-cortical discharges) are likewise diminished.

Lesions in the Brain Stem and Coma

The physiological analysis of consciousness should not be confined to the sleep cycle and those forms of experimental coma which are induced by changes in the internal environment, but should include brain-stem lesions. In addition to the well-known fact that tumors of the hypothalamus, injury to the medial thalamic nuclei, or, generally speaking, conditions which interfere with hypothalamic-cortical discharges are accompanied by somnolence or coma, it was observed by Penfield and others that compression of the mesencephalon and metencephalon leads to loss of consciousness. Martin reported a case involving a lesion in the middle of the pons which caused an irreversible coma.† An increase in pressure in the posterior fossa may induce these symptoms even though the hemispheres are completely normal (White, 1233; Jefferson, 738; and others). These observations raise the question to what extent brain-stem structures caudal to the diencephalon influence cortical activity and the state of consciousness. The bril-

* See the next section of this chapter.

† See also the recent paper by M. Jefferson (739).

liant experimental work of Magoun and his collaborators (848, 952) seems to provide the answer.

Cats with chronic bilateral lesions in the brain stem were studied in their overt behavior and through the reactions of the EEG to afferent stimuli. It was found that lesions in the lateral part of the mesencephalon which eliminate the medial and lateral lemnisci and spinothalamic tracts are not followed by coma. Such animals show normal sleep cycles and are aroused by appropriate stimuli. These states are accompanied by typical changes in the EEG, as in normal animals. However, lesions involving the midbrain tegmentum or extensive destruction of the hypothalamus (726) are associated with somnolence or coma from which the animals can be aroused, but stimuli of greater intensity are required than in normal sleeping cats, and the effect is frequently confined to the period of stimulation. During the arousal the slow, large potentials are replaced by frequent potentials of low amplitude, as in normal cats. The fundamental difference in behavior and potentials between animals in which the central tegmentum is injured and those in which it is spared while the ascending sensory tracts are destroyed is indicated in Figure 64.*

It is of great interest that in human cases with mesencephalic lesions spindles were recorded from the cortex and the posterolateral nucleus of the thalamus which coincided with the occurrence of stupor (Williams and Parsons-Smith, 1235). These observations suggest the applicability of Magoun's work to the human brain.

The relation of the reticular substance in the brain stem to cortical activity and arousal is likewise apparent from stimulation experiments. Activation of the "central core of the brain stem, extending from the bulbar reticular formation forward through the pontile and mesencephalic tegmentum into the caudal diencephalon" abolishes slow chloralosane potentials and induces fast potentials of low amplitude in all parts of the cortex. The widespread effect of this stimulation is

* Acute experiments on Bremer's isolated brain yielded similar results (847). It was shown that mere transection of the brain stem at the first cervical segment does not abolish the normal activity pattern of the EEG. If, however, the lesion is made increasingly rostrally, alphalike potentials and finally spindles and slow, large sleep potentials appear. Systematic exploration of the midbrain revealed that lesions around the aqueduct do not induce sleep potentials. This is the more remarkable as Bailey (60, 61) reported akinetic mutism after such lesions. Sectioning of the sensory pathways (at the level of the anterior mesencephalon) combined with that of the optic nerves and the removal of the olfactory bulbs causes only a slight degree of synchrony in the cortical potentials, but on sectioning of the tegmentum, typical sleep potentials are recorded.

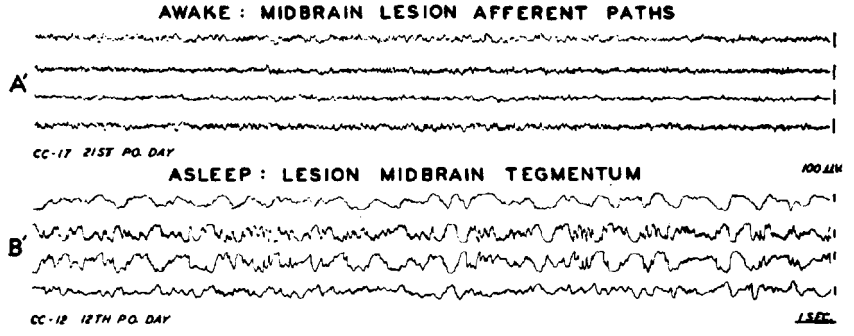

FIGURE 64. *A'*: record from a cat after the interruption of the sensory paths in the midbrain, sparing the central tegmentum; characteristic waking electroencephalogram. *B'*: record after the interruption of the mesencephalic tegmentum, sparing the sensory paths; characteristic strip of the sleeping electroencephalogram. (Lindsley *et al.*, 848.)

similar to that seen in the arousal reaction and involves the same diffuse thalamic projection to the cortex.*

The problem of the physiological basis of consciousness has been put on a firm anatomical basis through these investigations. Apparently the anterior part of the tegmentum sends tonic impulses to the hypothalamus. From there the activation of the cortex proceeds largely through the diffuse (reticular) thalamic system and leads to an arousal reaction.

It is interesting to note that auditory or nociceptive stimuli will awaken animals despite complete interruption in the midbrain of sensory tracts which transmit these impulses in the normal animal to the diencephalon and cortex. As was pointed out earlier, collaterals from these tracts exist which join the reticular substance below the lesions and account for temporary arousal.

One other important difference between the medial lemniscus and spinothalamic systems and the tegmental-hypothalamic-reticular thalamic-cortical system should be mentioned. The former functions in very deep narcosis, as mentioned earlier. This made it possible for various investigators to outline sensory cortical projection areas in conditions in which the spontaneous cortical action potentials were practically abolished. The arousal reactions studied by Magoun and his collaborators and by us require, on the contrary, preparations with

* That stimulation of the reticular substance in the medulla abolishes alpha potentials in the cortex (Moruzzi, 951) is interesting, but it cannot be concluded from these findings that periodically decreased activity of the reticular system is responsible for physiological sleep.

very little or no anesthesia. This suggests that deep barbiturate anesthesia involves the blocking of relays in the reticular system at the mesencephalic or diencephalic level (see Figure 107, p. 481).*

On the basis of this work a scheme seems to evolve gradually which gives the outline of the anatomical and physiological basis of consciousness. It emphasizes the stream of impulses which originate in the reticular substance of the tegmentum and activate the cortex via the hypothalamus and the diffuse thalamic system. These impulses maintain the posterior hypothalamus in a high degree of excitability. Cyclic changes, probably originating in the thalamo-anterior hypothalamic system, temporarily lower this state of excitability and thereby the state of awareness. If the activating reticular impulses are eliminated, a state of coma supervenes which is fundamentally different from sleep in spite of the fact that some degree of arousal is possible in both conditions. It may be added that the transmission of tegmental impulses to the diencephalon is rather easily blocked in this multisynaptic system not only by chemical substances, such as barbiturates, but also by pressure, since coma may result from increased pressure in the posterior fossa, which does not interrupt the conduction of cerebrospinal pathways (Jefferson, 738).

In the investigations described in this chapter emphasis has been placed on the anatomical and physiological separateness of two systems which through the thalamus activate either specific cortical projection areas or the cortex as a whole in unspecific arousal reactions. This division is confirmed by experiments † on the action of carbon dioxide which in non-narcotic concentrations increases diffuse hypothalamic-cortical discharges but diminishes the reactivity of the specific projection systems (462). However, the two systems are functionally interrelated, since afferent impulses, particularly of proprioceptive and nociceptive origin, invade the hypothalamic-cortical system, as our earlier experiments showed. One would assume, then, that cortical activity and thereby alertness are increased as a result of the interaction of the two systems at the cortical level. Such a facilitation of the motor cortex results from the subthreshold stimulation of the hypothalamus (957). Complementary evidence for this phenomenon is found in Hunter's study (717) on the unanesthetized cat, according to which mild hypothalamic stimuli are accompanied by an increased awareness of environmental stimuli. Finally, new experiments show that the acoustic response of the auditory projection area is increased when, through nociceptive stimuli, the hypothalamic-cortical system

* See Chapter 19 for similar changes in high carbon-dioxide anesthesia.

† See Chapter 19.

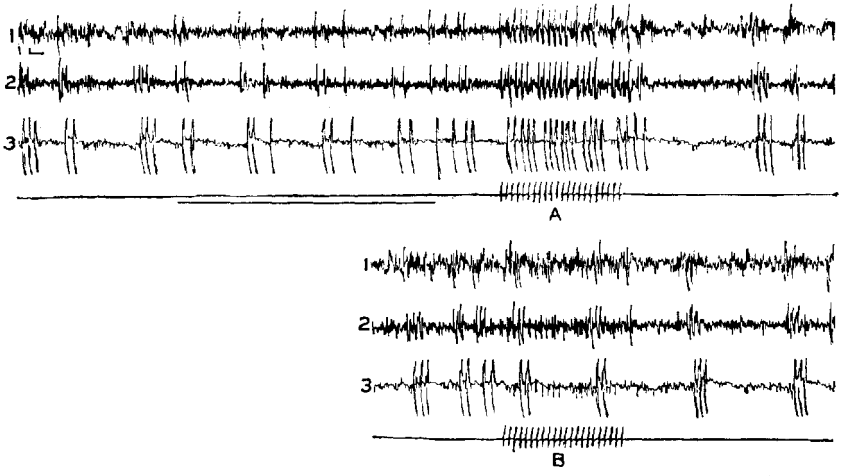

FIGURE 65. The interaction between nociceptive and auditory impulses, as shown by recordings from three points of the auditory area (posterior part of the ectosylvian gyrus). Left cortex in records 1 and 2; right cortex (record 3) strychninized. *Records A:* nociceptive stimulation (indicated by horizontal line) is followed by acoustic stimulation. *Records B:* acoustic stimulation alone. The individual clicks are indicated by the signal magnet at the bottom of A and B. (Gellhorn and Koella, unpublished observations.)

has been activated (464) (Fig. 65). Similarly, the perception of touch is facilitated under the influence of slight pain (791).

Convulsive Activity and Consciousness

The various conditions, discussed in the preceding sections, which lead to the loss of consciousness are almost always accompanied by an increasing degree of synchrony of the cortical potentials, associated with an increase in their amplitude and a decrease in frequency. With progressing coma the neurons become less excitable and the potentials decrease in frequency and amplitude (decruitment) until they finally disappear. In another condition involving likewise the loss of consciousness, highly synchronized, large potentials are found in the cortex in the form of convulsive spikes. The spike and dome pattern is associated with petit mal epilepsy and is also evoked by stimulation of the intralaminar thalamic nuclei (717, 718, 1134). The convulsive discharges occurring under these conditions appear in all parts of the cortex. They are not accompanied by overt convulsions, but only by a lapse of consciousness which, although often lasting but a few seconds, represents the predominant clinical symptom.

A study of the relation between consciousness and cortically induced

convulsions (as in focal lesions or Jacksonian epilepsy) seems to indicate that awareness depends on the extent to which the convulsive discharge spreads over the cortex. Martin (902) states that a patient becomes unconscious "by the time the convulsions involve the whole of one half of the body, and certainly by the time it shows any extension to the other half." Under these conditions the thalamus and the brain stem will probably also show convulsive discharges, since local strychninization of the cortex leads to strychnine discharges in the thalamus, basal nuclei (Dusser de Barenne and McCulloch, 305) and hypothalamus (Murphy and Gellhorn, 958; Ward and McCulloch, 1210). Whether this spread of convulsive activity to subcortical areas is a prerequisite for the loss of consciousness appears to be doubtful.

It is, of course, well established that a major seizure is accompanied by loss of consciousness, and clinical signs (e.g., anesthesia of an extremity following a sensory seizure) and physiological indications suggest an exhaustion of neurons. The latter appears as a period of electrical silence following experimentally induced (through convulsants or electroshock) and clinical seizures. However, a lapse of consciousness occurs in petit mal epilepsy during the spike and dome discharge, although no period of electrical inactivity occurs. Moreover Foerster states that the loss of consciousness may precede the convulsive discharge (369).

Instead of assuming that the loss of consciousness in convulsive disorders results from neuronal exhaustion,* it seems more in line with experimental and clinical experience to suggest that uniform synchronous activity of all or the greater part of the cortex is incompatible with a high degree of awareness.† Although cortical potentials express very incompletely the complexity and specificity of the function of various cortical areas, they reveal different cortical patterns in the unanesthetized animal. On the other hand, in conditions involving the loss of consciousness, as in barbiturate anesthesia, synchrony of cortical discharges exists which eliminates areal differences. Such synchronous discharges suggest a hypothalamic-thalamic origin. This seems to follow from Hunter and Jasper's experiments with stimulation of intralaminar thalamic nuclei and from the analysis of the generalized convulsive discharge in asphyxia.‡ Apparently a very fine balance regulates the level of consciousness; tonic discharges from the tegmental-hypothalamic-thalamic system to the cortex account

* The cessation of potentials following convulsions (1075) is discussed on p. 161.

† This opinion is shared by Adrian (11), who points out that uniform alpha potentials or convulsive discharges are incompatible with consciousness.

‡ See p. 152.

for wakefulness and increased awareness; the diminution of these impulses leads through drowsiness and sleep to coma; finally, synchronous discharges, either of cortical origin, provided that they influence a large part of the cortex, or as the result of diencephalic discharges, cause loss of consciousness.

These data indicate that loss of consciousness is due to grave alterations in cortical activity. Under strictly physiological conditions a diminution in cortical activity occurs in diurnal cycles, which are related to cyclic changes in hypothalamic activity and associated with corresponding alterations in hypothalamic-cortical discharges. Lesions in the posterior hypothalamus or reticular substance have similar effects on the cortex except that the changes are more profound and less reversible. Experimentally, loss of consciousness may also be induced by pharmacological means (anesthesia) or by variations in the internal environment (anoxia,* hypoglycemia, etc.). In these instances the chief point of attack seems to lie in the cortex, and different degrees of reduction in cortical activity appear to be associated with different levels of awareness. With an increasing reduction in cortical activity subcortical influences become more prominent and may lead to synchronous discharges in the cortex. A high degree of synchrony appears to be incompatible with the maintenance of consciousness no matter whether the discharges originate in subcortical structures or, as in Jacksonian epilepsy, in the cortex itself. Consequently, *consciousness seems to be the result not only of a certain level of cortical activity, which depends on the integrity of the reticulo-hypothalamic-cortical system, but also of the retention of the specific function (indicated in the areal specificity of the electrocorticogram) of different parts of the cortex.*

It may be reiterated that consciousness, or awareness, as a physiological concept cannot be dissociated from its content. To be conscious means to be conscious *of something.* Now, afferent impulses, whose effect on the cortex has been shown to be so important for the maintenance of consciousness, probably fail to affect the convulsive cortex in a normal manner. It should be remembered that the appearance of cortical responses in the form of action potentials to sensory stimuli does not prove sensory perception, as the observations on the action of optic and acoustic stimuli on the cortex of deeply anesthetized animals clearly indicate. Although optic stimulation will "drive" the convulsive spikes resulting from the topical application of strychnine to the visual cortex, or the synchronous discharges recorded from the occipital part of the human skull, the cortical processes elicited under

* See the next section.

these conditions are too far removed from the norm to mediate sensations and perceptions.*

Consciousness and Its Dependence on Respiratory and Circulatory Functions

Of the changes in the internal environment which are accompanied by diminished cortical activity and loss of consciousness, reduction in the carbon dioxide content of the blood has been studied extensively, particularly in man. If, during voluntary hyperventilation, carbon dioxide is blown off, the voltage of the brain waves increases and their frequency decreases. When the mean frequency of the potentials is reduced below 5.0 per second, changes in consciousness appear (318). Hill (651) mentions that respiratory alkalosis (induced by hyperventilation) is associated with "light headedness, inability to respond to commands and usually subsequent amnesia." Delta potentials appear, particularly in the frontal cortex. These changes are aggravated in neurotics.

The great sensitivity of the cortex of the brain to the supply of oxygen accounts for the loss of consciousness on inhalation of gas mixtures low in oxygen or on reduction in the barometric pressure. The loss of consciousness is apparently in part due to the hyperventilation (and loss of carbon dioxide) associated with anoxia, since the subjective and objective changes (indicated by behavior, sensory functions, EEG, and blood pressure) are greatly reduced when the loss of carbon dioxide from the blood is prevented (445, 446, 489).

The oxygenation of the brain may be lowered through carotid sinus reflexes. Mechanical stimulation (massage) of the region of the carotid sinus elicits a fall in the blood pressure through vagal slowing of the heart rate or, and this is rare in man, through vasodilatation. The slowing of the pulse, followed by asystole for several seconds, is accompanied by large, slow potentials in the EEG and a loss of consciousness. Deficient oxygenation of the brain as a result of temporary circulatory failure causes the subjective and objective changes.

Stimulation of the carotid sinus induces a loss of consciousness without asystole and a fall in the blood pressure in the so-called cerebral type of carotid sinus hypersensitivity (317, 938). In such

* Obviously consciousness can be maintained in the normal individual if afferent impulses are kept at a minimum. Under these conditions remembered events may form the content of consciousness. Penfield showed that previous experiences can be re-evoked by electrical stimulation of large areas of the cortex, particularly of the temporal lobe. It may be assumed that this excitation presupposes the integrity of the reticular-hypothalamic-cortical system (Penfield's centrencephalic system, 1000) as well as an absence of abnormal degrees of cortical synchrony.

cases the slow potentials of the EEG, probably based on cerebral vasoconstriction, are confined to the side of the stimulated carotid sinus, while cerebral symptoms appear, as would be expected, contralaterally to the affected side of the brain. Occasionally, associated symptoms point to the diencephalon, and to the hypothalamus in particular, as the source of the disturbance, since crying spells* and loss of muscle tone may occur at the same time. This is interesting in view of the close relation between the hypothalamus, muscle tone, and wakefulness. Finally, fainting, involving a fall in the blood pressure and vagal slowing, occurs under conditions of psychic stress. Here again changes in the circulation, a slowing of brain potentials, and the loss of consciousness, preceded by marked signs of sympathetic discharge (pallor, sweating), run parallel (Engel, 317).

It should be added that *physiological* variations in the state of oxygenation of the brain seem to be related to the state of consciousness. Doust (295) observed that attention is accompanied by increased oxygenation of the peripheral (and presumably of the cerebral) blood. While a person becomes drowsy, the oxygen saturation of the blood declines, but it returns to the normal level on arousal. These investigations, based on oximetric determinations of the blood, are interesting, but the relation of these peripheral changes to the oxygen supply of the brain remains to be established.

The fact that acapnia leads to a slowing of cortical potentials and a progressive loss of awareness appears to be explainable on the basis of altered hypothalamic-cortical relations. It will be shown later that hypercapnia increases hypothalamic-cortical discharges and the reactivity of the hypothalamus to proprioceptive and nociceptive stimuli. Consequently, a loss of carbon dioxide must lower the state of awareness through a diminution of these discharges. This lowering occurs even though the reactivity of sensory projection areas to their specific stimuli is increased, as indicated by action potential studies.†

Concluding Remarks

In spite of the considerable experimental and clinical work which has been discussed in order to throw some light on the mechanism by which various degrees of consciousness are maintained, the problem has still many more facets. Thus Martin (902) points out that clinical observations have established sectional disturbances of consciousness. They involve defects in the body image or in visual perception and are based on lesions in the parieto-occipital cortex,

* On the relation of the hypothalamus to emotional expression, see Chapter 14.
† For further details see Chapter 19.

Penfield (1002) describes a case in which after excision of a cortical area comprising a large part of the right parietal lobe and extending into the temporal and occipital lobes on the nondominant side the patient "had difficulty in visualizing what he was to do with the left hand on the left side of the body when tasks were set him. He had trouble in dressing and was apt to ignore the left arm as though it did not belong to him." Closely related is the phenomenon of "tactile inattention," observed in cases with parietal lesions. If the eyes are closed and both hands are pricked simultaneously with a needle, the patient perceives only the prick contralateral to the normal parietal cortex, but with open eyes he "actually feels as well as sees the pin on both sides" (Critchley, 247).

Attention is obviously a part or a particular form of awareness, and although no attempt is made to explain its physiological mechanism, it is interesting to point out that "tactile inattention" is the result of a defect not in the specific projection area (postcentral gyrus) but of the parietal lobe. This is in agreement with the general thesis according to which consciousness requires cortical activation through the reticular substance and through the hypothalamus, which are the two mechanisms through which association as well as projection areas are excited. In order to perceive an object, it is not sufficient that the specific afferent sensory system should function but that the hypothalamic-cortical apparatus be adequately activated. Perception seems to require the interaction of these two systems. In this connection it is very interesting to quote Lashley (822): "A good guess is that the phenomena which we designate as attention and interest are the result of partial, subthreshold activation of systems of related associations which have a mutual facilitative action." Psychological considerations and physiological experiments seem to lead to similar conclusions.

Although consciousness is in the last analysis a cortical phenomenon, no particular part of the gray mantle is specifically involved. Certainly the frontal lobes are not necessary, since even bilateral lobectomy does not interfere with consciousness, nor does the removal of one cerebral hemisphere.

From this attempt to outline the physiological basis of consciousness the impression might be gained that consciousness represents a well-defined state of cortical excitability which depends on impulses from the reticular substance of the brain stem and on the hypothalamus. Nothing, of course, is farther from the truth. The continuous variations in the activity underlying consciousness are well expressed by the term "stream of consciousness" introduced by W. James (731a). The physiological equivalent of the constant changes in the level of aware-

ness and the shift of attention is probably associated with fleeting changes in the location of foci of maximal excitation in the cortex indicated by small, high frequency potentials in the EEG.

Kleitman's "evolutionary theory of consciousness" (780) is perhaps best suited as a basis for the understanding of the ever fluctuating processes which underlie the state of consciousness. This author takes as his point of departure the fact that the diurnal rhythm between sleep and wakefulness is different in the newborn and the adult. In the former it consists of periods of four to five hours of sleep interrupted by brief periods of wakefulness which apparently are related to afferent impulses from the viscera (bladder, rectum) and are characterized by a relatively low level of awareness. This low level of consciousness is called "wakefulness of necessity." "The newborn baby probably wakes up only when it is hungry, wet, cold, or otherwise disturbed, falling asleep again after it has been taken care of or the disturbance removed. Our decorticate dogs almost invariably moved about for a few minutes after being fed, apparently because of afferent impulses from the colon resulting from the gastrocolic reflex. They would then defecate and immediately go to sleep" (Kleitman, 781). The similarity between the decorticate animal and the newborn human being is apparently due to the fact that the cortex is not excitable to afferent impulses at this early stage of development. As Smith (1120) pointed out, no cortical potentials exist in the newborn except during sleep.

With the myelinization of the afferent system, reactivity of the cortex to sensory stimuli develops. Afferent impulses, particularly those originating in proprioceptive end-organs, increase in potency with the development of the muscular system and contribute to the excitation of the cortex directly through the medial lemniscus and, as we have also seen, via the reticulo-hypothalamic-cortical system. At this time the cerebral cortex shows alpha potentials during rest and excitation (asynchrony of potentials) in response to distance receptors. A higher level of consciousness arises, which Kleitman calls "wakefulness of choice." At this level, in response to environmental stimuli, finely graded reactions involving sensorimotor integration at the cortical level occur. With increasing age and further development of the brain the adaptive responses increase in complexity through the utilization of individual experience and memory.

This evolutionary concept is perhaps best suited to dispel Sherrington's notion that psychic events are not translatable into physiological processes. As Lashley (821) expresses it: "Mind, when analyzed to its definable constituents, has no discernible properties other than

organization or integration of processes which differ through a range of complexities as wide as the structural differences between the virus and the human body." *There is a phylogenetic as well as an ontogenetic development of the mind, and mind is not a phenomenon per se but one of the expressions of biological organization.* "A physiological plan, refined and far more complex in the cells of our nervous system but essentially like the developmental plan, . . . is that which in man can be experienced as conscious purpose" (Sinnott, 1116).

No matter how this outline of the physiological basis of consciousness may be modified by future research, the vigorous experimental approach to this problem in recent years is the best proof that understanding the mind from the point of view of neurophysiology is not an entirely hopeless task. Furthermore it is of some interest to point out that the fundamental features disclosed by the physiological analysis of the most primitive mental activity – mere awareness – reflect the general mechanism which underlies the highest form of activity of the human mind – creativeness. In both forms of "mental" activity the functions of the cortex depend on the "upward discharge" of subcortical origin. In the former state these impulses are just sufficient to permit the functioning of the cortex to a degree leading to a dim recognition of environmental stimuli, followed by appropriate motor reactions; in the latter the hypothalamic-cortical discharge, heightened by the emotional drive, increases the reactivity of the various parts of the cortex which subserve specific functions.* It has been pointed out earlier that the reactivity of a sensory projection area to a specific impulse is augmented under the influence of a hypothalamic-cortical discharge (see Figure 65), and Murphy and Gellhorn (957) stressed the significance of this discharge for the heightened reactivity of the motor cortex and for the greater muscular endurance in emotional stress.

* From a thoughtful paper by Schiller (1096) which appeared after the manuscript of this book had been completed, some remarks concerning the "seat" of consciousness may be quoted. Schiller feels that "the term of a 'center' or 'seat' of consciousness does not seem apposite. . . . 'Consciousness,' 'circulation,' 'contractility' are convenient abstract terms signifying the organization of complex processes in complex anatomical structures." To outline this organization has been the chief aim of this chapter.

PART IV

Some Aspects of Autonomic Physiology

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Neurohumors and Neuropharmacology of the Autonomic Nervous System

SOME aspects of the role of electrical potentials in excitability, conduction, and synaptic transmission have been discussed earlier. Important as this work is, it gives only an incomplete picture of the basic physiological characteristics of the neuron. It is supplemented by another wide field of neurophysiological research, the study of neurohumors, which, at least in part, deals with fundamental intraspinal and intracerebral processes and seems to have great potentialities for neurology and clinical medicine. A discussion of this work and some related questions concerning the action of certain drugs on the central nervous system has therefore been chosen as the topic of the present chapter. No attempt will be made to survey this field completely; the interested reader will find valuable information in the monographs of Cannon (205) and Rosenblueth (1067), Minz (933), Feldberg (338, 339), Nachmansohn (964), and Bacq (52, 53). We shall try to give a bird's-eye view of the basic work and the leading ideas, and then concentrate on recent developments in this field.

Otto Loewi's fundamental work (854, 855) established the fact that stimulation of the vagus leads to the liberation of acetylcholine from the endings of this nerve in the heart and that excitation of the accelerator fibers causes the appearance of an adrenalin-like substance (sympathin) from the corresponding sympathetic endings of the frog's heart. He showed that under these conditions the neurohumor diffuses to a slight extent into the perfusion fluid, as indicated by the fact that the transference of this fluid into another test heart induced in it typical parasympathetic- and sympathetic-like effects, although to a lesser degree than was recorded by the donor heart.

These results remained valid under conditions in which mechanical alterations of the heart were completely eliminated by having donor and test heart fed from a common reservoir (Kahn, 752). This is the groundwork on which the theory of neurohumors has been erected.

The Older Work on Sympathin

Cannon and his collaborators succeeded in proving the validity of this discovery for the mammalian sympathetic nervous system, utilizing the fact that denervated structures such as the nictitating membrane of the cat and also the heart become highly sensitive to neurohumors (206). A few examples may illustrate procedures and results. Stimulation of sympathetic nerves such as the splanchnics was found to increase the rate of the denervated heart. Since this action persisted after elimination of the adrenal medulla, it seemed to indicate the liberation of a sympathetic neurohumor, which was named sympathin. Stimulation of the abdominal part of the sympathetic chain, which resulted in piloerection, also caused the appearance of sympathin in the blood of adrenodemedullated, eviscerated animals (1068, 195). Other sympathetic nerves, such as the superior cervical, released sympathin on stimulation, as indicated by the contraction of the denervated nictitating membrane and of the smooth muscles of the palpebrae (Rosenblueth, 1067; Isola and Bacq, 728). Such nerves are called adrenergic in contradistinction to those which on stimulation liberate acetylcholine and are named cholinergic. These terms are based on purely physiological characteristics, without regard to anatomical boundaries.

Vasoconstriction resulting from the activation of sympathetic fibers in visceral, muscular, and cutaneous vessels was shown to be accompanied by the liberation of sympathin. Feldberg found that salivary secretion induced by the stimulation of sympathetic fibers is associated with the production of sympathin. Bacq (53) noted that stimulation of the abdominal sympathetic chains in cats subjected previously to bilateral vagotomy, inactivation of the adrenal medullae, removal of the sympathetics from the stellate to the seventh dorsal ganglion, and section of the spinal cord at the level of the sixth vertebra, lead to an increased blood sugar, which he attributed to the liberation of sympathin. These and many other investigations led Cannon and Rosenblueth to the conclusion that sympathin may be liberated from almost any postganglionic sympathetic nerve, the sympathetic nerve fibers supplying the sweat glands being an exception since they belong to the cholinergic group.

The liberation of sympathin was shown not to be restricted to

sympathetic nerves which when stimulated cause excitation but also to occur when stimulation causes inhibition. Thus stimulation of sympathetic nerves innervating a piece of intestine leads to the appearance of a substance which inhibits the activity of an isolated part of the gut when added to the fluid in which the smooth muscle is suspended (358). The sympathin thus liberated likewise increases the rate of the denervated heart. A similar effect was observed when the sympathetic nerves were stimulated which supply the uterus or bladder and cause inhibition of these organs (195). Finally, Rosenblueth and Cannon reported that sympathetically induced coronary dilatation is due to sympathin.

It may be thought that the liberation of a chemical substance subsequent to stimulation of a nerve with electrical currents is the result of an injury and consequently lacks physiological significance. The experiments, therefore, which have shown the liberation of sympathin under strictly physiological conditions are of particular importance. Emotional excitement in cats with denervated liver, adrenals, heart, and nictitating membrane resulted in an activation of the last two structures (causing an increase in the heart rate and a contraction of the nictitating membrane) (Newton, Zwemer, and Cannon, 970). Bodo and Benaglia (108) found that cold and insulin hypoglycemia are followed by the appearance of sympathin in the blood. Sham rage in decorticate animals was seen to produce sympathin from the liver, since the acceleration of the denervated heart, which served as the indicator of sympathin, was diminished after sectioning of the liver nerves. The secretion of adrenalin did not play any part in these reactions, since the adrenal medullae had been previously denervated (109). Central autonomic structures seem to be responsible for the appearance of sympathin in the blood stream under these conditions, since cold, emotional excitement, etc., lead to autonomic discharges from the diencephalon and medulla oblongata. Moreover stimulation of the hypothalamus causes a contraction of the denervated nictitating membrane in adrenalectomized animals (Magoun, Ranson, and Hetherington, 888).

The reflex liberation of sympathin was likewise demonstrated. Liu and Rosenblueth (850) found that the stimulation of afferent nerves leads to a contraction of the denervated nictitating membrane. The degree of response depends on the number of activated efferent sympathetic fibers, since removal of the stellate ganglion reduces the contraction of the denervated nictitating membrane which follows stimulation of the central end of the sciatic nerve. According to Youmans and his collaborators (1254, 1255), mechanical stimulation

of the rectum causes a distinct inhibition of the denervated jejunum in vagotomized and adrenodemedullated unanesthetized dogs. Such animals react also to injected acetylcholine with an initial activation of the denervated gut due to the direct action of this drug and with a delayed and prolonged inhibition. The latter appears to be due to the reflex liberation of sympathin, probably via carotid sinus presso-receptors, since acetylcholine lowers the blood pressure.* This reflex activates in the normal animal not only the adrenal medulla but also the sympathetic system as a whole. From the former "adrenalin" † is liberated, from the latter, sympathin. Consequently the delayed inhibition of the denervated gut is more intense and prolonged before than after inactivation of the adrenal glands.

A great similarity between the action of adrenalin and the action of the sympathin that is set free on the stimulation of sympathetic nerves was noted by Cannon and Rosenblueth (203, 204). Thus, to cite only one example of their research, the sympathin liberated on stimulation of the accelerator nerves of the heart exerts an adrenalin-like action on the blood pressure, the nictitating membrane, and the smooth muscle of the iris (pupillary dilatation), and it also raises the blood sugar. The similarity between sympathin and adrenalin is further illustrated by the work of Bacq (51). Stimulation of the peripheral end of the sciatic nerve led to the liberation of a substance which inhibits the activity of the gut and the iris and induces a contraction of the spleen, all test organs being denervated. That the substance originates in the sympathetic nervous system follows from the fact that sciatic stimulation exerts no humoral effects in animals in which the lumbar and sacral parts of the sympathetic chains have been removed previously.

Pharmacological procedures may be used to induce a discharge of sympathin. Bacq (52) found that in the adrenalectomized cat, nicotine and acetylcholine lead to the liberation of sympathin, since the nictitating membrane shows a contraction after the administration of these drugs, provided the membrane has been sensitized to sympathin by cocaine and chronic denervation. In support of this interpretation Bacq mentions that sympatholytics prevent this effect and that substances which delay the oxidation of adrenalin augment it (54). Finally, neither nicotine nor acetylcholine exerts any effect on the denervated nictitating membrane after complete bilateral extirpation of the sympathetic chains, although the reactivity of the nictitating

* It would be important to repeat this experiment in animals with denervation of the sino-aortic area.

† See below on the nature of adrenalin liberated through carotid sinus reflexes.

membrane to injected adrenalin persists. Apparently sympathin is liberated by these drugs through action on the sympathetic ganglia.

As to the nature of sympathin, chemical tests showed similar reactions for sympathin and adrenalin. Sensitization of a structure by denervation increases its sensitivity to adrenalin as well as to sympathin (206). This holds true for sensitization by cocaine (57). However, as early as 1933 Cannon and Rosenblueth (203) noted some difference between the reactions of adrenalin and sympathin which led them to the assumption that actually two forms of sympathin are liberated. Thus they found that whereas the effect of sympathetic stimulation could be matched by adrenalin in appropriate concentra-

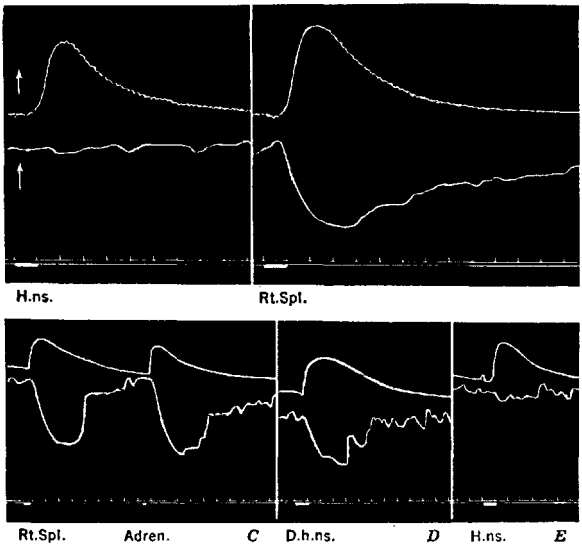
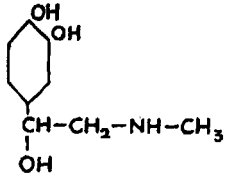


FIGURE 66. The effects of sympathin of different origins on indicators which contract or relax. The upper tracings are of the nictitating membrane with the cervical sympathetic cut; the lower tracings, the nonpregnant uterus with the nerves cut. The arrows indicate contraction. Time signal: 30 seconds apart. In the top figures a cat is under "Dial" and sensitized with cocaine. In the bottom figures another cat with brain pithed is under ether, cocaine, and curare. *Left top records:* effects of stimulating the hepatic nerves, purely excitatory. *Right top records:* effects of stimulating the right splanchnic nerves (adrenals excluded), excitatory and inhibitory. *Left bottom records (C):* effects of stimulating the splanchnic nerves and of injecting adrenalin (0.3 cc., 1:200,000). *Middle bottom records (D):* effects of stimulating the duodeno-hepatic nerves, excitatory and inhibitory. *Right bottom records (E):* same stimulus as in D but after severance of the duodenal nerves; effects of stimulating the hepatic nerves, excitatory only. (Cannon and Rosenblueth, 203.)

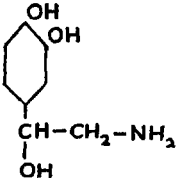
tions when the stimulation involved inhibitory sympathetic nerves, this statement no longer held true for some excitatory sympathetic effects. Stimulation of the hepatic and of the accelerator nerves causes a contraction of the denervated nictitating membrane (sensitized by cocaine), but it does not induce any changes in the nonpregnant uterus, whereas the injection of adrenalin in a concentration which matches the effect of the stimulation of the hepatic nerves on the nictitating membrane produces a marked inhibition of the tone of the uterus (Fig. 66). These data were interpreted by Cannon and Rosenblueth to mean that from all sympathetic nerve fibers an adrenalin-like substance *A* was liberated, which combines with a receptive substance, *E* and *I* respectively in the responsive cells. In those structures in which sympathin exerts an excitatory effect it was thought to be due to the formation of *AE*, whereas the inhibitory action appeared to be linked to the production of *AI*.

An alternate hypothesis would be to assume that the substances liberated from excitatory and inhibitory sympathetic nerves, although adrenalin-like in character, are not identical. Barger and Dale (71) in 1910 had already called attention to the fact that nor-adrenalin, which is demethylated adrenalin, shows the excitatory but little of the inhibitory action of adrenalin.

Adrenalin



Nor-adrenalin



Bacq (52) suggested in 1934 that sympathin *E* is nor-adrenalin, but he abandoned this assumption later. However, the work of the last years has left little doubt in the minds of most investigators that nor-adrenalin is indeed liberated on the stimulation of sympathetic nerves and also secreted from the adrenal medulla. The evidence for this statement may now be presented.

The Newer Work on Sympathin (1147)

It is convenient to divide the experimental material available at the present time into several groups. In the first, experiments are discussed in which sympathetic nerves were chemically extracted and the nature of the extracts was ascertained by biological tests in which

the effect of the unknown substance was compared with that of adrenalin and adrenalin-like substances (325). If, measured on the blood pressure of the cat, equipressor concentrations of nor-adrenalin, adrenalin, and extracts of spleen nerves were used before and after ergotoxin, it was found that through this drug the pressor effect of adrenalin was reversed (fall in blood pressure), whereas the pressor effect of nor-adrenalin and of the nerve extracts was not reversed but only reduced, and reduced to a similar degree (von Euler, 326). Similar effects were obtained with dibenamine as a sympatholytic; and studies using as indicators the cat's uterus and fowl's caecum, together with chemical assays, furnished further evidence of the presence of nor-adrenalin in extracts of splenic nerves. This work, confirmed by Bacq and Fischer (56) and extended to extracts of the sympathetic chains, led von Euler to conclude that the sympathin extractable from the nerves of the spleen is identical with the laevo-form of nor-adrenalin. It is of interest to mention that nor-adrenalin has also been found in extracts of human sympathetic chains (566).

Cannon and his group were already well aware of the fact that the liberation of sympathin following the stimulation of adrenergic nerves may in part originate in the walls of the blood vessels. Consequently they extracted and assayed these structures for neurohumors. In the light of the new knowledge about nor-adrenalin this work was repeated and extended by Schmiterlöw (1097). Such extracts were found to contain histamine and acetylcholine in addition to pressor substances. When the former were eliminated by atropine and antihistamine drugs, the pressor substance obtained from the arteries and veins seemed to be nor-adrenalin. Only the renal artery of the horse contained adrenalin. The nor-adrenalin content was different in different parts of the aorta and also at different layers and corresponded roughly to the number of nerve fibers present.

Important as are these experiments showing the presence of nor-adrenalin in extracts of sympathetic nerves and sympathetically innervated blood vessels, they are insufficient to justify the assumption that nor-adrenalin is the neurohumor involved in sympathetic excitatory effects. Two more groups of studies were necessary in order to establish this fact: one showing that on electrical stimulation of a sympathetic nerve nor-adrenalin is liberated, and another in which this liberation is accomplished in a strictly physiological manner, i.e., through reflex activation or as a result of the excitation of central autonomic structures. Here again various methods of assay were employed to determine the chemical and biological nature of the liberated sympathin.

Stehle and Ellsworth (1137) and later Greer (575) noted that not adrenalin but nor-adrenalin matched hepatic sympathin in action, since the pressor effects of nor-adrenalin and sympathin were not reversed by ergotoxin,* and similar observations were made by Melville (926) with sympathin liberated from the splanchnics in animals in which the adrenal glands had been inactivated. In its action on the pupil, nictitating membrane, and gut, sympathin resembled more closely nor-adrenalin than adrenalin. Gaddum and Goodwin (403) came to similar conclusions on the basis of experiments using the blood pressure and nictitating membrane as indicators. They found that stimulation of the splenic nerve induced a substance to appear in the blood plasma which exerted typical excitatory sympathetic effects on the nictitating membrane and the blood vessels of the perfused rabbit's ear, while it inhibited the colon of rats. The quantitative comparison of these effects with several sympathomimetic substances led to the result that the main substance liberated was nor-adrenalin, while adrenalin appeared only in smaller amounts and with lesser regularity (997).

On the other hand, clear evidence for the liberation of adrenalin from sympathetic inhibitory nerves is available not only from the earlier work of Cannon and Rosenblueth but also from recent investigations (894). West (1225) found a similarity of action between sympathin (from stimulation of the hypogastric nerves) and adrenalin on the uterus in conditions which greatly change the reactivity of this organ. On the nonpregnant uterus (cat) adrenalin and stimulation of the hypogastric nerves produce inhibition. These actions are reversed by progesterone. Furthermore the parallelism existing between adrenalin and nerve stimulation persists during lactation, when these procedures cause relaxation of the uterus, while nor-adrenalin induces a contraction or a biphasic effect. Finally, after the administration of dibenamine the effects of adrenalin and of nerve stimulation remain similar and are sharply distinguished from the action of nor-adrenalin. Apparently both adrenalin and nor-adrenalin can be liberated from sympathetic nerves, the former especially from nerves with an inhibitory action, the latter from those with an excitatory action.†

* Cannon and Rosenblueth (203, 204) had already found that the blood pressure action of hepatic sympathin was, in contradistinction to that of adrenalin, not reversed by ergotamine and yohimbine.

† It should, however, be emphasized that the identification of the inhibitory sympathin with adrenalin and the excitatory with nor-adrenalin is not without exceptions. Gaddum *et al.* (404) found that the stimulation of sympathetic nerves which causes vasoconstriction in the rabbit's ear liberates a substance in the perfusate which in its color reactions and the inhibition of the hen's

The experiments reported thus far give evidence for the liberation of nor-adrenalin and of adrenalin from different types of sympathetic nerves. Further studies indicate the validity of these findings under conditions of activation and excitation of central structures.

Holtz and Schümann (703) studied the neurohumors activated when the carotid sinus reflex was diminished by a clamping of the common carotid arteries. The blood pressure rose but the blood sugar level failed to do so, a result suggesting that the sympathin liberated might be nor-adrenalin rather than adrenalin, since the former is only 1/20 as effective on the blood sugar as the latter. This suggestion is further strengthened by the following observations. After ergotamine the rise in the blood pressure induced by the clamping of the carotids or the administration of nor-adrenalin is not reversed, although a blood pressure rise caused by the injection of adrenalin is converted into a fall. A simultaneous study of the activity of the gut revealed that the carotid sinus reflex, although markedly increasing the blood pressure, does not appreciably alter the tone of the gut. If adrenalin and nor-adrenalin are injected in isopressor concentrations, it is found that adrenalin distinctly inhibits gastrointestinal activity whereas nor-adrenalin causes only a slight inhibition. These experiments seem to indicate that the sympathin effects elicited reflexly via the carotid sinus pressoreceptors can be matched with nor-adrenalin but not with adrenalin.

This conclusion is confirmed by studies on the carotid sinus reflex by Folkow and Uvnäs (372), who used an ingenious cross-circulation technique, and by Graham (566), who used the blood pressure, the chronically denervated nictitating membrane, and the acutely denervated nonpregnant uterus as indicators. Lowering the pressure in the carotid sinus by clamping the carotid arteries caused the blood pressure to rise without altering the tone of the uterus, and the nictitating membrane was slightly relaxed. An equipressor concentration of l-adrenalin produced a relaxation of the uterus and a strong contraction of the nictitating membrane, whereas the effect of l-nor-adrenalin resembled that of the carotid sinus reflex inasmuch as the uterus remained unchanged and the nictitating membrane contracted to a lesser degree. Finally, studies by Walker *et al.* (1200) showed that a new sympatholytic which reverses the adrenalin pressor effect in small doses must be given in a 30 $\times$ stronger concentration in order

rectum resembles adrenalin and not nor-adrenalin (405). Moreover, after sensitization of the nictitating membrane to adrenalin and not to nor-adrenalin by adrenochrome, stimulation of the cervical sympathetic seems to liberate both nor-adrenalin and adrenalin (826).

to block either the carotid sinus reflex or the pressor effect of nor-adrenalin.*

Our own work (474) seems to support these conclusions under conditions involving the stimulation of central autonomic structures. In these experiments the hypothalamus was stimulated with condenser discharges in anesthetized cats, and the effect on the blood pressure was matched with appropriate doses of adrenalin and nor-adrenalin respectively. Thereafter sympatholytics (dihydrogenated ergocristine or dibenamine) were injected and the test was repeated. It was found uniformly that concentrations of sympatholytics which reverse the effect of injected adrenalin (fall in the blood pressure instead of rise) cause only a slight change in the pressor action of hypothalamic stimulation and of injected nor-adrenalin (Fig. 67). Moreover the pressure curves resulting from hypothalamic stimulation and injected nor-adrenalin remain similar. These experiments suggest that the substance responsible for the excitatory sympathin liberated on mild stimulation of the hypothalamus is nor-adrenalin and not adrenalin.

If it is true that a large part of the postganglionic nerves of the autonomic nervous system liberate nor-adrenalin and if their tonic activity is taken into consideration, one would expect nor-adrenalin to be constantly produced, and since adrenalin and its derivatives are fairly stable in blood and plasma, one would expect nor-adrenalin to be present in the blood. That the blood contains a pressor principle has been known for some time (986). Von Euler and Schmiterlöw (332) tested alcoholic extracts of human and bovine plasma after depressor factors had been eliminated by adsorption. They found that the pressor substance behaved like nor-adrenalin when assayed on the blood pressure of the cat. Its action was potentiated by cocaine, but not reversed by ergotamine, whereas, as was mentioned earlier, the pressor action of adrenalin is converted into a depressor effect. When this extract and the equipressor concentrations of adrenalin and nor-adrenalin were tested on the gut (rabbit) and the nonpregnant uterus (cat), the inhibitory effect of the extract was similar to that of nor-adrenalin and much less than that of adrenalin. From these studies it may be concluded that the quantity of sympathin in whole blood corresponds to 2–4 micrograms of dl-nor-adrenalin hydrochloride per 100 cc.

* However, Kaindl and von Euler (753) found on the basis of assays made with blood from the adrenal vein evidence for liberation of adrenalin *and* nor-adrenalin from the adrenal medullae following occlusion of the carotids. Lecomte and Fischer (826) claim similar results when the cervical sympathetic nerve is stimulated and the effect is studied on the nictitating membrane which is specifically sensitized to adrenalin (and not to nor-adrenalin) by adrenochrome.

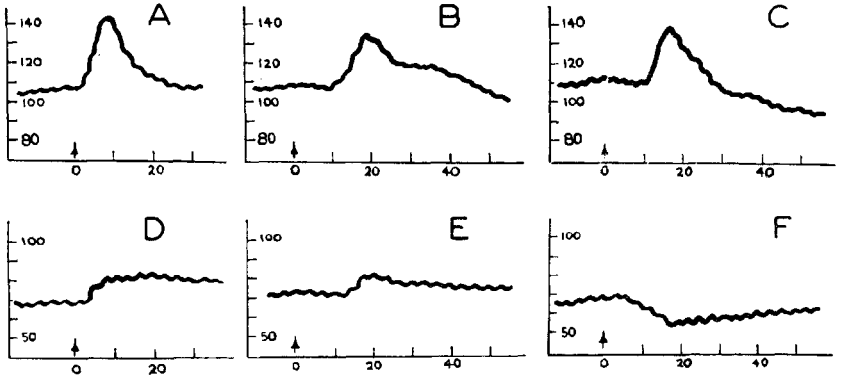


FIGURE 67. The effect of a sympatholytic substance (dehydrogenated ergocristine, 0.9 mg/Kg) on the reaction of the blood pressure to three different types of stimulation. *Records A and D:* hypothalamic stimulation, at the point indicated by the arrow, of 1.7 volts, at 82 per second, for 3 seconds. *Records B and E:* injection of nor-adrenalin, 2.5 gamma/Kg. *Records C and F:* injection of adrenalin, 5 gamma/Kg. *Top records (A, B, C):* before the injection of ergocristine. *Bottom records (D, E, F):* after the injection of ergocristine. Note the similarity in the blood pressure curves produced by hypothalamic stimulation and by the injection of nor-adrenalin. Ordinate: blood pressure in mm. Hg. Abscissa: time in seconds. (Gellhorn and Conley, 474.)

Finally, it should be mentioned that nor-adrenalin appears in the human urine. Von Euler (328) showed recently that a mixture of nor-adrenalin and adrenalin appears in the urine of normal persons, the concentration of the former being almost three times that of the latter. Physical work and hypertension are said to increase the concentration of nor-adrenalin in the urine (Holtz *et al.*, 701). This work urgently needs confirmation. Perhaps important light will be thrown on the problem of hypertension from this angle. Moreover the knowledge of the chemistry of sympathin ought to give new impetus to the study of sympatholytic drugs that may prevent the harmful effect of excessively formed nor-adrenalin on the blood vessels and other structures.

The Nature of the Secreted Adrenalin

In view of these findings a reconsideration of the nature of the hormone of the adrenal medulla seems necessary. Is it adrenalin, as we believed it to be after Abel's brilliant investigations, or is it nor-adrenalin, or a mixture of the two, and if a mixture, is the quantitative composition of it dependent on the type of the sympathetico-adrenal discharge? Recent work which has given some insight into these

important problems will be outlined in a manner similar to that in the section on sympathin. Consequently three questions are considered: (1) What is the chemical nature of the hormone which can be extracted from the adrenal medulla? (2) What is the nature of the hormone secreted on stimulation of the splanchnics which activate the adrenal medulla? (3) What is the nature of this secretion if the adrenal medulla is excited through central nervous impulses initiated reflexly or by stimulation of central autonomic structures?

In 1949 three papers (47, 553, 1173) appeared in the same issue of *Science* in which the presence of nor-adrenalin in extracts of the adrenal medulla (U.S.P. epinephrine) was established and l-arterenol (l-nor-adrenalin) was chemically isolated. Von Euler (89) succeeded likewise in the isolation of nor-adrenalin from the adrenal medulla of cattle, and the nor-adrenalin content of U.S.P. epinephrine was found to vary between 10 and 17 per cent. The results of these chemical investigations were supplemented by biological assays in which medullary extracts were compared with adrenalin and nor-adrenalin in their action on the blood pressure and blood sugar. If isopressor concentrations are used, nor-adrenalin is only about 1/20 as effective in raising the blood sugar as is adrenalin. The assays indicate that the extracts of the adrenal gland consist 25 per cent of nor-adrenalin and 75 per cent of adrenalin (Schümann, 1102). In tumors of the adrenal medulla the extracts were found to consist from 50 to more than 90 per cent of nor-adrenalin (553, 700).

The secretory product of the adrenal medulla resulting from stimulation of the splanchnics was studied by Bülbring and Burn (182). These authors found that when equipressor doses of nor-adrenalin and adrenalin are used in the spinal cat, the effect on the contraction of the normal and on the denervated nictitating membrane is different for the two substances, the ratio of the contraction of the denervated nictitating membrane to that of the normal membrane being much greater for nor-adrenalin than for adrenalin. Stimulation of the splanchnics leads to a contraction ratio which is intermediate between that of each of the two substances (Fig. 68). Quantitative assays showed that the secreted product consists of adrenalin and nor-adrenalin, the former amounting to 20–30 per cent of the total concentration, a result which is similar to that found in the analysis of adrenal tumors. Concordant observations were reported by Gaddum (406), with different indicators for adrenalin and nor-adrenalin.

The metabolic relation of nor-adrenalin to adrenalin is still obscure. It may be that nor-adrenalin is a precursor of adrenalin (Blaschko, 105). Perfusion of the gland with nor-adrenalin increases the production of

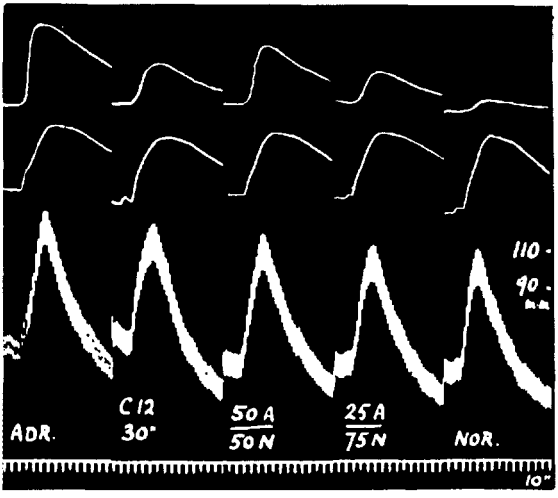


FIGURE 68. An estimation of the proportion of adrenalin and nor-adrenalin liberated by electrical stimulation of the splanchnic nerve (C 12). The record shows the effect of adrenalin and nor-adrenalin in different proportions on the normal (*top*) and denervated (*middle*) nictitating membrane and on the blood pressure (*bottom*) of the eviscerated cat. (Bülbring and Burn, 182.)

adrenalin. Apparently nor-adrenalin can be converted into adrenalin by adrenal tissue (177, 183).

From the physiological point of view more study is needed to determine the action of nor-adrenalin and also its interaction with adrenalin, since both substances are normal products of physiological secretion. A pertinent observation should be mentioned (925). Whereas in the normal animal the intravenous injection of small amounts of adrenalin causes vasodilatation, this reaction is reversed after adrenalectomy. However, it can be restored by a slow infusion of nor-adrenalin. This is an interesting example of physiological interaction between the two secretory products and also an indication of a *resting* secretion of nor-adrenalin from the adrenal medulla.

The important question concerning the nature of the adrenalin secreted under conditions of reflex stimulation or on excitation of centers of the autonomic nervous system can be answered only inadequately. Holtz and Schümann (702) report that lowering the pressure in the carotid sinus induces a contraction of the denervated spleen which disappears on removal of the adrenals. They believe that nor-adrenalin and not adrenalin is responsible for this effect, since in matching experiments on the spleen and gut (both organs are denervated) adrenalin showed a far greater inhibitory action on the

gut. On the other hand, it must be borne in mind that several drugs, such as acetylcholine and morphine, elicit through reflex action (fall in the blood pressure) and central stimulation of autonomic centers a sympathetico-adrenal secretion which is characterized by a marked hyperglycemia (1182). Since, as mentioned earlier, the hyperglycemic action of nor-adrenalin is much weaker than that of adrenalin, it appears certain that in these conditions as well as in asphyxia and anoxia the product of adrenal secretion must consist to a considerable extent of adrenalin. Moreover, emotional excitement raises the blood sugar chiefly through the secretion of the adrenal medulla and, to a small extent, through sympathin elaborated by postganglionic sympathetic nerves (108, 109). Therefore it is suggested that, depending on the type of central or reflex activation, the type of the product of adrenomedullary secretion varies.

The Nature of the Sympathetico-Adrenal Discharge

In view of the fact that central autonomic excitation leads physiologically and clinically to a liberation of sympathin from the nerve endings *and* to an increased secretion from the adrenal medulla, it may be well to consider the total effect of these processes.

Investigations were undertaken to determine the nature of the sympathetico-adrenal discharge when autonomic centers were stimulated by electrical currents or through changes in the internal environment (1039). For the former purpose the hypothalamus was electrically excited; for the latter asphyxia was employed. The humoral response following these types of stimulation was analyzed on the basis of the reactions of the acutely denervated spleen and the nictitating membrane, the contractions of which were recorded. Such analysis is possible because the responsiveness of the nictitating membrane relative to a given contraction of the spleen is much greater for adrenalin than for nor-adrenalin. If the results of the injection of these substances are plotted with the spleen volume as abscissa and the height of the contraction of the nictitating membrane as ordinate, with different adrenalin and nor-adrenalin concentrations as parameters, the nor-adrenalin curve deviates little from the horizontal line whereas the adrenalin curve is nearly vertical. Figure 69 illustrates that increasing degrees of hypothalamic stimulation follow the calibration curve for nor-adrenalin. However, in other experiments an adrenalin-like response was noted under the same conditions. Although various parts of the hypothalamus were stimulated, no correlation could be established between the site of excitation and the type of neurohumoral response. However, several experiments showed that

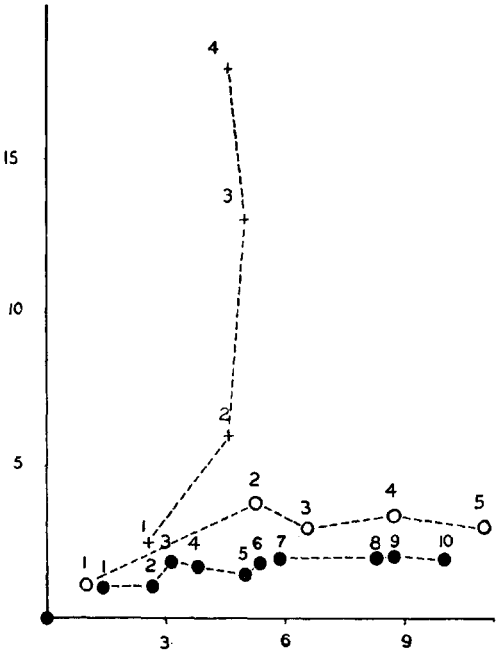


FIGURE 69. The effect of increasing concentrations of adrenalin and nor-adrenalin and of hypothalamic stimulation on the contraction of the denervated nictitating membrane (ordinate, in mm.) and on the contraction of the denervated spleen (abscissa, in cc.). The injection of adrenalin is indicated by the broken line with small crosses at points 1 through 4; of nor-adrenalin, by broken line with o's at points 1 through 5; hypothalamic stimulation of increasing degrees, by broken line with solid o's at points 1 through 10. The experiment shows that hypothalamic stimulation elicits a reaction which is similar to that produced by the injection of nor-adrenalin. (Redgate and Gellhorn, 1039.)

as the intensity of stimulation is increased, the nor-adrenalin response changes to an adrenalin response, a result suggesting that the degree of hypothalamic excitation is the determining factor. Since hypothalamic excitability varies from animal to animal, it is easily understandable that the neurohumoral response varies accordingly.

This interpretation is in agreement with experiments on asphyxia. Measured by the duration of the response and the change in the blood sugar, asphyxia represents a more severe stimulation of the sympathetico-adrenal system than stimulation of the hypothalamus with relatively mild stimuli. It is interesting to note that asphyxia causes a neurohumor to appear in the circulation which on the basis of the spleen and nictitating membrane reactions seems to be adrenalin

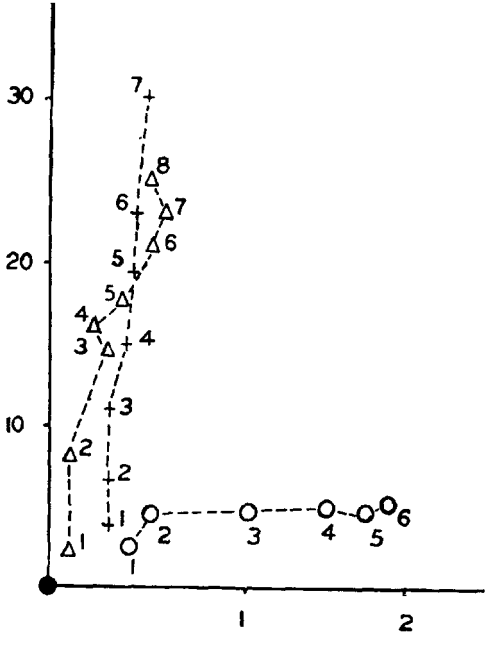


FIGURE 70. The nature of the neurohumoral secretion in asphyxia. The injection of adrenalin is indicated by the broken line with small crosses; of nor-adrenalin, by the broken line with o's; asphyxia, by the broken line with small triangles. Ordinate and abscissa as in Fig. 69. Asphyxia causes a liberation of adrenalin. (Redgate and Gellhorn, 1039.)

(Fig. 70). These experiments strengthen the hypothesis of Holtz and Schümann that nor-adrenalin represents the resting secretion of the adrenal medulla and serves to replenish the store of the postganglionic sympathetic nerves which elaborate nor-adrenalin continually (tonic innervation of blood vessels), whereas the secretion of adrenalin occurs, as Cannon has emphasized, in conditions of emergency. (See Table 11.)

In spite of obvious gaps in our present knowledge, the discussion has shown that research during the last few years has brought unexpected progress in a field which, owing to the classical chemical investigations of Abel and others and the fundamental physiological work of Cannon and his school, appeared to be almost complete. Now it is realized that the product of the secretion of the adrenal medulla is not fixed but variable, depending on the intensity of the stimulation activating the centers of the sympathetico-adrenal system. If it is correct that nor-adrenalin represents the resting secretion of the adrenal medulla and also the product of the main excitatory postgan-

TABLE 11. Recent Work on the Nature of Sympathin

Source	Results of the Assay	Authors
A. Chemical Extraction of Nerves and Tissues		
Splenic nerves	Nor-adrenalin	von Euler
Sympathetic chain	Nor-adrenalin	Bacq and Fischer; Graham
Blood vessels	Nor-adrenalin except for extracts of renal artery, which yields adrenalin	Schmiterlöw
B. Stimulation of Nerves		
Hepatic nerves	Nor-adrenalin	Stehle; Greer
Splanchnic nerves (after denervation of adrenals)	Nor-adrenalin	Melville
Splenic nerves	Nor-adrenalin	Gaddum and Goodwin
Splenic nerves	Nor-adrenalin and small quantities of adrenalin	Peart
Superior cervical sympathetic nerve	Nor-adrenalin and adrenalin	Lecomte and Fischer
Hypogastric nerves	Adrenalin	West
Vasoconstrictors to rabbit's ear	Adrenalin	Gaddum
C. Reflex Excitation of the Sympathetic System		
Vasoconstriction due to diminution of pressure in sino-aortic area	Nor-adrenalin	Holtz; Folkow and Uvnäs; Graham; Walker
Vasoconstriction due to diminution of pressure in sino-aortic area	Nor-adrenalin and adrenalin	Kaindl and von Euler
D. Stimulation of Central Autonomic Structures		
Hypothalamus, brief stimulation	Nor-adrenalin	Gellhorn and Conley
Hypothalamus, prolonged stimulation	Nor-adrenalin or adrenalin	Redgate and Gellhorn
Asphyxia	Adrenalin	Redgate and Gellhorn

glionic sympathetic fibers, it may be one of the important factors in the development of clinical hypertension and other conditions of neurovascular pathology.

Before these clinical questions are discussed, the most recent development of these problems may be mentioned. Von Euler (329) found that the ratio nor-adrenalin/adrenalin as assayed from the spleen is altered by hypophysectomy and restored to its original value by the

injection of ACTH. The adrenotrophic hormone was also found to influence the adrenalin content of the adrenal medulla and the excretion of nor-adrenalin in the urine (331). It would be premature to speculate about the significance of these findings, but it seems of interest to point out that the hypophysial-adrenocortical system, which is activated by sympathetico-adrenal discharges, influences in turn the amount of adrenalin found in the adrenal medulla and in sympathetically innervated structures such as the spleen. Apparently ACTH has an effect on adrenalin metabolism and thereby on the ratio of nor-adrenalin to adrenalin. Perhaps homeostatic mechanisms are involved.

Acetylcholine and Parasympathetic Effectors

After Loewi's discovery (854, 855) that vagal stimulation of the frog's heart leads to the liberation of acetylcholine into the perfusate, extensive studies were performed in order to determine the validity of the principle of neurohumoral transmission for the parasympathetic nervous system throughout the animal kingdom. Its applicability to invertebrates was demonstrated by Bacq (55). That acetylcholine mediates parasympathetic effects in warm-blooded animals could be convincingly shown only after the important discoveries had been made (1) that the instability of acetylcholine in the blood and tissues is due to the presence of an enzyme (321, 1021) or, as is now known, a group of enzymes, the cholinesterases (794, 857), which rapidly split acetylcholine into choline and acetic acid; and (2) that certain drugs, particularly eserine, inhibit this enzyme and thereby make the assay of acetylcholine possible (321, 857). Numerous biological tests had also to be devised for the identification of acetylcholine.

Briefly, but not exhaustively stated, acetylcholine is assumed to be present in a perfusate if several tests for this substance are positive and lead to quantitatively similar results. The tests most commonly used are performed (1) on smooth or skeletal muscles, such as the leech muscle or the rectus abdominis of the frog, which contract in solutions of acetylcholine in the presence of eserine; (2) on the hearts of frogs or of certain invertebrates (1029), which are highly sensitive to acetylcholine and show on application of this substance a decrease in the height of contraction and eventually a standstill in diastole; and (3) on the blood pressure of the eserinized cat, which responds to acetylcholine with a fall.

A few examples illustrating the liberation of acetylcholine at different parasympathetic endings may be cited. Feldberg and Krayer (344, 801) showed that stimulation of the vagus in the eserinized dog leads

to the appearance of a substance in the coronary venous blood which, on the basis of tests with the leech muscle and the cat's blood pressure, could be pronounced to be acetylcholine. Moreover the tests were negative in the presence of atropine, a finding in agreement with this interpretation since acetylcholine, although liberated in the presence of atropine, remains ineffective on the effector organ under this condition (Loewi, 854).

That the *excitatory* effects of vagal stimulation are associated with the liberation of acetylcholine was shown by Finkleman (358) on the rabbit's intestine. This author recorded the activity of two segments of the gut *in vitro*. A salt solution flowed from an innervated piece of gut *A* to a denervated piece *B*. On stimulation of the nerves supplying *A*, the tone increased not only in *A* but, although to a lesser extent, in *B*, indicating that a neurohumor had been liberated on stimulation of the vagus nerve. Evidence that the liberated substance was acetylcholine was presented by Dale and Feldberg (248) and Bunting, Meek, and Maaske (186). These authors perfused the blood vessels of the stomach and small intestine respectively with an eserinized salt solution and found the perfusate positive for acetylcholine after vagal stimulation, as indicated by the reaction of the leech muscle, frog's heart, and blood pressure of the eserinized cat.

Using the greatly increased sensitivity of the denervated gut to acetylcholine as an indicator, Meek *et al.* devised an interesting experiment to show the liberation of acetylcholine on vagal stimulation in the stimulated animal itself. When they recorded the intestinal activity from a normal and a chronically denervated section of the gut, they noted on vagal stimulation only an increased tone in the innervated part of the intestine. However, after eserine, which prevented the destruction of acetylcholine set free on stimulation, the denervated gut reacted likewise, and its increased tone appeared after a latent period which corresponded approximately to the time necessary for the blood to flow from the innervated to the denervated part of the gut.

Babkin *et al.* (49, 50) showed that parasympathetic excitation of the submaxillary gland by electrical stimulation of the chorda tympani leads in the eserinized cat to salivary secretion not only on the stimulated but also on the contralateral side if the latter has been chronically denervated. In addition this stimulation causes in the eserinized cat a fall in the blood pressure which appears to be due to the systemic effect of acetylcholine liberated from the parasympathetic endings in the salivary gland, since it is prevented by ligation of the submaxillary veins.

Tests with the leech muscle and blood pressure give evidence of the liberation of acetylcholine from the vagal endings of the lungs in the guinea pig (1158). Vasodilator action induced in various parts of the body by the stimulation of appropriate nerves seems likewise to be associated with this neurohumor. Bain (62) and Feldberg (336, 337), perfusing the blood vessels of the tongue, found that during stimulation of the lingual nerve acetylcholine appears in the perfusate while the blood flow through the tongue increases. Wybauw (1251) elicited vasodilatation on stimulation of the posterior roots in the cat and showed that the perfusate contains in the experimental period a substance which, assayed by several methods, behaves like acetylcholine. Finally, it should be mentioned that excitation of the oculomotor nerve leads to the liberation of an acetylcholine-like substance into the anterior chamber of the eye (320).

It may be inferred from the evidence presented that acetylcholine accompanies the stimulation of parasympathetic endings throughout the body. Following the same general outline as in the presentation of the work on sympathin, the question must be answered whether acetylcholine appears also when parasympathetic nerves are activated not by the artificial means of electrical stimulation but by more physiological processes, as in various types of reflexes. The carotid sinus reflex and the light reflex have been studied from this point of view. As is well known, the injection of adrenalin elicits vagal discharges reflexly initiated by the rise in pressure in the carotid sinus and these discharges increase with increases in the blood pressure. Krayer and Verney (801) found that the acetylcholine content of the coronary vein of the eserinized dog increases under these conditions in relation to the increased blood pressure. Furthermore stimulation of the carotid sinus nerve, leading to a fall in the blood pressure, causes the appearance of an acetylcholine-like substance in the separately and under-constant-pressure perfused abdominal blood vessels (Gollwitzer-Meier, 556). Finally, it was noted that under the influence of the light reflex acetylcholine appears in the aqueous humor of the eserinized rabbit (320) and cat (878). The experiments give clear evidence that autonomic reflexes leading to parasympathetic action are accompanied by the liberation of acetylcholine.

Not only the parasympathetic nerves but the sympathetic fibers innervating the sweat glands belong to the cholinergic group. This fact was foreshadowed by the well-known observation that drugs of the muscarin group elicit sweat secretion and that the latter is blocked by atropine. Dale and Feldberg's fundamental experiments (249) showed that the sweat gland behaves on electrical stimulation

also as if it were innervated by parasympathetic fibers. They perfused the cat's paw with an eserinized salt solution and found on sympathetic stimulation, which induced sweat secretion, a substance in the perfusate which on the basis of its action on the blood pressure and leech muscle appeared to be acetylcholine. Moreover its activity increased in the presence of eserine and was abolished by atropine. This is the basis for including the sympathetic nerves supplying the sweat glands in the cholinergic group.

Sympathetic vasodilators seem likewise to be cholinergic, although no full agreement has been reached on this point. In order to obtain sympathetic dilator effects, the hind legs of a dog were perfused with defibrinated blood to which some adrenalin had been added so that the blood vessels were in a moderate degree of constriction. Stimulation of the sympathetic chain causes vasodilatation under these conditions. Its cholinergic nature is shown by the fact that eserine intensifies the vasodilator action and that the perfusate contains a substance which causes contraction of the leech muscle (Bülbring and Burn, 178). These authors believe that, on the contrary, vasodilators in the cat are adrenergic, but the recent work of Folkow, Uvnäs, and their collaborators (371) seems to give clear evidence for the cholinergic nature of vasodilator fibers in this species.

The basis for the statement that cholinergic nerves act by liberating acetylcholine from their endings may be summarized as follows:

1. It has been shown that acetylcholine is liberated from cholinergic nerve endings on electrical stimulation and in reflex action.

2. There is a parallelism between the action of acetylcholine and the stimulation of cholinergic nerves, and this statement holds true whether nerve stimulation leads to secretion or to the contraction or inhibition of smooth muscles.

3. Atropine blocks the effects both of the stimulation of cholinergic nerves and of acetylcholine. As Loewi showed, atropine does not interfere with the liberation of acetylcholine from the nerve endings but only with its action on the ultimate structure.

Humoral Transmission through Autonomic Ganglia

The work discussed in the preceding section leads to the obvious question whether a neurohumor may not be responsible for the transmission of nervous impulses across autonomic ganglia. Such an assumption appeared to be not unlikely after Dale, Feldberg, and Vogt (250) had shown that acetylcholine was released from somatic nerve endings, for the close resemblance between neuromuscular and synaptic transmission has often been emphasized. Experimental work

has indeed established the fact that acetylcholine acts as a transmitter of impulses from the preganglionic to the postganglionic nerves in autonomic ganglia.

The first evidence for a neurohumoral transmission through the superior cervical sympathetic ganglion was obtained by Kibjakow (773), who perfused this ganglion before and during prolonged stimulation of the preganglionic nerve. In the latter condition a substance appeared in the perfusate which, on injection into the same or a similar preparation, induced a contraction of the nictitating membrane. Feldberg and Gaddum (342) were unable to repeat this experiment but succeeded in confirming the principle involved. They showed by perfusing the ganglion with an eserinized salt solution that following the stimulation of the preganglionic nerve there appeared in the solution a substance which on the basis of the quantitative agreement in six different tests was pronounced to be acetylcholine.

The specificity of acetylcholine in autonomic synaptic transmission is obvious from the fact that only stimulation of preganglionic, not of postganglionic, sympathetic nerves leads to the liberation of acetylcholine (349). Its role as a synaptic transmitter is also supported by experiments showing that the effect of acetylcholine and that of preganglionic nerve stimulation are similarly altered by eserine. Moreover curare blocks the action of preganglionic nerve stimulation as well as that of acetylcholine. Since other sympathetic ganglia behave similarly, it may be assumed that preganglionic sympathetic nerve fibers are cholinergic and that the liberation of acetylcholine plays an important role in the transmission of impulses through autonomic ganglia.*

This argument derives further support from quantitative studies on cholinesterase (ChE). The presence of this enzyme at the neuromuscular junction and in sympathetic ganglia in quantities adequate to inactivate quickly the liberated acetylcholine and to prevent the accumulation of relatively large amounts of it has been a cornerstone in the development of the theory of neurohumoral transmission (962). Experiments on denervated ganglia are of special interest. After preganglionic denervation the ChE concentration of sympathetic ganglia declines. The application of the more recent distinction

* The light reflex leading to pupillary constriction is a parasympathetic reflex. It can be inhibited by the injection of ChE (Mendel, 927). However, since acetylcholine is liberated at the ending of the oculomotor nerve, the paralysis of this reflex by ChE could be due to the action of this enzyme at the nerve endings. That the central synaptic transmission is cholinergic is not proved by this experiment.

between specific and nonspecific* ChE to this problem seems to indicate that true ChE, which is more rapidly lost after preganglionic denervation, is primarily concerned with synaptic transmission (Sawyer, 1086; Koelle, 795).

Since the splanchnic fibers innervating the adrenal medulla are generally considered to be preganglionic nerves, one would expect them to be cholinergic. Feldberg (346–348) and Minz (933) and their collaborators have indeed adduced good evidence that acetylcholine appears in the blood of the adrenal vein on stimulation of the splanchnics and have also shown that the injection of acetylcholine leads to the liberation of adrenalin. To demonstrate this effect it is necessary to inject acetylcholine into the eviscerated cat, in which the peripheral vascular effect of this substance is blocked by atropine. The secretion of adrenalin is indicated by a rise in the blood pressure and is enhanced by eserine. Similarly it is found that in the same preparation the pressor effect induced by splanchnic stimulation is augmented by eserine.

Koelle's work (794) showing that true ChE is localized in the adrenal medulla lends further support to the assumption that stimulation of the splanchnic nerves involves the liberation of acetylcholine as an intermediary link in the release of adrenalin. It would be very interesting to know whether sectioning of the splanchnics would lead to the rapid disappearance of specific ChE, in analogy with the denervation experiments on the superior cervical sympathetic ganglion reported above.

Is Acetylcholine Responsible for Nervous Conduction?

The facts described in the preceding sections raise the question whether acetylcholine is responsible for the conduction of nerve impulses in various types of nerve fibers. This assumption has been defended vigorously by Nachmansohn (964, 965), whose chief arguments may be listed as follows: ChE, which is able to split acetylcholine at very high speed, is present in nerves throughout the animal kingdom and is located at the surface of the nerve trunks where the bioelectrical phenomena take place. Moreover, as mentioned earlier, ChE concentration and the production of electricity run parallel in the electric organ of the fish. Systematic studies with drugs inhibiting the action of ChE (eserine, strychnine, di-isopropylfluorophosphate

* The specific ChE hydrolyzes acetylcholine faster than other cholinesters, whereas no such difference exists in the action of the nonspecific ChE. For further distinctions between both forms of ChE see Koelle's excellent review (795).

[DFP]) seem to show that nerves cease to conduct when the ChE is inactivated.

Against this interpretation speak the following facts emphasized by Gerard (525, 526) in a recent review of these problems. Studies on frog nerves poisoned with different concentrations of DFP showed that there is no parallelism between ChE activity and nerve conduction. Concentrations which completely abolish the activity of this enzyme do not interfere with nerve conduction, although in still higher concentrations (presumably owing to general toxic effects) nerve conduction is blocked (156). Feldberg (338, 339) stresses the fact that acetylcholine is probably absent in sensory nerve fibers whose conduction does not differ from that of other nerves, and Koelle finds that specific ChE is absent in sensory neurons. Moreover, if acetylcholine were involved in nerve conduction, one would expect it to alter the electrical charge of the membrane, but Lorente de Nó (868) found it rather inert and the objection of Nachmansohn to these experiments on the ground that acetylcholine does not penetrate the nerve membrane from the outside can be countered by the observation that the introduction of acetylcholine into the nerve fiber by a micropipette does not alter the membrane potential (Gerard). Acetylcholine is undoubtedly liberated from nerves on stimulation, but other substances, such as histamine and potassium, likewise appear in the medium in which the nerve is suspended (327, 955). That acetylcholine is an extremely important substance is not denied, but its presence in all tissues, even those which are free from nerves (placenta), suggests that it plays a general role in cellular metabolism and not a specific role in conduction.

Acetylcholine and the Central Nervous System

The brilliant investigations through which the concept of the neurohumors was firmly established for the autonomic nervous system and also for the cholinergic endings of the somatic nerves in the muscles led to studies on the role of neurohumors in the central nervous system in general. Here again the discussion will take up relatively few investigations, and the reader is referred to reviews by Feldberg (338, 339) and Gerard (525, 526) for details.

There is ample evidence that acetylcholine applied topically is capable, under conditions ensuring its stability (eserinized animals), of exciting motor neurons. The action of acetylcholine on the motor cortex results in contralateral movements (930). Also, on application to the floor of the fourth ventricle (trigonum of the hypoglossal

nucleus), acetylcholine elicits activation of this structure in the form of deglutition and tongue movements (Miller, 931). From Gesell and Hansen's work (535) it may be inferred that the respiratory center behaves in a similar way, since respiration is stimulated by the intra-arterial injection of acetylcholine, and the responsiveness of this center to reflex stimulation from the carotid sinus or from stretch receptors in the lung is likewise increased under these conditions. Finally, it should be mentioned that perfusion of the isolated head with eserine leads to jerky movements of the head and blinking. This action is presumably due to the stimulating effect of acetylcholine accumulated in the brain under the influence of eserine on various motor neurons of the brain stem (Chute and Feldberg, 225).

Similar effects have been established for the spinal cord. Bülbring and Burn (180) noted a series of contractions of the anterior tibial muscle provided that acetylcholine was added to the blood with which the spinal cord was perfused and that eserine and adrenalin were likewise present in the perfusate. These experiments are in line with those of Brown, Dale, and Feldberg (161), who had shown that intra-arterial injections near the point where the artery enters the muscle give rise to a contraction. The work of Bülbring and Burn suggests that acetylcholine stimulates the anterior horn cells of the spinal cord.*

This interpretation of acetylcholine-eserine effects on various neurons is supported by studies on action potentials. The diminution in the amplitude of the cortical potentials after eserine (Chatfield, 220), contrary to the opinion of the earlier investigators, is due to the increased asynchrony of cortical activity and reflects excitation. The latter is magnified by the addition of acetylcholine through the recruitment of neurons and results in spike potentials. Moreover acetylcholine as well as eserine increases the effectiveness of several convulsive drugs, as indicated by the appearance and the frequency of spikes (720).

It was mentioned earlier that the local application of mecholyl to the motor cortex may induce a rise in the blood pressure (803). This effect is due to the activation of cortical neurons which in turn transmit impulses to the autonomic centers in the hypothalamus and medulla. It was also noted that eserine injected intravenously greatly increases the responsiveness of the hypothalamus. Piloerection, frequently absent on stimulation of this area with mild condenser discharges which evoke other sympathetic symptoms such as a rise

* Kennard (766) reports in a preliminary paper that the injection of traces of acetylcholine into the anterior horn cells causes excitation.

in the blood pressure, pupillary dilatation, and contraction of the nictitating membrane, occurs commonly after the administration of eserine.*

A direct action by acetylcholine on the autonomic centers in the hypothalamus which regulate the internal secretion of posterior pituitary hormones is shown by Pickford's interesting experiments. She found (299, 1009, 1010) that acetylcholine inhibits diuresis just as stimulation of the supraoptic nuclei in the hypothalamus and excitation of the nerves in the hypothalamic stalk do. This effect is not of vascular origin and persists after denervation of the kidney. Most important is the observation that the urine produced in the acetylcholine experiments contains the antidiuretic hormone, which is absent in similar acetylcholine experiments performed on animals in which the posterior pituitary had been previously removed.

The site of action of acetylcholine was determined by injecting it into the brain itself. From earlier work it was known that the secretion of the antidiuretic hormone is controlled by the supraoptic nuclei. If acetylcholine is capable of exciting these neurons, one would expect that injecting it into these nuclei would inhibit water diuresis; also that such an effect would not be elicited from other hypothalamic structures; and finally that injections of physiologically inert material (isotonic sodium chloride solution) would not activate the supraoptic nuclei. Pickford showed experimentally that these assumptions are valid. Moreover it was observed that the action of acetylcholine was prolonged in the presence of eserine and that eserine by itself produced some inhibition of diuresis (1010).

These experiments, extended by similar studies with DFP which resulted in prolonged effects, give strong support to the assumption that acetylcholine is a physiological activator of the supraoptic neurons (300). It is interesting to note that the concentration of ChE is high in the supraoptic nucleus (339). Important as these contributions are, the crucial experiment remains yet to be done which would prove the liberation of acetylcholine when under physiological conditions an increased secretion of the antidiuretic hormone takes place. Although there can be little doubt that neurons of the central nervous system proper can be activated by acetylcholine, this fact in itself is no adequate basis for assuming that this chemical substance is responsible for or involved in synaptic transmission. What would decisively justify such a conclusion would be to prove that neuronal activity at various levels of the central nervous system is accompanied by the liberation of acetylcholine and that the degree

* Unpublished observations.

of activation is related quantitatively to this substance. Although such proof is not yet available, the following work aiming at a decisive demonstration is worthy of attention.

Bülbring and Burn (180) perfused the spinal cord with a salt solution and eserine and found that stimulation of the central end of the sciatic nerve leads to the appearance of acetylcholine in the venous effluent from the cord. However, the authors admit as a possible source of acetylcholine, in addition to the neurons, the striated muscles surrounding the spinal column. Chang *et al.* (215) found evidence for the liberation of acetylcholine on stimulation of afferent vagal fibers in the isolated head connected with the trunk solely by the carotid and jugular vessels. The acetylcholine liberated led to the secretion of adrenalin in the eserinized trunk and was identified as acetylcholine through tests on the leech muscle and blood pressure.

A great deal of work has been carried out in recent years to enlarge our knowledge of the action of acetylcholine on the central nervous system in general and the function of synaptic transmission in particular, but we are still far from the goal. Although acetylcholine and ChE are found in the brain, the concentration of the latter does not increase in higher animals in line with the increase in the number of synapses (340). Analyses of the brain for acetylcholine in various functional conditions have shown changes, but they are far from consistent, and to a certain extent are even diametrically opposed to the results to be expected if acetylcholine were necessary for neurohumoral transmission.*

Experiments with eserine, DFP, and other inhibitors of ChE have likewise failed to give consistent results (Gerard, 525). This may in part be due to the fact that these drugs have other effects in addition to the inhibition of ChE. Thus several "anticholinesterases," including DFP but not eserine, alter the oxygen consumption of the brain (156). Consequently the action of these drugs may be related to the brain metabolism and not to their influence on acetylcholine. For this reason eserine appears to be more suitable for investigations of the physiological role of acetylcholine than the newer anticholinesterases (DFP and others). Feldberg (339) mentions that the action of eserine depends on the presence of acetylcholine. Thus, although eserine as well as acetylcholine constricts the normal pupil, only the latter retains this effect after parasympathetic denervation of the iris.

* Richter and Crossland (1052) found an increase in the acetylcholine content of the brain in anesthesia and a decrease in convulsions. Earlier investigations failed to show significant changes in the acetylcholine content of the brain in anoxia and hypoglycemia, but an increase in prolonged strychnine convulsions was reported (240).

Eserine cannot act under these conditions, since as the result of this degeneration the iris is depleted of acetylcholine. However, even the use of eserine as an experimental tool is not without great difficulties, since it may induce effects which are not related to its action on ChE (Heymans, 643).

In recent years extensive studies have been made with a new enzyme, choline acetylase (Nachmansohn and Machado, 966), which is responsible for the synthesis of acetylcholine in the brain. Since it is rather irregularly distributed in the brain, the assumption appeared necessary that some synapses in the central nervous system may be cholinergic and others noncholinergic (Feldberg, 350). Even if we accept this assumption, the question remains undecided whether the noncholinergic synapses transmit impulses through electrical means or use a different chemical transmitter. On the other hand the opinion has been expressed occasionally that electrical transmission and humoral transmission represent two separate mechanisms. Is it possible that the humoral mechanism is the more primitive means of spreading excitation and is normally confined to the phylogenetically older parts of the central nervous system, particularly its autonomic division? And could it be that acetylcholine plays the role of a synaptic transmitter in the somatic central nervous system only in special conditions? *

Before we try to answer these questions in the next section, it may be emphasized that no matter what the ultimate result of investigations into the role of acetylcholine in synaptic transmission may be, the study of this substance is of great interest for our understanding of cellular functions in general. Thus Feldberg (339) showed that only a small fraction of the effect of acetylcholine on the gut is due to its action on ganglionic stimulation. Abdon (1) stresses the fact that in the heart and muscle a breakdown of acetylcholine occurs which is independent of nervous action, and Bülbring and Burn (184) made the fundamental observation on the auricles of the rabbit's heart that in different conditions acetylcholine either may start the beat after it has stopped spontaneously and increase it in amplitude and frequency or may inhibit the activity of this structure. Studies on the differential ability of a powder to synthesize acetylcholine when the powder is prepared from stopped auricles and when it is prepared

* Eccles (310) found that physostigmine has an influence on synaptic transmission only when repetitive and not when single preganglionic stimuli are involved. This observation may be related to the blocking effect of certain convulsions by TEA (see p. 263) although normal somatic processes remain unaltered, since Adrian and Moruzzi (17) have shown that the rate of neuronal discharge is greatly increased in convulsions.

from fresh auricles led to the conclusion that "the activity of auricular muscle and the synthesis of acetylcholine are inseparably linked" and "that activity is perhaps responsible for maintenance of the synthesizing power." Perhaps these investigations provide a new lead for an explanation of the rather bewildering variety of the effects described for the action of acetylcholine on central nervous activity.

The Action of Tetraethylammonium Chloride on the Central Nervous System (935)

The discussion has shown that acetylcholine is the neurohumor involved in the transmission of impulses via autonomic synapses but that clear evidence for a similar role of this or any other chemical substance in the synapses of the somatic nervous system is lacking. On the other hand, the great sensitivity of neurons to acetylcholine and the presence of cholinesterase and choline acetylase in the central nervous system suggest that acetylcholine plays an important role in the life of the neuron. The impasse we have reached seems to indicate that a new approach to this problem is needed. The contribution of neuropharmacology to the question of neurohumoral transmission may now be considered.

Investigations of recent years have clearly established the fact that tetraethylammonium chloride (TEA) is able to block transmission through autonomic ganglia (2, 3). Preganglionic stimulation of the superior cervical ganglion no longer leads to a contraction of the nictitating membrane after the injection of TEA, and acetylcholine added to the perfusate of the superior cervical sympathetic ganglion after a previous injection of TEA fails to evoke a contraction of the nictitating membrane (223), although such an effect can be induced by potassium. Similar results were obtained on the stellate ganglion, using the heart rate as an indicator of ganglionic transmission. Finally, it could be shown that postganglionic potentials are abolished by TEA in experiments with electrical stimulation of preganglionic nerves, although the excitability of postganglionic nerves remains unchanged (936).

If TEA abolishes transmission via autonomic ganglia, one would expect it to interfere with the liberation of adrenalin from the adrenal medulla, since this process requires the action of acetylcholine as an intermediary step. Using the nictitating membrane as an indicator, Morrison and Farrar (948) showed that stimulation of the splanchnics evokes no secretion of adrenalin after TEA, although the reactivity of the nictitating membrane to injected adrenalin is not altered.

Profound changes in carotid sinus reflexes after TEA give further

evidence for the blocking of sympathetic and parasympathetic impulses at synapses by this drug. The sympathetic effects on the blood pressure and heart rate which follow the clamping of the carotid arteries below the sinus are depressed after TEA, and the depressor action following the rise of the pressure in the carotid sinus is weakened (111). The bradycardia and fall in the blood pressure following stimulation of the carotid sinus in man are abolished by TEA (1149). The rise in the blood pressure on stimulation of the central end of the vagus is likewise suppressed. That parasympathetic synapses are blocked is indicated by the fact that vagal stimulation becomes ineffective on the heart rate after TEA, although the injection of acetylcholine still produces bradycardia (2). Moreover TEA has been shown to block impulses in the parasympathetic ciliary ganglion (879). In the human being TEA paralyzes the activity of the stomach and small bowel, as indicated by fluoroscopic studies.

The injection of TEA leads to a fall in the blood pressure owing to the blocking of impulses which originate in the vasomotor center. In conditions in which the tone of the vasomotor center is increased, the fall in the blood pressure in response to TEA is correspondingly greater. Thus TEA becomes a useful indicator of the sympathetic tone (705, 969).

Drugs which alter the blood pressure through peripheral action show increased effects under the influence of TEA (936). This is due to the fact that the compensatory reflexes of sino-aortic origin are weakened or abolished. Consequently the rise in the blood pressure in response to adrenalin and the depressor effect of glyceryl trinitrate are augmented after TEA (934). However, pressor effects which are induced by the stimulation of autonomic centers such as the hypothalamus are diminished or abolished under the influence of this drug (Fig. 71) (238). The pressor effect in this experiment involves sympathetic synapses which are blocked by the drug. As the effect of TEA gradually diminishes with the passage of time, the pressor action of injected adrenalin decreases and that induced by hypothalamic stimulation increases. The former results from the restoration of the buffer reflexes of sino-aortic origin, the latter from the restitution of synaptic transmission within the sympathetic nervous system.

In experiments with mild hypothalamic stimulation the pressor effect is largely of sympathetic origin, since it persists after inactivation of the adrenal medulla. However, central excitatory effects leading to a discharge of adrenalin can likewise be blocked by TEA. Van den Heuvel-Heymans (1182) showed in rabbits that the hyperglycemic actions of acetylcholine and of morphine are prevented by either TEA

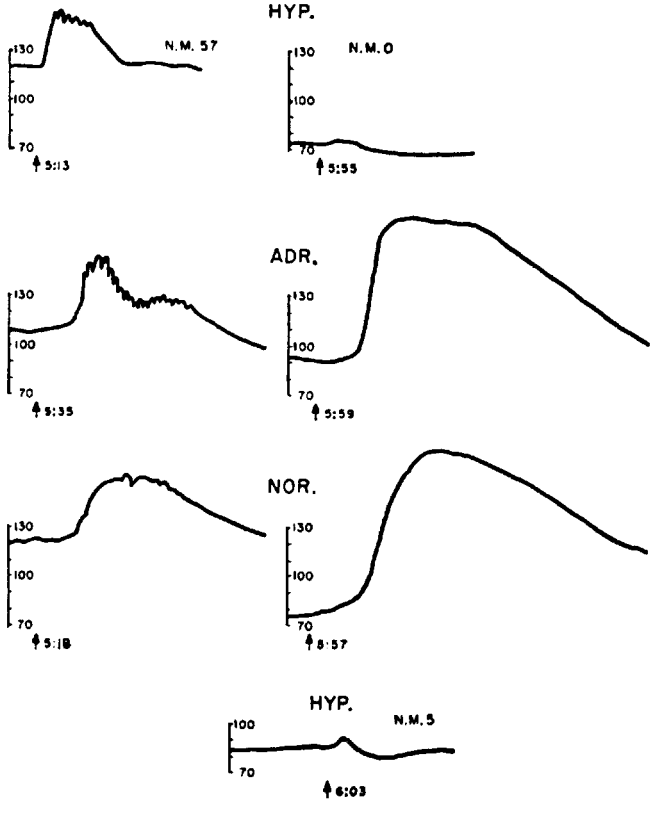


FIGURE 71. The effect of TEA on the response of the blood pressure to hypothalamic stimulation (HYP.) and to the injection of adrenalin (ADR.) and nor-adrenalin (NOR.). The curves on the left side show the response before the injection of TEA; those on the right side, after the injection. N.M. followed by a number indicates the contraction of the nictitating membrane in millimeters. (Conley and Gellhorn, 238.)

or removal of the adrenal glands. The experiments suggest that the sympathetico-adrenal discharge is blocked by TEA. It appears likely that this discharge is initiated in the acetylcholine experiment by the fall in the blood pressure, which in turn induces a sympathetico-adrenal discharge via the sino-aortic reflexes. In the morphine experiment the release of autonomic centers of the brain stem from cortical inhibition may account for the increased secretion of adrenalin.

These experiments show convincingly that TEA can effectively block parasympathetic and sympathetic impulses at autonomic synapses and in both branches of the autonomic nervous system can thereby eliminate or greatly diminish tonic activity and excitatory

effects whether these are of reflex origin or are due to the excitation or release of autonomic centers. Other drugs seem to show a similar specificity for the autonomic system and are even more effective than TEA (581). Neuropharmacological investigations of this kind may be of great value for the study of the problems of neurohumoral transmission. The experiments described thus far seem to indicate that TEA exerts a specific action on cholinergic synapses. If somatic synapses are not blocked, do not such experiments give at least indirect evidence for the different nature of the synaptic process in these neurons?

It was mentioned earlier that acetylcholine is liberated at the myoneural junction. The somatic nerve fibers supplying striated muscle are consequently considered to be cholinergic. The similarity between the myoneural junction and the synapses has often been emphasized, and the discussion whether the transmission of impulses across synapses can be explained on a purely chemical basis, through liberation of a neurohumor such as acetylcholine which in turn excites the postganglionic neuron, or whether the transmission involves chiefly electrical phenomena has been extended to the neuromuscular junction. There is evidence for both types of mechanisms: an end-plate potential adequate to evoke action potentials in the muscle and a liberation of acetylcholine at this structure. Experiments with TEA suggest that humoral transmission plays only a minor role at the myoneural junction, since even with lethal doses of TEA neuromuscular transmission is unimpaired (Moe, 935).

Only scattered information exists about the action of TEA on the central nervous system. Variations in spinal reflexes have been reported (1082) while the respiratory slowing initiated by an increased blood pressure — a carotid sinus reflex — remained unchanged. The clinical observations that pain resulting from spasms of smooth muscles is relieved by TEA suggest that the spasms are abolished through autonomic blockage. Other findings that TEA alters the threshold for pain are hardly suitable for a physiological analysis (935).

In order to determine whether TEA influences synapses of the central nervous system, experiments were performed on various sensory and motor phenomena in cats before and at the time of the maximal action of TEA. The latter is conveniently indicated by maximal pupillary dilatation. If TEA is injected slowly so that a sudden fall in the blood pressure is avoided, no changes occur in cortical potentials. The effect of stimulation of the motor cortex on skeletal muscles does not suffer any decline whatever; and various sensory functions, indicated by the response of the auditory projec-

tion area to clicks, of several cortical areas to nociceptive impulses (sciatic stimulation), and of the sensorimotor area to proprioception, remain unchanged (472). These are rather surprising findings, since the motor and sensory phenomena studied involve multiple synapses which show an unimpaired transmission at a time when parasympathetic and sympathetic impulses are completely blocked. The data suggest that the elimination of acetylcholine in synaptic transmission by TEA is compatible with the normal functioning of the neuromuscular junction and somatic synapses but causes a complete block at autonomic ganglia.* In view of the fact that the autonomic nervous system is phylogenetically older† than the neocortex and also because of the widespread existence of neurohumoral transmission in the central nervous system of invertebrates (Bacq, 55), it seems not unlikely that this mechanism is of greater importance for the function of the autonomic than for that of the somatic nervous system. Chemical analysis supports this interpretation, since the acetylcholine content of the brain is about $\frac{1}{10}$ that of autonomic ganglia (340).

The intimate relation existing between the excitation of somatic neurons and acetylcholine suggests that neurohumoral transmission involving the liberation of acetylcholine may represent an alternate mechanism which is called into action only in special conditions. Since acetylcholine and eserine greatly influence convulsive activity,‡ it appeared not unlikely that the latter may utilize electrical as well as neurohumoral transmission. There is some support for such an assumption. Eserine produces convulsive twitchings which are, as Langley and Katō (817) showed, at least partly of central origin. In experiments on rats it was found that this convulsive action was markedly diminished and delayed by pretreatment of the animals with TEA (471).

That more experimental work is needed before the ideas presented in the last few paragraphs can be fully accepted is readily admitted. It is believed, however, that no matter what the result of such experiments may be, they will definitely contribute toward clarifying some of the most puzzling problems of neurophysiology.**

* That possibly some sympathetic synapses are not blocked by TEA is suggested by Pardo, Rennick, and Moe (990).

† In this respect it is of interest that the acetylcholine content of the human brain is the lowest, that of other mammals intermediate, and that of the frog the highest (340).

‡ See pp. 143ff.

** Space does not permit a discussion of the work of Paton and others (994) on the action of hexamethonium compounds and their importance for the treatment of hypertension.

Sympathin, Tetraethylammonium Chloride, and Hypertension

It is perhaps not superfluous to indicate the relation of the physiological investigations reported in this chapter to the problem of hypertension, without attempting to review in more than barest outline the vast amount of clinical and experimental work in this field.

That essential hypertension is in part based on increased sympathetic impulses is suggested by the fact that splanchnicectomy or more extensive elimination of the sympathetic outflow decreases, at least in a certain percentage of cases, the diastolic blood pressure level. The administration of TEA produces similar effects (882). The considerable number of the cases which do not react to either procedure, however, indicates clearly that the central sympathetic tone is only one factor involved in the genesis of clinical hypertension and that anatomical changes in the vascular bed and humoral factors play in addition a very important role.

The fall in the diastolic blood pressure after TEA could be due to a decrease in the cardiac output and/or a lowered peripheral resistance. Since the cardiac output is either unchanged or slightly increased, the diminished sympathetic tone seems to account for the fall in the diastolic pressure. An increased heart rate due to a blocking of parasympathetic synapses in the heart is probably responsible for the increased cardiac output in some instances and makes TEA unsuitable for the determination of the sympathetic vascular tone in man.*

In spite of these shortcomings, tests with TEA have shown that the diastolic blood pressure falls in proportion to the resting blood pressure level. Even the percentage drop is somewhat larger in cases with a very high resting diastolic pressure. The loss in sympathetic tone may produce orthostatic hypotension, since this condition is physiologically counteracted by a sympathetico-adrenal discharge, now blocked by TEA. An increased peripheral blood flow and postural hypotension have been found to persist at a time when the blood pressure has returned to its resting level.

The fact that TEA reduces the blood pressure primarily through a diminution of the sympathetic tone is further indicated by a fair degree of parallelism between the effects of this drug and of sympathectomy on the blood pressure.† Moreover the depressor action of TEA is greatly reduced in splanchnicectomized patients. No marked changes in motor or sensory functions have been reported. Apparently

* Perhaps the use of TEA after previous atropinization would be a better procedure.

† TEA and also methonium salts are more effective on dogs with a neurogenic hypertension than on normal or renal hypertensive animals (988).

the blocking of cholinergic synaptic transmission does not cause any symptoms on the part of the somatic nervous system in man. This is in agreement with the animal experiments described above.

That TEA is not helpful in the treatment of hypertension is in part due to its brief action and in part to its undesirable side effects. These consist mainly of the blocking of parasympathetic synapses, the result being interference with the accommodation of the eye, gastrointestinal activity, and salivary secretion. Obviously a drug with greater affinity to sympathetic than parasympathetic synapses would be desirable.

Another approach to this problem would involve the blocking of the "sympathin" effects on the blood vessels which, probably in conjunction with many other factors, cause the rise in the blood pressure first on a functional and later on an anatomical basis. The reader remembers that this "sympathin" seems to be in part adrenalin and in part nor-adrenalin and that the adrenal medulla liberates a secretory product consisting of varying amounts of both substances. Unfortunately it is not fully known what the ratio adrenalin/nor-adrenalin is for various conditions leading to a sympathetico-adrenal discharge, but clinical studies suggest nor-adrenalin as an important neurohumor in patients with hypertension. Goldenberg and his collaborators (554) noted fundamentally different responses in the human vascular system to adrenalin and nor-adrenalin. Adrenalin was found to be a powerful stimulant of the heart, leading to an increased cardiac output and to a decrease in the peripheral resistance. These results were obtained on normals and hypertensive patients. On the other hand, nor-adrenalin caused an increase in the peripheral resistance and a rise in the blood pressure without any significant action on the heart, and this type of reaction was particularly marked in hypertensives. It is interesting to note that the effect of nor-adrenalin can be offset by a simultaneous injection of adrenalin. The authors suggest as the possible cause of hypertension a "disturbed balance between both sympathetic transmitters."

These findings make it imperative to investigate the influence of dietary, hormonal, and other factors on the adrenalin/nor-adrenalin ratio* of the secretory product of the adrenal medulla and to determine whether this quotient differs in hypertensive animals and in controls. Holtz *et al.* (701) have reported that nor-adrenalin appears in increased amounts in the urine of patients with clinical hypertension. This awaits confirmation; studies on the nor-adrenalin content of the blood of hypertensives are urgently needed.

* Bülbring and Burn (182) attempted to relate this quotient to the methionine content of the diet, but the experiments were inconclusive.

There is some indication of an increased concentration of a pressor substance in the blood in conditions of shock and experimental hypertension. The fact that its pressor action is abolished by dibenamine in much higher concentrations than are required for the reversal of adrenalin, and the similarity of the changes in the action of nor-adrenalin and of the pressor substance under various conditions, make it probable that it is identical with nor-adrenalin (Page, 987). The close association of emotional strain and hypertension and, as reported above, of hypothalamic excitation and the appearance of nor-adrenalin in the blood adds weight to this argument.

If this is the case, renewed research for a pharmacological blocking agent specific for nor-adrenalin is obviously imperative. We are still very far from the goal of controlling or preventing hypertension, but the data resulting from this recent research in autonomic physiology and pharmacology promise new avenues of approach to an old and difficult problem. At any rate, they pose some relevant questions which experimental physiology should be able to answer.*

The Supersensitivity of Denervated Structures†

This chapter should not be concluded without reviewing some data on the effect of denervation. That chronic denervation sensitizes autonomically innervated structures such as the nictitating membrane and the heart to neurohumors has been mentioned repeatedly, since this phenomenon has played an important methodological role in the development of the theory of neurohumors. Systematic studies have shown that sectioning the preganglionic nerve leads to a lesser sensitization of the ultimate structure than severance of the postganglionic nerves, as seen for example by the response of the nictitating membrane to adrenalin (1113). This observation has important clinical implications. The sympathetic denervation of an extremity by the sectioning of postganglionic sympathetic nerves may so sensitize the blood vessels to circulating "sympathin" and possibly other constrictor substances as to offset the effect of the operation. The elimination of impulses from the central nervous system to the sympathetic chain by preganglionic section may therefore be preferable, although decentralized ganglia‡ retain their activity (Govaerts, 563, 564).

If an organ is only partially denervated, its reactivity to chemical substances such as neurohumors as well as to nervous stimuli (via

* That numerous other facets of the hypertension problem have not been discussed does not imply that this type of research is less important.

† Further information and literature are to be found in Cannon and Rosenblueth's book bearing this title (206).

‡ I.e., ganglia subjected to preganglionic denervation.

the remaining intact nerve fibers) can be studied. Under these conditions parallel changes in the responsiveness to both types of stimuli are found. Thus partial chronic decentralization of the superior cervical ganglion by the sectioning of T_1 and T_2 makes the nictitating membrane more sensitive to the stimulation of T_3 and T_4 on this than on the acutely decentralized side (206). Similar results were obtained with the adrenal medulla. After the partial denervation of this organ the stimulation of some intact nerves elicits a greater secretion of adrenalin than in the acutely denervated organ. On the other hand, the greater sensitivity of the decentralized superior cervical sympathetic ganglion to acetylcholine injected intra-arterially is well established. One would expect that the sensitivity of the chronically denervated adrenal medulla to acetylcholine would be likewise increased, since acetylcholine is the physiological neurohumor of the secretion of adrenalin. This experiment, however, has apparently not yet been performed.

An important and somewhat unexpected development resulted from the application of these findings to the somatic nervous system. Cannon and his students found that the partial denervation of spinal neurons leads to their sensitization to chemical and nervous stimuli. Chronic hemisection of the thoracic spinal cord increases the responsiveness of the partially denervated lumbar motor neurons of the same side. This appears in the form of greater contractions and a longer duration of the response to acetylcholine, sodium carbonate, convulsants such as strychnine, and asphyxia (Cannon and Haimovici, 198). Stavraky (363, 1136) extended these observations to the brain and obtained evidence for the increased responsiveness to acetylcholine of somatic and autonomic neurons partially denervated by unilateral removal of one frontal lobe. Mecholyl injected into patients with unilateral cerebral lesions involving the motor area led to motor discharges on the contralateral side and an increased responsiveness to reflex stimulation. Autonomic phenomena were likewise unilaterally enhanced. Finally, Cannon and Rosenblueth (207) noted that partially denervated spinal neurons show a greatly increased responsiveness to afferent stimulation. The fact that the reactivity of partially denervated neurons increases in response to afferent stimuli as well as to chemical substances, including acetylcholine, and the validity of the "law of denervation" for autonomic and somatic neurons are of great interest for the theory of neurohumors. However, it should be borne in mind that denervation creates an increased sensitivity that is not confined to acetylcholine but involves other chemical substances as well.

The cause of the increased sensitivity of denervated structures is not well understood. Loewi (856) cites several facts which seem to be incompatible with Cannon's assumption that increased permeability of the cells is involved, and he proposes that the reduction or disappearance of activity in partially or completely denervated organs is related to their sensitization to neurohumors. There are chiefly two observations which support this interpretation: (1) An increased sensitivity of the muscle to acetylcholine occurs if its activity is nearly annihilated by fixation (1125), although this procedure does not interfere with the integrity of the nerve supply. (2) Wolff and McKeen Cattell (1244) observed that the increased sensitivity of the nictitating membrane to adrenalin which follows decentralization of the superior cervical sympathetic ganglion is temporarily abolished after the postganglionic fibers innervating the nictitating membrane have been stimulated. That activity is closely related to excitability is evident from the appearance of the refractory period. However, whether through extension of this general concept the increased sensitivity of a denervated structure is adequately accounted for can only be determined by further investigations.

~ 12 ~

The Eye as an Indicator of Autonomic Activity

SINCE it is not possible within the framework of this book to treat the autonomic nervous system systematically, an attempt will be made to illustrate on a single organ some of the principles which guide its activity. The eye has been chosen because of its obvious significance for clinical neurology and the importance which reactions on autonomic ocular indicators have played in the development of the physiology of the involuntary nervous system.

Some Observations on the Innervation of the Iris

It is well established that stimulation of the oculomotor nerve causes constriction of the pupil whereas stimulation of the superior cervical sympathetic trunk induces dilatation. Moreover sectioning of the parasympathetic supply results in dilatation, the pupil becoming very large; but its diameter can be further increased by sympathetic excitation. Contrariwise, the removal of the sympathetic reduces the diameter of the pupil as compared with that of the contralateral intact eye, although both pupils, depending on the intensity of the light to which the eyes are exposed, vary in width over a wide range.

The antagonistic action of parasympathetic and sympathetic nerves on the diameter of the pupil is commonly explained by their action on two different smooth muscles, the constrictor and dilator respectively. While the existence and function of the former is undisputed, that of the latter is still in doubt. Langworthy and Ortega (818) have reviewed the extensive literature on this question and pointed out that according to Kölliker the dilator consists of radial smooth muscle fibers located between the blood vessels of the iris and in addition in

the posterior membrane. Their own investigations have furnished only meager evidence for the existence of a dilator muscle. Consequently the width of the pupil in dependence on its vascular supply was emphasized in agreement with old observations of Claude Bernard and Budge (see Langworthy). However, the work of Poos (1022) and of Hess *et al.* (638, 639) on *isolated* radial preparations of the iris demonstrated contraction in response to small concentrations of adrenalin and nor-adrenalin. Since these substances, as was shown earlier, are responsible for neurohumoral transmission in sympathetically innervated structures, it must be assumed that a dilator muscle exists which responds to sympathetic excitation. In addition the influence of the state of the blood vessels on the width of the pupil must not be neglected. Injection with dyes shows that the iris is richly supplied with blood vessels. As they are filled, the pupils progressively decrease in size. "The iris has more or less the structure of an erectile tissue" (818), and variations in the blood supply induced by mechanical processes or through vasomotor action must be expected to alter the diameter of the pupil; but the separation of nervous and mechanical factors is often difficult.

The Blood Pressure and the Pupil

The pupil of the anesthetized cat is a fine indicator of the state of the circulation. Blood pressure and pupillary diameter are inversely related. Anoxia is not a decisive factor, since the decrease in the size of the pupils is seen with a rise in the blood pressure from, for example, 110 to 130 mm. Hg – i.e., under conditions in which oxygenation of the brain is optimal (Table 12). This relation between blood pressure and pupillary diameter remains valid after elimination of the adrenals and denervation of the sino-aortic area (480). It is therefore independent of pressor reflexes originating in the carotid sinus or arch of the aorta and of the secretion from the adrenal medulla.

These pupillary changes occur in the normal and sympathectomized eye and seem to indicate that the parasympathetic tone of the pupil increases with an increasing blood pressure. Since under these conditions the sympathetically innervated nictitating membrane relaxes progressively, it follows that variations in the blood pressure are associated with reciprocal changes in the parasympathetic and sympathetic tone. The fact that sino-aortic pressure receptors are not indispensable for these effects suggests that similar end-organs in other parts of the vascular system, such as those discovered by Heymans *et al.* (645) in abdominal blood vessels, are involved. It is, of course, conceivable that the variations in the blood pressure influence the

pupil through corresponding changes in the amount of blood present in the extensible blood vessels of the iris; but if this is a factor, it is probably only of secondary importance. The great sensitivity of the pupil to slight variations in the blood pressure requires explanation on

TABLE 12. The Relation of the Blood Pressure to the Pupil of the Eye (Gellhorn, Darrow, and Yesinick, 480)

Blood Pressure, mm. Hg	Pupillary Diameter, mm.
110	5.0
120	4.0
130*	0.8

* Increased through the infusion of Ringer's into the femoral vein of an anesthetized, adrenalectomized cat.

a nonmechanical basis, and the accompanying changes in the tone of the nictitating membrane give weight to the argument that pressoreceptor reflexes act on both branches of the autonomic system reciprocally.*

Pain and the Pupil

That nociceptive impulses cause a pupillary dilatation is well established, but the mechanism involved has only recently been clarified.† In cats, on which most of the experimental work has been performed, the dilatation of the pupil in response to nociceptive stimuli seems to be based on inhibition of the tone of the oculomotor nucleus. When the third nerve is cut, the pupil dilates almost maximally, but it constricts promptly upon the instillation of eserine. Such a pupil remains unchanged in spite of the application of strong painful stimuli to the skin or sciatic nerve, although the normal pupil dilates greatly or maximally (Fig. 72). Since the eserine pupil reacts to stimulation of the cervical sympathetic trunk as promptly as the normal pupil, the drug does not interfere with sympathetic effects on the pupil. The conclusion that pain acts on the normal pupil of the cat through inhibition of the parasympathetic (1180) has been confirmed in several investigations (678, 814, 1105). Since in the normal eye the pupil dilates more than in the sympathectomized one, in spite of the lack of evidence for the activation of sympathetic pupillary fibers under conditions of pain it must be concluded that the sympathetic

* It would be crucial to determine whether changes in the blood pressure are associated with corresponding changes in the tonic activity of the oculomotor nerve as indicated by action potentials.

† See p. 281 for further interpretation.

supplies only basic tone to the pupil, the phasic changes in response to pain being due to inhibition of the oculomotor nucleus.

An exhaustive analysis of the afferent path involved in the pupillary inhibition resulting from the stimulation of nociceptive fibers in the abdomen was made by McSwiney *et al.* (63, 593). Stimulation of the central end of the vagus or splanchnic in the abdomen or dilatation of various parts of the viscera resulted in pupillary dilatation which persisted after sectioning of the cervical sympathetic trunk. However, sectioning of the spinal cord in its cervical part abolished the pupillary

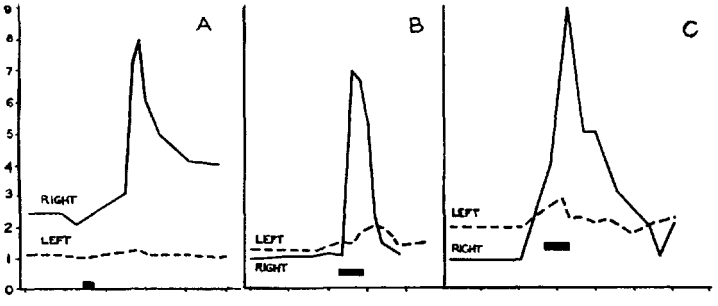


FIGURE 72. The effect of nociceptive stimulation for 5 seconds (Fig. A), 10 seconds (Fig. B), and 20 seconds (Fig. C) on the diameter (mm.) of the right pupil (solid line) and left pupil (broken line). The right pupil is normal. The left has the third nerve cut and has had a local application of 1-per-cent eserine. (Ury and Gellhorn, 1180.)

dilatation on stimulation of the splanchnics, although this reaction remained if nociceptive stimulation was applied to nerves entering the spinal cord above the level of transection. The loss of this pupillary reaction after cervical cord transection and its persistence in the intact animal after elimination of the cervical sympathetic again illustrate that this reaction involves the third nerve center but not the cervical sympathetic.

In the intact animal the pupillary dilatation resulting from stimulation of the central end of the splanchnic nerve is due to impulses which reach the spinal cord via the white rami through the posterior roots from the third thoracic to the first lumbar segment. Sectioning of these roots abolishes this effect of splanchnic stimulation. Similarly, afferent stimuli transmitted to the central nervous system through the abdominal branches of the vagi reach the third nerve nuclei via the vagi from the medulla oblongata or enter the spinal cord through the third, fourth, and fifth dorsal roots.

Neither the cortex nor the hypothalamus is necessary for this reaction of the pupil. The afferent path from the medulla to the third nucleus seems to be independent of the lateral spinothalamic tracts, which are said to convey nociceptive impulses to the brain (594).

From these investigations it may be concluded that nociceptive impulses originating in various parts of the body (including the viscera) induce pupillary dilatation through inhibition of the tone of the third nerve center. However, it is not suggested that the sympathetic system is without influence on ocular structures in these conditions.

First, it is known that nociceptive stimulation causes retraction of the nictitating membrane in the normal and anesthetized cat (254). Apparently, contrary to the teaching of Cannon, who emphasized that the sympathetic system discharges en masse, this system may be activated in part. Thus sympathetic effects may be restricted to the nictitating membrane without affecting the pupil. However, if the excitability of the sympathetic system is greatly increased as, for example, through the injection of metrazol, an appreciable dilatation of the parasympathectomized pupil occurs on nociceptive stimulation and an even more extensive sympathetic effect is seen during convulsions (1180). Consequently, sympathetic phasic reflex effects on the pupil are possible provided that the excitability of sympathetic centers has been raised.

The observations of Weinstein and Bender (1216) call attention to possibly important differences between species. Whereas the pupillary dilatation to pain is abolished in the cat by sectioning of the third nerve, it persists under these conditions in monkeys; conversely, sympathectomy eliminates the pupillary dilatation to nociception in the monkey but remains without influence in the cat. A repetition of these observations and a study of pupillary reactions to pain on sympathectomized human eyes are urgently needed. Foerster (366) mentions in a short note that pupillary dilatation to pain is not abolished in man after extirpation of the superior cervical sympathetic ganglion.

Differences between species may be based on central factors (the excitability of sympathetic centers and their influence on the pupil) or on the reactivity of the dilator of the pupil to adrenalin (638, 639), but more work is needed to establish the relative importance of these factors.

The tonic function of the sympathetic system for the pupil is of course well known in man. The Horner syndrome develops after a

lesion of the preganglionic fibers which in man issue from C_8 to T_4, with the chief fibers originating from T_1 and T_2 (1037). The sympathetic impulses to the eye and face are likewise abolished by unilateral lesions of the cervical spinal cord or any part of the brain stem which interferes with the transmission of sympathetic impulses from the hypothalamus to the ciliospinal center. Anterolateral cordotomy induces miosis of the pupil and ptosis of the ipsilateral eyelid (366).

The Pupil in Anoxia and Asphyxia

The normal pupil dilates in anoxia or asphyxia and even maximal dilatation occurs reversibly under these conditions in normal and in adrenalectomized animals. Therefore adrenomedullary secretion plays no significant part in this reaction. Systematic analysis has shown that the normal and the sympathectomized pupil of the cat have the same threshold to anoxia as seen in experiments in which the barometric pressure is gradually lowered. Both pupils show a maximal dilatation under these conditions or in asphyxia, and in general the normal pupil dilates more rapidly with an increasing degree of anoxia. These observations suggest that, as in pain, the pupillary dilatation is due to inhibition of the tone of the third nucleus and that the constant tone of the sympathetic contributes largely to the rate of dilatation when the sympathetic acts against a progressively diminishing tone of the oculomotor nerve. This conclusion is confirmed by experiments on cats with the third nerve sectioned intracranially at one side. If in addition both cervical sympathetic trunks are cut, the difference between the size of the pupils is a measure of the contribution of the inhibition of the parasympathetic innervation to the dilatation of the pupil. It is seen that the sympathectomized pupil dilates maximally in anoxia or asphyxia whereas the completely denervated pupil shows a slight degree of dilatation (503). Since the latter occurs in the denervated pupil in normal and adrenalectomized animals, it must be due to factors which are neither nervous nor humoral. This work was confirmed by Hoorens (706) in the dog, studied with Heymans' method involving the isolated head which is perfused through a donor dog.

The predominance of parasympathetic inhibition rather than excitation of the sympathetic as a factor in pupillary dilatation is obvious from these experiments. Whether monkey (and man) behave differently under these conditions is not known.

The fact that in anemia, anoxia, or asphyxia the completely denervated iris shows a dilatation in the adrenalectomized cat and in the isolated head requires some further comment. This dilatation increases

with the severity of asphyxia and may become considerable if asphyxia is continued until death occurs. Since under these conditions the blood pressure falls progressively, it is probable that the dilatation of the denervated pupil is the result of diminished vascularization, as in the injection experiments of Langworthy; however, a direct action by acid metabolites may also be involved.

The Sensitized Pupil and Nictitating Membrane

It was mentioned earlier that the pupil and nictitating membrane are sensitized to adrenalin and nor-adrenalin by chronic denervation. These structures react then to pain, anoxia, and asphyxia* with a humorally transmitted dilatation of the pupil and contraction of the nictitating membrane. The effect of pain is much greater in the anesthetized than in the normal animal, a fact indicating the release of autonomic centers in narcosis. Although it is easy to show that anoxia, asphyxia, nociceptive stimulation, and numerous other conditions lead to the liberation of adrenalin and nor-adrenalin, their action on the pupil and nictitating membrane does not seem to occur unless these tissues have been sensitized through drugs or denervation.

Observations on cats in which the superior cervical sympathetic ganglion was removed at one side gave an opportunity to evaluate the role of nervous and humoral factors in ocular changes under various conditions (511). The eye of the operated side disclosed the liberation of adrenalin, to which it was sensitized, while the normal nictitating membrane served as an indicator for sympathetic impulses. If both pupils dilated, inhibition of the third nerve was involved. In the waking state any arousal reaction is accompanied by a contraction of the normal nictitating membrane and a prompt dilatation of both pupils (the normal pupil being slightly larger as the result of the sympathetic tone). Since it is seen in both pupils and no signs of secretion of adrenalin occur—the denervated nictitating membrane remains unchanged—this pupillary dilatation is said to be due to inhibition of the third nerve nucleus. Attention, arousal, and, as already mentioned, slight pain involve according to these investigations parasympathetic inhibition (shown in the pupils) and sympathetic excitation (indicated by the normal nictitating membrane). More severe pain elicits in addition the secretion of adrenalin, shown by the contraction of the denervated nictitating membrane. However, in anesthesia the contraction of the normal nictitating membrane disappears in response to pain while that of the denervated nictitating

* Concerning other factors which activate the sympathetico-adrenal system see p. 295.

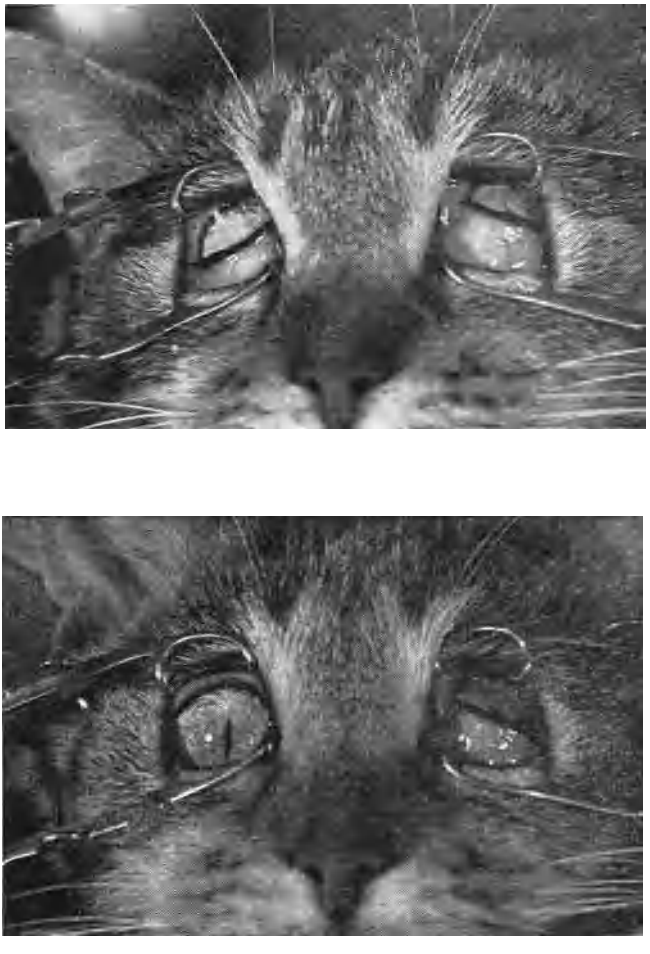


FIGURE 73. The effect of chloralosane anesthesia on the action of nociceptive stimulation on the denervated nictitating membrane. Right nictitating membrane (left side of photographs) chronically denervated by removal of the right superior cervical sympathetic ganglion. Left nictitating membrane normal. Maximal prolonged contraction of the denervated nictitating membrane following pinching of the ears. In the waking animal (*lower figure*) a slight pain stimulus evokes a contraction of the normal but not of the denervated nictitating membrane. (Gellhorn and Redgate, 511.)

membrane becomes prominent (Fig. 73). Two factors seem to be involved here: (1) the sympathetic impulses which cause retraction of the normal nictitating membrane are, like those involved in the palmar sweat secretion, of cortical origin and disappear in anesthesia with the depression of cortical functions; (2) the centers of the

autonomic system are released from cortical control and react with a secretion of adrenalin to nociceptive stimuli, which fail to elicit this effect in the unanesthetized animal.

Insulin hypoglycemia leads to sympathetico-adrenal discharges. The completely denervated pupil and nictitating membrane dilate and contract respectively. But if hypoglycemia persists for a relatively long period, additional effects are noted. The denervated pupil shows a delayed phase of constriction. If the experiment is repeated after elimination of the adrenals, the dilator phase is absent and only the constrictor action appears (84). This experiment suggests that hypoglycemia leads to a release of cholinergic and adrenergic neurohumors, with the latter predominating in the normal animal. The result is in agreement with numerous studies in which it could be shown that processes leading to discharges of autonomic centers involve both divisions of the visceral nervous system.*

The Role of the Central Nervous System in Pupillary Dilatation and Contraction of the Nictitating Membrane

Since the classical investigations of Budge it has been known that stimulation of the spinal cord at its upper thoracic level or of the first anterior thoracic roots causes maximal dilatation of the pupil and contraction of the nictitating membrane and that these reactions are eliminated by sectioning of the superior cervical sympathetic trunk or ganglion. This effect is obviously of sympathetic origin. In view of the fact that nociceptive stimulation induces sympathetic effects on the nictitating membrane but not on the pupil in the waking animal, it is interesting to determine the central conditions of such partial activation of the sympathetic system.

Electrical stimulation of the dorsal spinal cord shows that from T_4 and often T_3 a maximal contraction of the nictitating membrane is induced without any dilatation of the pupil or with a slight dilator effect. Since the latter is of equal magnitude in the normal and sympathectomized pupil, it is interpreted as the result of parasympathetic inhibition. A similar dissociation between the sympathetic effect on the pupil and nictitating membrane is seen on stimulation of the medulla oblongata and hypothalamus (477). The converse phenomenon, maximal pupillary dilatation without contraction of the nictitating membrane, may also be obtained on hypothalamic excitation. Although under conditions of emergency produced by drastic changes in the internal or external environment the sympathetic system discharges as a whole, it can be partially activated either reflexly (as

* See p. 293.

TABLE 13. The Differential Effects of the Stimulation of Autonomic Centers on the Pupil and Nictitating Membrane (Gellhorn, Cortell, and Murphy, 477)*

I. Stimulation of the Medulla Oblongata

Volts	Effect on Normal Eye		Effect on Sympathectomized Eye	
	N. M.	Pupil †	N. M.	Pupil
5	++	0.5 → 1.8	0	0.5 → 1.8
6	+++	1.0 → 3.5	0	1.0 → 3.5
8	+++	1.0 → 5.5	0	1.8 → 4.0

II. Stimulation of the Hypothalamus

Structures	Intensity of Stimulation (Coil Distance‡ in cm.)	Pupillary Dilatation	Nictitating Membrane Contraction
Dorsomedial thalamic nucleus	11	0	+++
Medial mammillary nucleus	7	0	+++
Lateral hypothalamic area	10	0	+++
Lateral hypothalamic area	9	+++	0
Ventromedian hypothalamic nucleus ..	9	++	0

* This table furnishes examples of partial activation of the sympathetic system under conditions of stimulation of central nervous structures. Note that maximal contraction of the nictitating membrane may occur without maximal pupillary dilatation, and vice versa.

† The numbers indicate the horizontal diameter in millimeters of the pupil before and after stimulation.

‡ Inductorium.

in the previous experiments on pain) or through appropriate stimulation of spinal, medullary, and hypothalamic centers (Table 13). Sympathetic ocular reactions may or may not be accompanied by a rise in the blood pressure (Fig. 74). Various sympathetic and parasympathetic effects appear in different combinations and thereby simulate the great variability in autonomic syndromes which accompany emotional processes (209, 477).

The stimulation experiments show that the autonomic effects on the eye and other structures can be elicited from minute areas of the hypothalamus if currents of different intensity and frequency are used. In addition areas of optimal responsiveness for different sympathetic indicators do not coincide in the hypothalamus. It follows that the locus and degree of excitation determine whether a general or a partial sympathetic discharge is evoked and, in the latter case, what specific autonomic syndrome prevails.

The secretion of adrenalin, which can be evaluated by the reaction of denervated ocular structures as well as by other methods, may be produced by stimulation of the medulla oblongata (221) or the

hypothalamus (711). The vasomotor center of the medulla is actually a sympathetic center, as is the hypothalamus, since all sympathetic effectors are activated from this area and a mass discharge similar to that seen in the emergency reaction of Cannon is easily elicited from the medulla and hypothalamus. But even here the immediate neurogenic and the delayed humoral effect (indicated by the reaction of completely denervated structures) can be separated. The eye may again serve as an illustration. Hypothalamic stimulation elicits a brief dilatation of the pupil, which seems to involve both inhibition of the third nerve and sympathetic excitation (209), and is accompanied by a retraction of the nictitating membrane and other signs of sympathetic discharge, such as a marked rise in the blood pressure. These reactions have a short latent period of one or two seconds, but if the stimulation is prolonged a humoral reaction occurs, leading to a slow dilatation of the denervated iris. This effect is the result of adrenomedullary secretion, since it is abolished by adrenalectomy (85). However, through ocular sympathetic indicators a slow humoral

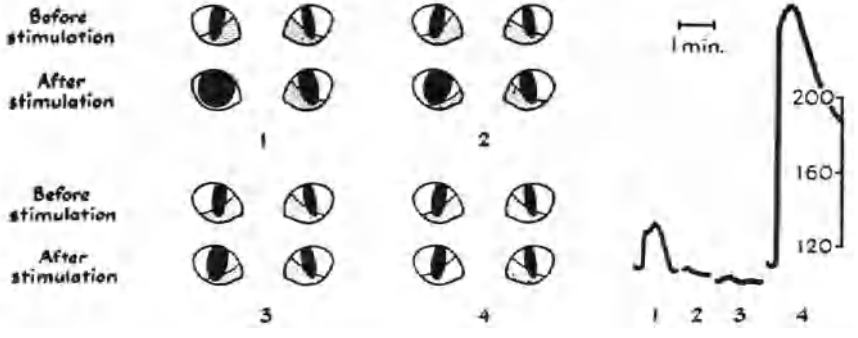


FIGURE 74. The effect of electrical stimulation of the spinal cord at various levels on the blood pressure, pupils, and nictitating membranes (n.m.). The upper pair of each group shows the appearance of the pupil and the n.m. before stimulation; the lower pair, the maximal change in each. *Group 1:* stimulation at T_3; coil distance 7 cm. Slight dilatation of the left (sympathectomized) pupil due to parasympathetic inhibition; no contraction of the left n.m. Maximal contraction of the right n.m. and maximal pupillary dilatation. Slight rise in blood pressure. *Group 2:* stimulation at T_1; coil distance 9 cm. Left pupil shows slight dilatation; left n.m. unchanged. Right pupil dilates (++) and n.m. contracts (++). No change in blood pressure. *Group 3:* stimulation at T_1; coil distance 10 cm. No change in left eye and blood pressure. Slight dilatation of pupil and contraction of n.m. on the right side. *Group 4:* stimulation at T_4; coil distance 8 cm. Maximal rise in blood pressure. No change in pupil and n.m. (Gellhorn, Cortell, and Murphy, 477.)

reaction involving sympathin can likewise be demonstrated following prolonged stimulation of the lateral hypothalamus in adrenalectomized animals (888).

In contradistinction, the effect of cortical excitation is rather limited. The contraction of the nictitating membrane elicited reflexly through sciatic stimulation is increased or inhibited from the sensorimotor cortex and also from the orbital gyrus in the cat (947). The dilatation of the pupil from the frontal and occipital cortex (1207), which in the cat is due to an inhibition of the third nerve tone and in the monkey (from the eye field, area 9) to sympathetic excitation (1211), is not accompanied by autonomic mass discharges but associated with specific movements with which the autonomic changes are closely integrated. Pupillary dilatation has also been observed on stimulation of cerebellar nuclei (211) and on stimulation of the gyrus cinguli (1123).

The fundamental difference between the mechanism of pupillary dilatation based on inhibition of the third nucleus and that based on sympathetic excitation is borne out by the determination of the areas in the brain of the cat from which these reactions are elicited. Sympathetic pupillary reactions are induced from the same structures in the brain from which other sympathetic effects are obtained (posterior hypothalamus and bottom of the fourth ventricle), whereas pupillary dilatation which is not of sympathetic origin results from the stimulation of a much wider area comprising the hypothalamus and thalamus and extending rostrally from the former to the basal telencephalon (683, 684).

The study of ocular reactions in cases with central lesions reveals important facts about the organization of the autonomic nervous system. Supranuclear paralysis of the sympathetic to the eye – i.e., a loss of sympathetic tone – in lesions of the cervical spinal cord or after anterolateral cordotomy leads to an increased responsiveness of the ciliospinal center. In such cases not only nociceptive stimuli but mere proprioception induced by the lifting of the arm causes dilatation of the pupil at the side of the lesion (366).

The tonic activity of the third nucleus is likewise modified by more rostrally located structures. Massive unilateral lesions in the cortex release the ipsilateral oculomotor center so that it reacts with a dilatation of the pupil to nociceptive stimuli of lesser intensity than are required to cause a similar reaction in the eye of the other side (1181).

The Nature of Parasympathetically Induced Pupillary Dilatation

It has been shown that under a variety of conditions pupillary dilatation occurs provided that the oculomotor nerve is intact. On nociceptive stimulation and in anoxia this change in oculomotor nerve activity is frequently associated with signs of sympathetic excitation in ocular (nictitating membrane) and extraocular structures (blood pressure, pulse rate, palmar sweating, etc.). Following stimulation of the hypothalamus, pupillary dilatation is in part due to sympathetic excitation and in part to an alteration in parasympathetic activity (209, 755, 756). These findings raise the question of the nature of the alteration in the parasympathetic (oculomotor) discharge under these conditions. In the literature (including the writer's papers on this subject) the parasympathetically induced pupillary dilatation has been interpreted as due to inhibition of the third nerve center. Such an explanation appeared justified because reciprocal innervation in the form of sympathetic excitation combined with parasympathetic inhibition is well established in autonomic reflexes (see 446). However, it has been shown in various experimental conditions that this type of "reciprocal innervation" is not always present. The question should hence be raised whether there is not an alternative interpretation of the dilatation of the pupil which involves the third nerve.

It is generally agreed, and some of the pertinent data were presented in the preceding chapter, that the effects of autonomic nerve impulses on peripheral structures are caused by adrenalin, nor-adrenalin, and acetylcholine. It is further known that sympathetic nerves liberate adrenergic and cholinergic effects at the same terminal organ. Thus the splanchnics induce vasoconstrictor and dilator action on abdominal blood vessels (372, 373). Is it not possible that a similar dual mechanism accounts for pupillary constriction and dilatation through cholinergic and adrenergic oculomotor nerve fibers? *

In vitro studies have shown that the isolated iris constricts in response to small concentrations of acetylcholine but reacts with a dilatation to adrenalin and nor-adrenalin (639, 1022).† It seems therefore possible that the dilatation of the pupil could be called

* There exists in addition the possibility of a synergistic action between cholinergic (parasympathetic) and adrenergic (sympathetic) methanisms. Since it is known that the sensitivity of the iris to adrenalin is increased in the presence of acetylcholine (793), the varying degrees of third nerve discharges in the waking state may determine the responsiveness of the pupil to adrenergic impulses.

† Poos (1022) showed the constrictory effect of adrenalin on the dilator and the inhibitory action on the sphincter of the isolated human iris.

forth, in addition to the action of the sympathetic, through increased discharges of adrenergic nerve fibers originating in the Edinger-Westphal nucleus. This mechanism of parasympathetically induced pupillary dilatation could be proved if, for example, nociception were to lead to the appearance of assayable quantities of adrenalin in the anterior chamber of the sympathectomized eye or if the action potentials of the Edinger-Westphal nucleus and the ocular motor nerve were to be found to increase in nociception and anoxia rather than to decrease. These crucial tests have not yet been performed, but some observations seem to support this interpretation.

Kuntz (814) noted that in the atropinized eye stimulation of the oculomotor nerve leads to further dilatation of the pupil. This finding suggests the presence of adrenergic fibers in the third nerve. Moreover, following extensive cortical lesions (1181) and in anoxia (503, 1178) the pupils dilate via the third nerve. Such conditions are known to release subcortical autonomic and somatic centers. The pupillary dilatation of the sympathectomized eye which occurs under these conditions would consequently be better understood if it could be proved to be the result of an increased activity of the oculomotor centers (through adrenergic fibers) rather than of an inhibition of this structure.* In view of the fact that nociceptive impulses lead to widespread excitation of the autonomic and somatic nervous system at all levels, the activation of the adrenergic portion of the efferent neurons of the Edinger-Westphal nucleus rather than its inhibition would appear to be the logical interpretation of the data. However, the final test must lie in decisive physiological experiments which are as yet not available.†

Pupillary Constriction

Pupillary constriction occurs on exposure of the retina to light or during accommodation when a near object is fixated while the eyeballs

* The observation of Ury and Gellhorn (1179) that the threshold for dilatation of the sympathectomized pupil on nociceptive stimulation increases in anoxia is not contradictory to this assumption. If inhibitory impulses originate in the cortex, their removal may lead to dilatation in anoxia, but the reactivity of the third nerve nucleus to nociception may be depressed progressively during the period of anoxia.

† It was mentioned earlier that stimulation of the frontal eye field (monkey) causes pupillary dilatation through sympathetic impulses. However, the sympathectomized pupil still reacts with a slight dilatation to the cortical stimulus. Instead of assuming inhibition of the third nerve nucleus, it is perhaps more probable that excitation of its adrenergic portion takes place under these conditions, since the strychninization of area 8 induces synchronous spikes in the oculomotor nucleus; that is, excitatory impulses are transmitted from the frontal eye area to the oculomotor nucleus (1211).

converge under the influence of cortically induced impulses to the oculomotor nuclei. Although the movements of the eyes and lids and those of the head frequently associated with them are under the control of the superior colliculi, these structures are not involved in the light reflex. Ranson and Magoun (887, 1035) showed that bilateral pupillary constriction results from stimulation of the optic tract and the brachium to the superior colliculus. However, stimulation of the superior colliculus does not cause pupillary constriction (228, 1035). Since it was found that excitation of the pretectal area to which the brachium of the superior colliculus goes produces miosis and that similar effects are obtained from the posterior commissure and from fibers which after having crossed the midline ventral to the cerebral aqueduct reach the oculomotor nucleus, it is assumed that these structures are involved in the light reflex. The partial crossing of the fibers accounts for the bilaterality of the pupillary constriction after the illumination of one eye.

While destruction of the superior colliculi does not abolish the light reflex, lesions in the pretectal area reduce or eliminate it (885). This effect is proportional to the extent of the pretectal lesion. If both optic nerves are cut and some weeks later tests are performed on the several links of the optic light reflex, it is found that while stimulation of the degenerated optic tracts fails to elicit pupillary constriction, excitation of the pretectal area yields positive results (592). This shows that second-order neurons originate in this area which convey impulses to the centers of the third nerve.

The threshold of the pretectal area to electrical excitation of the pupillary constrictor reflex depends on cortical and subcortical impulses. Removal of the cortex lowers the threshold of the contralateral pretectal area. Cocainization of the inferior colliculus exerts temporarily a similar action (228). In addition it is seen that excision of the cerebral cortex and inferior colliculus causes a distinct miosis. Apparently these structures inhibit the pretectal center of the light reflex.

From investigations on decorticate animals it is known that the light reflex but not the pupillary constriction to a threatening gesture is present, a fact suggesting that the latter reaction is of cortical origin. Since pupillary constriction follows excitation of the occipital lobe (74, 1206), it would be of interest to determine whether the elimination of the light reflex after destruction of the pretectal area influences the cortically induced pupillary constriction. Some observations suggest that such reactions may persist in cats which are blind and have wide pupils as the result of pretectal lesions. One may conclude that

they involve the visual cortex and the third nerve nucleus but not the pretectal area (887).

The connection of the pretectal area with both oculomotor centers accounts for the fact that in a case with destruction of the left optic nerve the light reflex is maintained bilaterally on retinal stimulation of the right eye but is absent on exposure of the left retina to light. On the other hand, a left oculomotor nerve lesion (or destruction of the left ciliary ganglion) abolishes the light reflex in the left pupil no matter which retina is stimulated, whereas light on either retina calls forth pupillary constriction in the right pupil (135).

Somato-Autonomic Integrations of Ocular Reactions

Autonomic ocular reactions are not confined to the pupil and nictitating membrane but affect also the smooth muscles in the eyelids (particularly the lower lid) (728), which are sympathetically innervated. Through these structures and the striated muscles of the eye, changes in the width of the palpebral fissure, the position of the eyes, and the diameter of the pupil are induced which accompany variations in the state of wakefulness. Smith (1122) noted that stimulation of the frontal eye field produces a typical awakening reaction of the eyes, based on a coordination of autonomic and somatic responses. Livingston (851) found on stimulation of the same area with electrical impulses of a high frequency a waking response characterized by pupillary dilatation, protrusion of the eyeball, and opening of the eyelids; at a low rate of stimulation the converse sleeping reaction was obtained. Differences in the frequency of stimulation and in the focus of excitation account likewise for marked variations in autonomic-somatic effects from the diencephalon. Hess (637) observed pupillary constriction associated with signs of diminished somatic excitability and muscle tone, particularly a lowering of the head, from thalamic and anterior hypothalamic foci, whereas activation of the posterior and lateral hypothalamus produced pupillary dilatation, contraction of the nictitating membrane, a raising of the head, and other signs of increased excitability.

Stimulation of the pretectal area calls forth, in addition to pupillary constriction, a lowering of the eye bulbs and a closure of the palpebral fissure (228); from the caudate nucleus a similar syndrome is evoked. Apparently somatic and autonomic effects are integrated at diencephalic and cortical levels; in general increased sympathetic discharges are combined with augmented motor activity, whereas increased parasympathetic discharges occur together with diminished tone, sleep, and other restorative processes. However, this typical

association of autonomic and somatic activity is not without significant exceptions. On stimulation of the cingular gyrus (1123, 1208) sympathetic excitation (pupillary dilatation, piloerection) is combined in part with motor excitation (vocalization, opening of the eyes), in part with the cessation of movements, a loss of muscle tone, and the disappearance of tendon reflexes.*

On the Pharmacology of the Eye

A study of the action of some drugs has thrown some light on the basic neurophysiology of autonomic ocular mechanisms.

The cholinergic nature of the activity of the oculomotor nerve under the influence of light is proved by the positive assay for acetylcholine in the anterior chamber of the eye (320) and the disappearance of the light reflex after the injection of cholinesterase (927). Conversely, the inhibitors of this enzyme (physostigmine and DFP) induce miosis. After DFP the constriction may last for several days, and even thereafter an increased contraction of the pupil to light persists because this drug is very slowly eliminated and the reflexly freed acetylcholine is no longer destroyed by cholinesterase. It is of considerable interest that this effect of physostigmine (34) and DFP (833) is absent in the chronically denervated iris (after removal of the ciliary ganglion), although experiments proved that DFP was in sufficient quantity present in the iris greatly to intensify the action of acetylcholine if it was applied locally. It must therefore be concluded (1) that the inhibitors of cholinesterase cause miosis through intensification and prolongation of the action of acetylcholine which is present in the iris under physiological conditions; (2) that the source of acetylcholine lies in the cholinergic nerve fibers, since after removal of the ciliary ganglion this substance is not found in the iris any more.

The light reflex is abolished by atropine and its derivatives, which block the action of acetylcholine on the constrictor muscle of the iris. Since the iris is under dual nervous control, the atropine mydriasis is not maximal. Stimulation of the sympathetic increases the pupillary dilatation of the atropinized pupil, and in conditions accompanied by an increased sympathetic tone (hyperthyroidism) atropine causes a greater dilatation of the pupil than in normal individuals (644).

Pupillary dilatation through adrenalin and nor-adrenalin and their action on the dilator (contraction) and sphincter (relaxation) were discussed earlier. The mydriasis induced by adrenalin is intensified by cocaine (395); the drug also increases the amplitude of the contraction

* The significance of this syndrome for the problem of emotion is discussed on p. 344.

of the nictitating membrane to adrenalin (1068). Cocaine itself acts as a mydriatic provided that the sympathetic innervation of the iris is intact. Apparently it causes maximal excitation of sympathetic nerve endings since stimulation of the cervical sympathetic trunk does not augment the cocaine dilatation. After removal of the superior cervical ganglion cocaine becomes ineffective on local application; therefore this drug has been used as an indicator of the state of sympathetic innervation of the pupil.

Clinical studies have shown that the reaction of the human iris to cocaine is also abolished by lesions interrupting the preganglionic sympathetic nerves (1249). Since in these conditions the mydriatic effect of cocaine can be restored when it is applied in conjunction with subthreshold concentrations of adrenalin, it follows that the steady liberation of adrenalin (or nor-adrenalin) from the intact sympathetic endings in the iris is necessary for the mydriatic effect of cocaine. In a physiological respect these observations seem to indicate that the liberation of adrenalin ceases or is greatly reduced after decentralization of the superior cervical ganglion, although, at least in animal experiments (564), this structure continues to send tonic impulses to the pupil and nictitating membrane. Foerster (370) mentions that hemisection of the cervical spinal cord increases the reactivity of the homolateral eye to cocaine. Apparently the ciliospinal sympathetic center is released from the inhibitory action of supraspinal centers through this lesion. The fact that a Horner syndrome (increased ocular sympathetic discharges) exists at the same time seems to agree with this interpretation.

Finally, drugs may be used to illustrate basic principles in autonomic organization. Langley distinguished between preganglionic and postganglionic nerves through the blocking action of nicotine on synapses of the sympathetic ganglia to which the drug had been applied. Its action on the superior cervical sympathetic ganglion abolishes the sympathetic effects of preganglionic stimulation on the pupil and nictitating membrane. Novocaine infiltration of the stellate ganglion interferes with the conduction of some preganglionic nerves innervating ocular structures and induces a temporary Horner syndrome.

Concluding Remarks

The purpose of the present chapter has been to elucidate in one organ, the eye, some fundamentals of autonomic physiology. The eye was chosen because of its importance in neurological diagnosis. The pupil and (in the experimental animal) the nictitating membrane serve as autonomic indicators. These structures may be activated

from all levels of the central nervous system since, as in the somatic nervous system, autonomic functions show multiple representation. There is, however, an important difference in the hierarchy of functions between the voluntary and involuntary nervous systems. In the former, complexity of function and physiological significance in the economy of the body increase as the cortical level is reached; the reverse is true for the autonomic nervous system. Thus motor functions of greatest variety are mediated by the cortex, and relatively primitive movements remain after its removal. Similarly, sensory sensitivity and discrimination and the synthesis of sensory data related to the excitation of sense organs of different modality (illustrated by the loss of stereognosis) (529) suffer considerably through cortical lesions. Sensorimotor integration is likewise greatly interfered with (1030). As will be shown later,* the proper evaluation of the external environment on the basis of sensory data is lost after removal of the occipital lobes, although light perception is still preserved.

On the other hand, the effect of the cortex on the autonomic system is only slight. Thus a stimulus which on application to the cortex will have only a small or no effect on the blood pressure will produce an enormous pressor effect when applied to the hypothalamus (446), the sympathetic medullary center, or the posterior surface of the dorsal spinal cord (477). Autonomic deficiencies resulting from cortical ablation are still controversial, whereas disturbances from hypothalamic lesions (e.g., in regulation of the temperature of the body) (1033) are indisputable.

Studies on cortically induced autonomic effects show clearly the functional integration of autonomic and somatic processes. The "waking" and "sleep" reactions of striated and smooth ocular muscles elicited on stimulation of the frontal eye area and the association of pupillary constriction with convergence are appropriate examples. The state of attention is characterized by increased muscle tone, pupillary dilatation, and contraction of the nictitating membrane, and the last is under these conditions of cortical origin. In these experiments as well as in others reported in this chapter, the sympathetic nervous system may discharge only in part. Thus contraction of the nictitating membrane may occur without any change in the state of the sympathetic in the pupillary dilator. The sympathetic mass discharge is only *one* form of sympathetic activation.

If the intensity and duration of stimulation are sufficient, sympathetic excitation leads to adrenomedullary secretion, as seen in the reaction of the chronically denervated smooth muscles of the eye.

* See Chapter 17.

With these indicators it can also be shown that sympathetic centers are released from cortical inhibition in anesthesia.

A multiplicity of mechanisms may attain the same end. Pupillary dilatation is most commonly due to relaxation of the sphincter of the iris (whether this is due to inhibition of the third nucleus or the increased action of adrenergic fibers of the third nerve is still unsettled) and is augmented by the steady tone of the sympathetically innervated dilator muscle. Conditions involving the hypothalamus or an increased excitability of sympathetic centers (metrazol) lead, in addition, to sympathetically induced dilatation. Although autonomic reflexes such as those originating in the pressoreceptors of the sino-aortic area show reciprocal innervation – i.e., parasympathetic excitation combined with sympathetic inhibition and vice versa – this form of autonomic discharge is by no means universal, as the action of nociception on the pupil indicates. If autonomic effects on the pupil during convulsions are also considered in which both divisions of the involuntary system are activated simultaneously (478, 1180), it is obvious that the concept of reciprocal innervation is far too limited to give an adequate description of the mutual relations of the two divisions of the autonomic nervous system under a variety of conditions. Depending on the state of excitability of the autonomic centers and the stimuli involved, the activity of the autonomic nerves supplying ocular structures may vary in degree and pattern. These autonomic changes may serve specific visual functions or reflect fundamental changes in the whole visceral nervous system.

PART V

Integrations

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~ 13 ~

Principles of Neuro-Endocrine Action

THE integration of the functions of the various organs in the body during rest and activity and under conditions of changes in the external and internal environment is accomplished through the functions of the nervous system and the endocrines. These mechanisms are likewise at work under pathological conditions. Thus tissue damage results in adjustment reactions consisting of nervous discharges and quantitatively altered internal secretions. Even the gross anatomical changes in various organs, particularly the adrenal cortex and the lymphatic tissue, as seen in Selye's alarm reaction (1104), are the result of neuro-endocrine activity. For a better understanding of the behavior of the organism a knowledge of the mutual relation of these two integrating systems is of paramount importance.

It is almost an axiom in endocrinology that the surgical removal of a gland of internal secretion followed by its implantation in some other part of the body is not accompanied by any endocrine disturbance provided that the implant remains viable. Thus no signs of castration appear in animals whose gonads have been removed and then been implanted into the same organism, and comparable results have been obtained with the removal and implantation of thyroid, adrenal cortex, pancreas, and the anterior hypophysis. From these findings it follows that the implanted endocrine organ retains its ability to produce an internal secretion. Factors such as the blood sugar level continue to influence insulin secretion in the denervated pancreas, and likewise the level of various hormones in the blood and tissues remains an effective regulator of the rate of internal secretion from implanted organs. These observations might suggest that the nervous system is only of minor if of any significance for the activity of the endocrine system. However, such a sweeping generalization

would be quite erroneous, since detailed investigations show that the role of the nervous system varies considerably for different glands of internal secretion.

The Neural Control of Insulin Secretion

Since the implanted pancreas secretes insulin in adequate amounts and prevents the occurrence of diabetes mellitus in pancreatectomized animals, the influence of nerves supplying the pancreas can consist only in modifying the rate of insulin secretion. The fact that fibers of the right vagus innervate the islets of Langerhans furnishes the anatomical basis for the possible significance of the vagus in the regulation of insulin secretion. The important observation (133, 815) that stimulation of the right vagus causes hypoglycemia, which is absent when the pancreatic vein is ligated, suggests that the secretion of insulin is regulated under physiological conditions, at least in part, by nervous impulses. Some evidence that the sugar content of the central nervous system may determine the degree of vagal insulin secretion may be cited.

That the hyperglycemia following the injection of glucose is prolonged after vagotomy (324), particularly in nephrectomized animals (691), shows that the increased blood sugar leads to stimulation of the vagus, which in turn causes an increased insulin secretion. Such an interpretation is supported by the experiments of Mehes (924), who found that the intracisternal injection of sugar causes a prolonged hypoglycemia, and by the perfusion experiments of Zunz and La Barre (1260–1262). In the latter, dog A perfused the head of dog B, whose trunk was connected with its own head only via the vagi, while the pancreatic vein of dog B was linked with the jugular vein of dog C. When glucose was injected into dog A, thereby raising the blood sugar concentration of the brain of dog B, hypoglycemia was observed in dog C, caused by an increased insulin secretion in dog B. The removal of the cerebral hemispheres of dog B did not interfere with this reaction. If, however, the thalamus and hypothalamus were removed, variations in the blood sugar of the brain of dog B no longer caused any alteration in the secretion of insulin in its own body. The experiments seem to indicate that an increase in the blood sugar of the brain leads to an increased vago-insulin discharge, thereby contributing to a re-establishment of the normal blood sugar level. This conclusion is strengthened by further experiments by Zunz and La Barre, who found that a decrease in the blood sugar concentration of the brain inhibits insulin secretion. Here again the authors used cross-circulation experiments as a method of insulin assay.

There is still one other condition known in which insulin secretion seems to be regulated by nervous factors. Geiger (419) observed that warming the blood in the carotid arteries caused a fall in the blood sugar provided that the vagi were intact. That this hypoglycemia was due to an increased secretion of insulin was established on mice by testing for insulin the blood thus obtained. After vagotomy neither hypoglycemia nor a change in the insulin concentration of the blood occurred. The conclusion that might be arrived at with regard to the effect of the blood sugar and temperature of the brain on a neurogenically regulated insulin secretion has not been generally accepted, since Gayet was unable to confirm these experiments (446).

In recent years the role of the vagus in stimulating the secretion of insulin has been investigated by Gellhorn and his collaborators (351–353, 481, 497) in a series of experiments in which the blood sugar was chosen as an indicator of insulin secretion. It was found that whereas anoxia, cold, fever, chemically or electrically induced convulsions, histamine, and centrally acting drugs such as cocaine and bulbocapnine produce hyperglycemia in normal rats, a fall in the blood sugar occurs under these conditions in adrenodemedullated or in adrenalectomized animals. This result suggested that in the normal organism both the sympathetico-adrenal and the vago-insulin systems are activated and that normally the former predominates over the latter. This interpretation is supported by several observations. First, it was found that the hyperglycemic reaction under various conditions of stress and drug action was intensified in normal animals by subdiaphragmatic vagotomy. Second, it was noted that animals subjected to anoxia etc. failed to show a significant change in their blood sugar if they had been vagotomized and adrenodemedullated. Finally, the assay of the blood for insulin was positive in adrenalectomized rats after anoxia or chemically induced convulsions, but no insulin could be detected if these experiments were performed on vagotomized, adrenalectomized animals (Table 14).

In the light of the effects on the vago-insulin system obtained by stimulation of the hypothalamus and in emotional excitation (476), it may be suggested that insulin secretion is regulated, at least in part, at the hypothalamic level. The mechanism by which hyperglycemia acts on the parasympathetic system in the diencephalon (Zunz) and the particular part involved are not known. With cocaine, metrazol, and electrically induced convulsions a direct excitatory effect on the autonomic centers of the brain stem is almost certain, whereas anoxia and histamine probably act largely through a reflex activation, the former via the chemoreceptors, the latter through the pressoreceptors

TABLE 14. An Assay of the Blood for Insulin, Using the Adrenalectomized Mouse as a Test Animal (Feldman, Cortell, and Gellhorn, 351)

	Values of Blood Sugar of Adrenalectomized Mice 2 Hours after Intraperitoneal Injection of Blood Taken from					
	Normal Rat	Adrenalectomized Rat	Anoxic and Adrenalectomized Rat	Anoxic and Adrenalectomized, Vagotomized Rat	Metrazol-treated * Adrenalectomized Rat	Metrazol-treated * Adrenalectomized, Vagotomized Rat
Average	58.7	60.5	52.6	64.0	47.5	63.8
Standard deviation ..		1.51	1.91	1.93	4.19	3.26
Probability coefficient ..			< 0.01	< 0.01	< 0.01	$= 0.02$

* Injected with 55 mg. metrazol/Kg subcutaneously.

of the sino-aortic area. The decrease in cortical function with the attending release of the brain stem in anoxia may play a role in activating not only the sympathetico-adrenal but also the vago-insulin system.

The Adrenal Medulla

The importance of neuro-endocrine relations is further clearly seen in the adrenal medulla: the chief function of the adrenal medulla, the adjustment of the rate of adrenalin secretion* to conditions of emergency (Cannon, 191), depends on the integrity of the splanchnic nerves.

The secretion of adrenalin is regulated by autonomic centers in the hypothalamus and medulla oblongata; the spinal centers play only a subordinate role and are less excitable. Stimulation of the postero-lateral hypothalamic area induces a secretion of adrenalin, as shown by the reaction of denervated structures such as the nictitating membrane (888) and by cross-circulation experiments involving an anastomosis between the adrenal vein of one dog and the jugular vein of another whose blood pressure serves as an indicator (711). An even greater influence must be attributed to the medulla oblongata (221). Glycosuria follows the puncture of the fourth ventricle (Claude Bernard's piqure) and is absent after the elimination of the adrenals (751).

* In this section "secretion of adrenalin" stands for adrenomedullary secretion; in other sections of this chapter "injection of adrenalin" stands for injection of commercial extracts of the adrenal medulla (epinephrine). The biological and chemical analysis of these extracts and secretions has been discussed in Chapter 11.

Since the adrenalin content of the adrenal medulla is lowered after piqure, the glycosuria appears to be due to increased adrenomedullary secretion (1167). The motor cortex or the basal ganglia do not seem directly to control the secretion of adrenalin, but the neocortex appears to inhibit the reactivity of the autonomic centers in the brain stem, since the hyperglycemia following bodily restraint is much greater in decorticate than in normal animals (80).

Observations on animals in which the spinal cord had been transected at the lower cervical region show that reflex stimulation through the sciatic nerve leads to an increased secretion of adrenalin (148–150). Effects such as the contraction of the denervated nictitating membrane and a rise in the blood sugar occur, but are absent after removal of the adrenals. Hemorrhage and hypoglycemia lead likewise to signs of increased adrenalin secretion in spinal animals. These experiments prove that spinal sympathetic centers can be excited directly or reflexly and induce an increased secretion of adrenalin.

Investigations, particularly those of Cannon and his school (191), have established the fact that a great variety of conditions may call forth the secretion of adrenalin. Thus exposure to cold under conditions in which emotional excitement was avoided led to an increase in the rate of the denervated heart in proportion to the degree of cooling. It was also noted that cold increased the blood sugar and that this effect was absent after splanchnicotomy (420) or adrenalectomy (481). That this reaction was due to a central autonomic discharge was supported by Geiger's observation on the effect of cooling of the brain. He succeeded in showing that cooling of the carotids induced a rise in the blood sugar in normal but not in splanchnicotomized animals, and this reaction occurred without a fall in the temperature of the body. Fever was likewise found to increase the rate of the secretion of adrenalin (353, 1080).

Reflex excitation via the carotid sinus pressoreceptors is thought to be responsible for the variations in the rate of adrenalin secretion when the blood pressure is varied experimentally. A rise in the pressure in the isolated carotid sinus lowers the rate of secretion, whereas a fall in the pressure has the opposite effect (646). The former reaction is likewise elicited by the stimulation of the depressor nerve; the latter is evoked in conditions of hemorrhage and various forms of shock. Finally, it may be added that muscular exercise and emotion are accompanied by the secretion of adrenalin (197).

Changes in the chemical composition of the blood, particularly with respect to oxygen and glucose, are known to activate the sympa-

thetico-adrenal system and to increase the concentration of circulating adrenalin (609). Anoxia and asphyxia as well as hypoglycemia are particularly potent activators of adrenomedullary secretion. It is of interest to mention that anoxia sensitizes the sympathetico-adrenal system to the effect of carbon dioxide. Whereas the inhalation of 5-per-cent carbon dioxide does not alter the blood sugar concentration, it greatly increases the hyperglycemic action of moderate anoxia (507). Since the hyperglycemic action of anoxia is abolished by denervation of the adrenals (351), it may be said that asphyxia (hypoxia plus increased carbon dioxide) is a more potent stimulus for adrenalin secretion than anoxia involving the same reduction of oxygen in the inhaled air. Drugs such as morphine, anesthetics, and convulsants cause a secretion of adrenalin via the splanchnic nerves (446).

It may be concluded that a great variety of conditions lead to the activation of the adrenal medulla through discharges originating in the centers of the sympathetic system. These discharges are initiated reflexly and/or directly. Stimuli such as a lowered temperature of the blood and the complex processes associated with emotion may serve as examples for direct action on the hypothalamus. In other conditions, such as barbiturate anesthesia (511) and hypoglycemia, the activity of the released brain stem, no longer under cortical control, seems to be the decisive factor in effecting a discharge of adrenalin.

The question arises whether the secretion of adrenalin continues after the denervation of the gland. Histological studies indicate that this procedure does not alter the structure of the adrenal medulla, and biological experiments show that the adrenalin content of denervated glands, although diminished, is still considerable (629).

Hermann and his collaborators (632) have carried out extensive studies to investigate the possibility of a secretion of adrenalin from the denervated gland. The adrenals were completely denervated by splanchnicotomy and removal of the abdominal sympathetic chains, and in some experiments the spinal cord was destroyed from D_1 downward. This procedure renders the animal highly sensitive to the pressor action of adrenalin. Under these rigorous conditions it was found that adrenalin is secreted in small quantities in the absence of neurogenic stimuli. Nicotine, faradization of the denervated gland, and severe asphyxia are effective (1263).

These experiments are interesting from a theoretical point of view in that they seem to establish that true secretion may continue for months in the adrenal medulla after it has been denervated. This functional survival is perhaps analogous to the persistence of tonic discharges in decentralized peripheral ganglia of the autonomic

nervous system such as the superior cervical and the stellate ganglia. But it must be emphasized that the denervated gland is hardly ever excited under physiological conditions. Whereas relatively slight stimuli applied to peripheral nerves reflexly elicit adrenalin secretion in the normal animal and numerous drugs and various physiological conditions, such as emotional excitement and cold, call forth general sympathetico-adrenal discharges, none of these stimuli will act on the denervated gland. Obviously the physiological role which adrenalin plays in the organism depends on the integrity of the splanchnic nerves.

The Neural Factor in the Secretion of the Antidiuretic Hormone of the Posterior Pituitary

The role of nervous impulses in the secretion of hormones is still greater for the posterior pituitary than it is for the adrenal medulla. The fundamental principles were established through the classical experiments of Fisher, Ingram, and Ranson (361), who determined the influence of discrete hypothalamic lesions on the secretion of the antidiuretic hormone of the posterior lobe. They found in cats and monkeys that diabetes insipidus results regularly from lesions which interrupt the supraoptico-hypophysial tract. Such lesions lead to a degeneration of the supraoptic nuclei and are followed by atrophy of the posterior lobe. The effect of such lesions is similar to the removal of the pars nervosa of the hypophysis, since after such operations in cats and monkeys diabetes insipidus ensues. The severity of this syndrome is directly related to the number of nerve fibers which have degenerated. If, however, the lesion involves the tubero-hypophysial tract no changes in posterior lobe function occur and the urinary secretion remains normal. (See Figure 75.)

The fact that diabetes insipidus develops its permanent phase about twelve days following the destruction of the supraoptic nuclei indicates that it is not due to an irritative process in the hypothalamus but rather to a loss of function. That experimental diabetes insipidus is due to a failure of the posterior hypophysis to secrete the antidiuretic hormone is proved by the fact that the injection of pitressin suppresses both polyuria and polydipsia. The atrophy of the neural division of the hypophysis not only is an anatomical fact but has been evaluated in its physiological significance through the assay of the hormones of the posterior lobe in animals which had been rendered diuretic by lesions of the supraoptico-hypophysial tract. The pressor, oxytocic, and antidiuretic hormones were found to be present only in traces in such animals, whereas no significant changes were observed in the

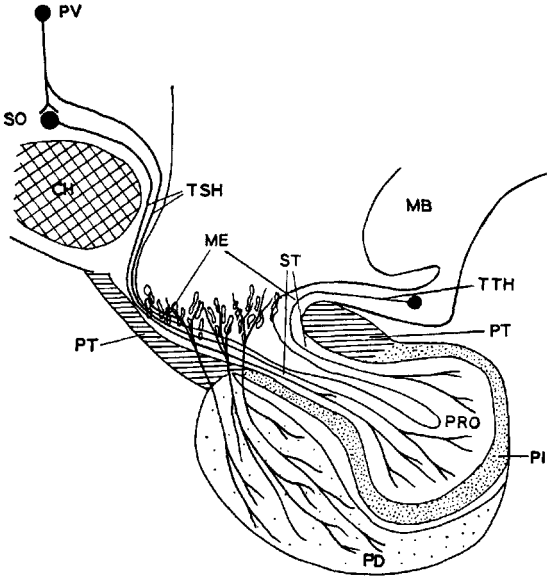

FIGURE 75. A diagram of hypothalamic-hypophysial relations. PV, paraventricular nucleus; SO, supraopticular nucleus; CH, optic chiasma; PT, pars tuberalis; TSH, supraoptico-hypophysial tract; ME, median eminence; ST, hypophysial stem; TTH, tubero-hypophysial tract; PD, pars distalis (adenohypophysis); PI, pars intermedia; PRO, infundibular process (posterior lobe). (W. P. Koella, with utilization of drawings by Rioch; Fisher, Ingram, and Ranson; and Harris.)

hormones of the anterior lobe of the hypophysis. The experiments seem to indicate that the supraoptico-hypophysial system regulates the secretion of the antidiuretic hormone.

The theory of Ranson and his collaborators has steadily gained ground and appears to be applicable to the human being. Biggart (100) cites clinical evidence for the involvement of the supraoptico-hypophysial tract in cases of human diabetes insipidus, and Dandy (251) notes that in one patient the transection of the human hypophysial stalk is followed by permanent diabetes insipidus (of eleven years' duration). No disturbances in menstruation, pregnancy, and blood sugar occurred during this time, a fact suggesting that the significance of the hypophysial stalk is different for the anterior and the posterior hypophysis.

If it is true that a degeneration of the supraoptico-hypophysial tract eliminates the secretion of the antidiuretic principle, it is to be expected that stimulation of this tract will lead to its increased secretion and thereby to an inhibition of urinary secretion. Haterius

(616) showed indeed that stimulation of the pituitary stalk resulted in the inhibition of urinary secretion in hydrated rabbits, but such effects were absent after stalk transection.

This work was extended by Harris (596, 601), who developed a method by which stimulation of the hypothalamus could be carried out in unanesthetized animals. When the electrode was inserted into the supraoptico-hypophysial tract, he produced an inhibition of water diuresis with an increase in the concentration of chlorides in the urine. If the electrode was more than 0.5 mm. removed from this tract, stimulation failed to inhibit urinary excretion. The stimulation of the supraoptico-hypophysial tract inhibited diuresis also in animals in which the adrenal medulla had been inactivated. There was at the same time a rise in the blood pressure of a type which was easily matched by the injection of extracts from the posterior pituitary.

At least three conditions are known which lead to the secretion of the antidiuretic hormone: reflex stimulation by painful stimuli (981), emotional excitement through noise or as the result of exercise (1077), and changes in the osmotic pressure of the arterial blood (Verney, 1185). These factors are no longer operative after removal of the posterior pituitary (980), but their action persists after inactivation of the adrenals. The effect can be matched with posterior pituitary extracts but not with adrenalin, which inhibits diuresis for a much briefer period. (See Figure 76.)

It is the function of the posterior pituitary to conserve water by reabsorption in the tubules of the kidney. The effect is hormonal in character, since it persists in the denervated kidney. Dehydration increases the rate of secretion of the antidiuretic hormone (546), and consequently the reabsorption of water through the renal tubules is augmented.

That the supraoptico-hypophysial system accounts for the regulation of the osmotic pressure was shown by Verney (1185) in a series of remarkable experiments. The injection of various hypertonic solutions into the carotid artery was found to release the antidiuretic hormone. If the experiment was repeated after removal of the posterior pituitary, the hypertonic solution was only $\frac{1}{10}$ as effective in conserving body water as before! The carotid sinus and the chemoreceptors play no role in these reactions, and the osmoreceptors must lie within the circulatory area supplied by the internal carotid artery, since its ligation abolishes the response to hypertonicity from the common carotid artery of this side. Since the reaction to this stimulus persists on the other side (although somewhat diminished), it may be concluded that the osmoreceptors are bilaterally present. It is highly

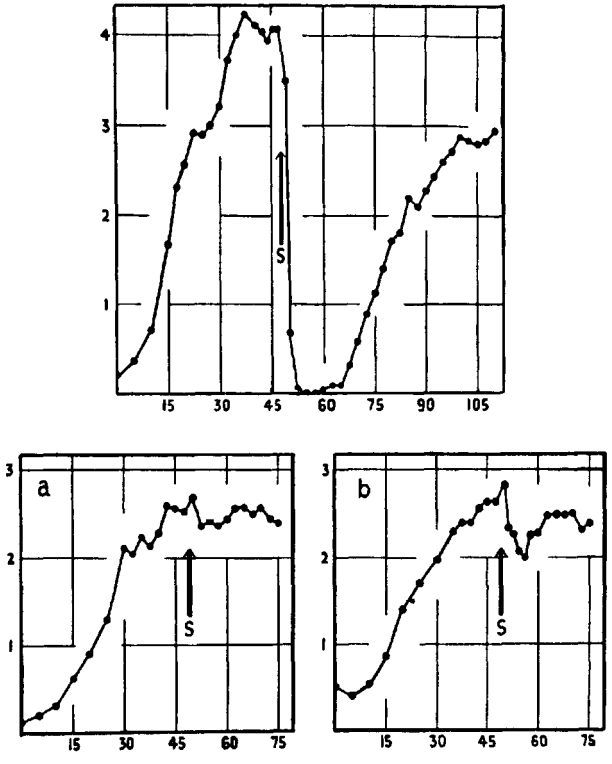

FIGURE 76. *Upper part:* the inhibition of water diuresis by emotional stress before section of the supraoptico-hypophysial tracts but after denervation of the kidneys and suprarenals. The test dose of 300 cc. of water was given at zero time. The ordinate shows the rate of urine secretion in cc. per minute. The abscissa indicates the time in minutes. At S the dog was excited by faradic stimulation. *Lower part:* the effect of the same emotional stimulus on the same animal but (part a) 35 days after section of the supraoptico-hypophysial tracts and (part b) 70 days after. (O'Connor, 980.)

probable that they are related to the supraoptic nuclei. In the latter Verney found vesicles which may act as osmometers and suggests that variations in their size may send impulses to adjacent stretch receptors and thereby release the antidiuretic hormone. It is obvious, however, that this is at present only an attractive hypothesis.

It should be added that rats kept on a high salt diet for several weeks show hypertrophy of the cells of the supraoptic (and of the paraventricular) nuclei. Apparently overproduction of the antidiuretic hormone is responsible for these changes. Under conditions of "acute overloading" of the supraoptico-hypophysial system severe chromatolytic changes appear in these nuclei (Hillarp, 654; Bargmann, 72).

This review shows an extensive body of facts relating the supra-optico-hypophysial system to the regulation of the osmotic pressure and raises the question whether this important function is solely dependent on that system or whether there is evidence of water regulation outside it. These matters are still controversial. The observations of Ingram *et al.* (727) indicate that in cats with diabetes insipidus no antidiuretic hormone appears in the urine even in very severe dehydration. On the other hand, Walker (1199) shows that some water-regulating mechanisms are still present in hypophysectomized animals, and Brouwer (158) reports that the destruction of the supraoptic nuclei is not invariably followed by diabetes insipidus. This seems to suggest that perhaps other parts of the hypothalamus may be involved in the regulation of the osmotic pressure.

The histological studies of Scharrer and his collaborators (1095) suggest a solution for this problem. He observed that the supraoptic nucleus contains acidophil granules, a fact which seems to indicate that the cells constituting this nucleus are capable of secretion. Moreover colloidal droplets are found along the supraoptic tract which appear to be identical with the granules seen in the cell bodies of the supraoptic nuclei (Fig. 77). Bargmann (72) found similar histological

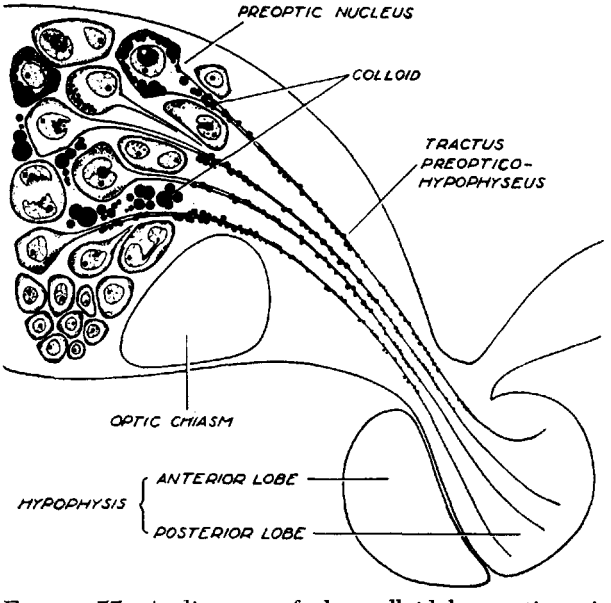

FIGURE 77. A diagram of the colloidal secretions in the hypothalamo-hypophysial system of a vertebrate. (Scharrer and Scharrer, 1095.)

changes in the rat. Histological pictures show that the posterior pituitary hormones are secreted by the cells of the supraoptic nuclei and are transported to the posterior pituitary through the supraoptico-hypophysial tract. If the neurosecretion is not confined to this system, it may account for some residual antidiuretic function after the nerves in the stalk have undergone degeneration. In some recent experiments it was found that the posterior pituitary hormones can be extracted from the supraoptic and paraventricular nuclei of the hypothalamus and also from the tuber cinereum and that the latter fulfills a storage function for these hormones (648).

There is still more evidence for a relatively widespread distribution of the antidiuretic hormones. Quantitative investigations based on the degree of staining of the ganglion cells (984) have shown that the so-called Gomori substance, which is intimately related to the activity

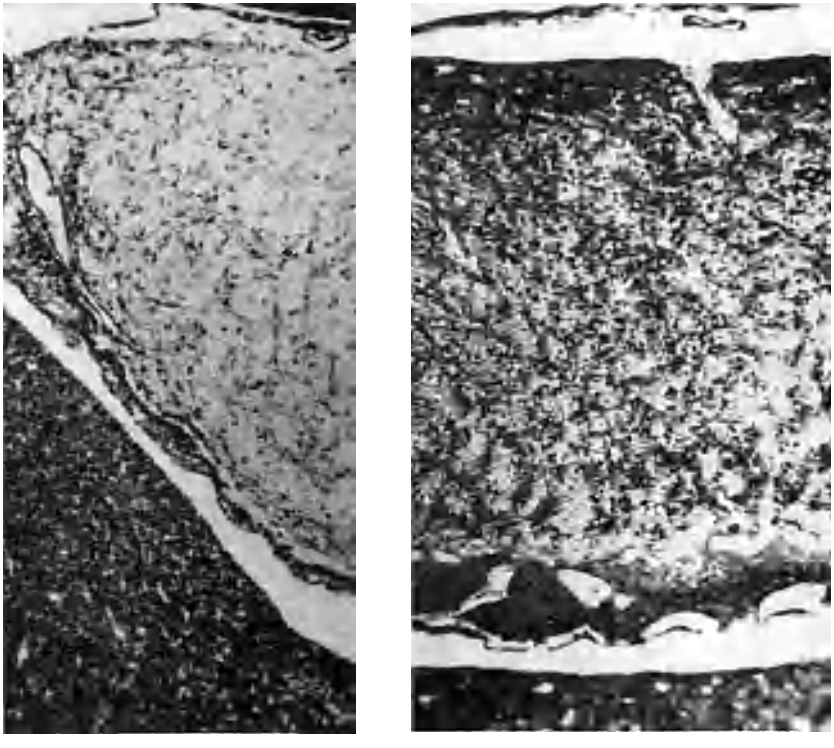

FIGURE 78. The effect of thirst on the histological appearance of the paraventricular nucleus of the rat (Gomori-stain). The Gomori substance is practically absent in the thirsting rat (13 days) as seen in the left figure. The right figure shows the nucleus in the control animal. (Ortmann, 984.)

of the antidiuretic system, is found not only in the posterior hypophysis and the supraoptic and paraventricular nuclei (Fig. 78) but also in scattered ganglion cells throughout the anterior hypothalamus. Koella's observation (789) that the secretion of the antidiuretic hormone can be elicited by the stimulation not only of the supraoptic nucleus but of a larger area in the anterior hypothalamus (between the supraoptic and filiform nuclei) is in agreement with these findings.

The Nervous Regulation of the Pressor Hormone of the Neurohypophysis

Since the pressor and antidiuretic principles of the posterior pituitary seem to represent two different effects of the same substance, one would expect that direct or reflex activation of the neurohypophysis would liberate this vasopressor hormone.

Chang and his collaborators (212–214) showed that a pressor response may be elicited through afferent vagal impulses in animals in which the nervous connections between the brain and the spinal cord are completely severed while the vascular connections between the head and the trunk remain intact. This effect on the blood pressure is abolished after transection of the stalk. The result indicates that vagal impulses lead to a release of the pituitary hormones which bring about a rise in the blood pressure. Since this pressor response is also abolished by a section through the anterior part of the hypothalamus which severs the connections between the supraoptic nuclei and the posterior lobe of the hypophysis, it may be assumed that vagal impulses reach the supraoptic nuclei, in a manner as yet undetermined, whence they are relayed to the posterior lobe of the hypophysis via the supraoptico-hypophysial tract. This conclusion is supported by the work of Clark and Wang (230), who obtained similar effects on the blood pressure by electrical stimulation of the anterior part of the hypothalamus, and also by Sattler (1085), who found the vagal reflex to be absent in animals with diabetes insipidus. The fact that this effect remains unaltered after transection of the spinal cord in the neck region excludes the participation of adrenalin or sympathin in the rise of the blood pressure (713).

Repeated stimulation of the vagus may lead to a diminution in the pressor response and at the same time to an exhaustion of the pituicytes in the posterior lobe. After suitable intervals have been allowed for recovery, the pressor response may be restored and secretory granules reappear in the pituicytes (216).

Direct stimulation of the supraoptico-hypophysial tract elicits only a slight pressor effect, but the long latent period and the form of the

pressure curve are similar to those seen after the injection of pituitrin. In addition to these vasopressor effects Harris (603) noted a definite action on the gastrointestinal tract upon stimulation of the supra-optico-hypophysial system. It appeared in the unanesthetized rabbit in the form of increased peristalsis of the large colon after a long latent period (one-half minute or more) and could be matched with the injection of pituitrin. Although these findings are thus far too incomplete to assume that the posterior pituitary secretes a hormone which activates the movements of the gut, it is interesting to note that, as Harris points out, Cushing observed chronic constipation in cases of destruction of the posterior pituitary.

The Nervous Regulation of the Oxytocic Hormone

In contradistinction to earlier work on the effect of removal of the posterior pituitary, recent studies seem to present rather conclusive evidence for a physiological role of the neurohypophysis in labor. This evidence rests on disturbances in parturition in animals with destruction of the supraoptico-hypophysial system, the liberation of the oxytocic principle on hypothalamic stimulation, and the similarity of the latter effect to the effect of posterior pituitary extract when injected intravenously.

Fisher, Magoun, and Ranson (362) frequently found a marked disturbance in parturition in cats with diabetes insipidus following hypothalamic lesions. Labor was greatly protracted, sometimes only a part of the litter was delivered, and some kittens were found in utero at autopsy. Some of the animals died in labor. This work suggests that the negative results of other authors may have been due to an incomplete removal of the posterior lobe. That the anterior lobe was not involved was shown by the continuance of growth, lactation after delivery, and the absence of gross changes in the thyroid and gonads.

The physiological importance of the oxytocic principle is further illustrated by Haterius and Ferguson (618), who showed that electrical stimulation of the infundibular stalk greatly increases the activity of the uterus of the rabbit post partum. This effect is abolished after transection of the stalk, but is not interfered with by spinal transection, splanchnicotomy, or vagotomy. Moreover the effect of stimulation of the stalk on the uterus can be matched by the injection of pitocin but not by the administration of adrenalin. The oxytocic principle may be liberated reflexly. Stimulation of the vagus leads to the appearance of a substance in the blood which, when injected into a guinea pig, frequently causes a contraction of the virgin uterus (217).

Harris's recent studies (603) are in agreement with these results. Using his method involving an implanted electrode, he showed that stimulation of the supraoptico-hypophysial system liberates in one minute the equivalent of 200 to 500 milliunits of pitocin. The effect can be matched better with pitocin than with pituitrin, since the latter produces a greater inhibition following the contraction of the uterus. The latent period of the nervous stimulation is again long and there is a marked parallelism between the reaction of the uterus to pitocin and stimulation of the neurohypophysis. The anestrous uterus, which shows no spontaneous activity, does not respond to either pitocin or stimulation of the supraoptico-hypophysial system, but with the uterus in estrus either spontaneously or as the result of administered estrogen both methods of activation become effective. The stimulation experiments remain positive after inactivation of the adrenal medulla, a fact indicating that adrenalin is not responsible for the contraction of the uterus.

That antidiuretic and oxytocic hormones are separate substances although both are regulated through impulses from the anterior hypothalamus has been asserted frequently. Harris mentions an observation which seems to justify this distinction under strictly physiological conditions. The injection of hypertonic salt solution elicits, as discussed earlier, an increased secretion of the antidiuretic hormone. About one hour later the hypophysis, in response to a standard stimulus applied to the supraoptico-hypophysial system, elaborates a hormone consisting of the same amount of pitocin but a lesser concentration of pitressin. The pitressin, supposedly closely related to if not identical with the antidiuretical principle, is probably diminished because depleted earlier in the experiment with the hypertonic solution, whereas the oxytocic fraction is not altered. This work seems to indicate that the supraoptico-hypophysial system may respond specifically to different well-defined stimuli.

There is still another function of oxytocin, and it depends likewise on the hypothalamus for its liberation: the ejection of milk from the lactating mammillary gland. The secretion of milk is regulated by the lactogenic hormone of the anterior pituitary, but its ejection in the lactating animals is influenced by the oxytocic fraction of the posterior pituitary. Through earlier work (985, 1004) it is known that the injection of posterior pituitary extracts aids in the removal of milk from the lactating gland and that mechanical stimulation of the teats leads to the increased secretion of oxytocin. It is assumed that the oxytocic hormone, secreted through activation of a reflex which involves the hypothalamus and posterior pituitary, causes a contraction

of the smooth muscles in the mammary gland so that milk passes from the alveoli into the milk ducts.

That lactation requires the regulating activity of the hypothalamus and the integrity of the anterior pituitary and neurohypophysis is clear from several studies. First it was shown on hypophysectomized rats with grafts of the anterior pituitary. In such animals milk secretion is undisturbed, but the withdrawal of the milk through suckling is interfered with and the nursing young animals starve unless the ejection of milk is aided by the continued administration of oxytocin.

This work has been confirmed and extended in recent investigations. Stimulation of the anterior hypothalamus, particularly of the supraoptic nuclei and their immediate vicinity (Andersson, 38; Harris, 603), induces the ejection of milk in the lactating animal. The hormonal nature of this effect is evident from its persistence after denervation of the udder and the long latent period following the application of the stimulus to the anterior hypothalamus. Since all hormones of the posterior pituitary depend on the supraoptic nuclei, it may not be surprising that stimulation of these structures produces in lactating animals not only the ejection of milk but a strong antidiuretic effect. Moreover the intra-arterial injection of hypertonic salt solution elicits, in addition to the previously discussed antidiuretic effect, an increased secretion of oxytocin. The latter, again indicated by its effect on milk ejection in the lactating animal, may also be activated reflexly through the vagus (38), the influence of which on the secretion of the pressor hormone of the posterior hypophysis was established in earlier studies (212).

The following facts stand out from this discussion:

1. The various hormones of the posterior pituitary are regulated by the supraoptic nuclei and its immediate vicinity (including the paraventricular nuclei), and these structures can be activated directly and through reflexes.

2. Although strong stimuli such as the intra-arterial injection of hypertonic solutions are apt to elicit the secretion of all hormones of the neurohypophysis, physiological stimuli activate this organ in specific fractions.

The Nervous Regulation of the Gonadotrophic Hormones

That certain activities of the gonads are dependent on the nervous system is common clinical experience. Menstruation is easily disturbed by fear, mental strain, and emotional states in general. That the diencephalon may play a part is suggested by the observation

that tumors of the third ventricle and encephalitis produce sexual prematurity. On the other hand, hypogonadism may follow hypothalamic pathology.

Factors which influence the endocrines via the nervous system are likewise responsible for the activation of the gonads in laboratory animals. Harris (599) mentions that the sight of another animal may elicit ovulation in the rabbit and even the reflected image of another bird may produce this effect in the pigeon. The systematic investigations of Brooks (151, 152) showed that numerous afferent pathways are involved. The simultaneous removal of the olfactory lobes and of the neocortex does not interfere with the ovulation process, nor is the process eliminated by the destruction of the labyrinths and cochleae along with that of the olfactory bulbs. Brooks also found that the extirpation of the sacral cord and the additional removal of the abdominal sympathetic chains, supplemented by hysterectomy and extirpation of the proximal half of the vagina, do not eliminate either sexual excitement or ovulation. His observations make it probable that afferent impulses in the muscles of the hind legs and hips play an essential part in this process.

The experimental work in which the hypothalamic-hypophysial relationship of the gonadotrophic hormones was established may be divided into several groups. In the first, the effect of stimulation of the hypothalamus and of the nerves supplying the anterior hypophysis was studied. In the rabbit ovulation (which does not occur spontaneously but follows sexual intercourse) (124) served as an indicator of the release of gonadotrophic hormones from the hypophysis.

Nerves reach the anterior hypophysis from three sources: the greater superficial petrosal nerve and the sphenopalatine ganglion, the cervical sympathetic trunk, and the nerves in the hypophysial stalk. In spite of some controversy most authors agree that the elimination of the first two sources does not interfere with the occurrence of coitus-induced ovulation (896). In order to judge the significance of the nerves of the stalk the following observations are pertinent.

The pioneer work was done by Marshall and Verney (900), who produced ovulation by applying electrical currents to the head or to the lumbosacral part of the spinal cord of the rabbit. Similar results were obtained by both Harris (597) and Haterius (617), who stimulated the hypothalamus and elicited ovulation, the former from the tuber cinereum, the latter from a region close to the optic chiasma. Whether in these experiments the stimulation was restricted to diencephalic centers which influence the glandular part of the hypophysis or acted on the hypophysis itself was not certain. Such a separation

was effected by Westman and Jacobsohn (1226–1229), who, studying these problems in rats and rabbits, proved that the stimulation of the hypothalamus fails to produce ovulation after transection of the stalk, whereas it regularly did so when the hypothalamic-hypophysial connections were intact. Moreover they observed that the secretion of the gonadotrophic hormones of the anterior pituitary is influenced not only by electrical stimulation of the hypothalamus but also under more natural conditions in which the hypothalamus is stimulated during the process of sexual excitement. If the stalk had been cut, the rabbits did not ovulate even when copulation took place shortly after the operation. If, however, the mating preceded the cauterization of the stalk, the results depended on the time interval preceding this surgery. If the operation was performed more than two hours after coitus, ovulation took place, but if the animals were operated fifty to sixty minutes after copulation, no ovulation or corpus luteum formation was seen.

The observations of Brooks (152, 155) support the theory of a neurogenic control of the gonadotrophic hormones in relation to ovulation. Not only did he confirm the absence of ovulation after coitus in rabbits whose stalk had been sectioned, but he observed that in animals with a partially transected stalk ovulation took place only after numerous matings. Moreover rabbits with the stalk transected failed to show any alteration in the amount of luteinizing hormone in the anterior hypophysis after mating, whereas it decreased regularly in unoperated control animals.

Stimulation of the hypothalamus has been greatly refined by Harris (595), who implanted electrodes in this part of the brain aseptically and stimulated it in the unanesthetized animal. He succeeded in inducing ovulation with minimal currents provided that the stimulus was applied to the tuber cinereum of the hypothalamus. A much longer stimulation applied to the infundibular stem, however, failed to induce this effect. Similarly it was noted that stimulation of the anterior hypophysis with currents which were highly effective when applied to the hypothalamus did not evoke ovulation (896). These results make it doubtful whether a simple transmission of nervous impulses from the hypothalamus to the anterior hypophysis is responsible for the hypothalamic control of the gonadotrophic secretion of the pituitary gland.

Similar results are obtained on stimulation of the hypothalamus with chemical substances. The intravenous injection of copper acetate produces ovulation in normal rabbits, but fails to do so after the stalk has been sectioned (152). Convulsive drugs such as picrotoxin and

metrazol, apparently acting on hypothalamic centers (443, 478), cause ovulation in normal animals, but after sectioning of the hypophysial stalk, these drugs persist in producing convulsions but no longer effect ovulation.

The regulation of gonadotrophic activity from the hypothalamus is also evident from the study of diencephalic lesions. Brookhart and Dey (147) observed in male guinea pigs with such lesions reduced or no sexual activity despite structural integrity of the testes and seminal vesicles and continued spermatogenesis; Bustamente (188) noted that following lesions in the tuber cinereum of young rabbits, an absence of libido, gonadal atrophy, and obesity occurred. Lesions in the mammillary bodies did not cause the appearance of any symptoms in the sexual sphere.

Other authors hold lesions in the anterior hypothalamus responsible for the secretion of gonadotrophic hormones (285, 286). If the lesions were bilateral and located at the caudal end of the optic chiasma, increased development of the ovaries occurred, the genital organs appeared hypertrophic, and the vaginal membranes were open. That this condition was due to the lack of secretion of luteinizing hormone was proved by the observation that in such animals the injection of this hormone led to rupture of the follicles, the formation of corpora lutea, and closure of the vagina.

This work was confirmed by Hillarp (655, 656) with lesions in the anterior hypothalamus extending laterally to the median forebrain bundle. The animals showed continuous estrus with the interstitial gland of the ovaries well developed, but no corpora lutea were formed. Apparently at least a part of the secretion of the luteinizing hormone is abolished through these lesions.* From the anterior hypothalamus a fiber system originates which runs "superficially on both sides of the median eminence towards the hypophysial stalk." Superficial lesions of these fibers caudal to the paraventricular nuclei likewise cause continuous estrus.

In view of the fact that experiments involving the stimulation or destruction of certain parts of the hypothalamus influence the activity of the gonads and sexual behavior, one would expect sectioning of the hypophysial stalk or other procedures interfering with the integrity of the hypothalamic-hypophysial connections to result likewise in disturbances of gonadal functions. This is by and large the case, although the degree of change seems to vary greatly. Harris (599) calls attention to the fact that in experiments on hypophysectomy and

* The development of the interstitial gland is a function of the luteinizing hormone.

implantation of the adenohypophysis, histological evidence of the completeness of the operation and an adequately long period of observation are necessary to evaluate the experimental data. He stresses the fact that the most complete recovery of all gonadal functions was observed in female rats with transplantation of the hypophysis in the sella turcica (573). Likewise it was found that when a silver plate was inserted between the cut ends of the stalk, gonadal atrophy occurred in rats (Westman and Jacobsohn, 1229). Moreover lesions involving the median eminence seem to produce greater sex disturbances than stalk transection.

Although the gonadotrophic functions of the anterior hypophysis depend on the hypothalamus, the following observations do not favor the assumption that only nervous transmission is involved: (1) electrical stimulation of the infundibular stem and of the adenohypophysis does not evoke secretion of gonadotrophic hormones; (2) the nerve fibers supplying the adenohypophysis are scarce (154) and unaltered after stalk transection (656); (3) the transmission of those impulses from the hypothalamus to the hypophysis which regulate ovulation takes minutes rather than fractions of a second. If excitation of the nerves in the stalk or in the anterior hypophysis were involved in the secretion of gonadotrophic hormones, one would expect a responsiveness of these nerves to minimal currents.

An alternate mechanism would be that of a neurohumoral transmission (599). The hypophysial-portal system seems to carry the neurohumors released by hypothalamic excitation to the anterior hypophysis. How well this system is adapted to this purpose is evident from Harris's (597, 600) description: "Small twigs of the internal carotid arteries supply a vascular plexus situated between the pars tuberalis and the median eminence, and from this plexus 'vascular tufts' or 'sinusoidal loops' penetrate the tissue of the median eminence. These loops are then in intimate contact with the wealth of nerve fibres in this situation. From these vessels the blood is drained into large portal trunks which pass to the pars distalis where they break up into the sinusoids of this part of the gland. Therefore at one end the wide trunks are continuous with the loops in the median eminence and at the other end with the sinusoids of the pars distalis, that is they are truly portal vessels. This system of vessels, with minor variations in pattern, has been found in all vertebrates so far examined from amphibians to man. Since the pars tuberalis has no proven endocrine function and since it bears a constant relationship to the sinusoidal vessels which penetrate the medium eminence it has been suggested (Harris, 1947) that the significance of the pars tuberalis lies in the

fact that it forms a bed for the vascular pathway between the hypothalamus and pars distalis." (See Figure 75, p. 298, a diagram of hypothalamic-hypophysial relations.)

Harris's suggestion that a neurohumor is transmitted through this vascular system to the anterior hypophysis is supported by Markee and his collaborators (1087–1090). These authors showed that the local application of adrenalin to the anterior pituitary elicits ovulation. This process is blocked by an adrenolytic agent such as dibenamine. That the action of this drug in inhibiting ovulation is due to its adrenolytic and not to other pharmacological effects is supported by the observation (1087) that a close relative of this drug which has a similar action on the central nervous system but lacks the adrenolytic property does not interfere with ovulation. Sawyer, Markee, and Townsend (1090) found further that atropine may likewise block ovulation and concluded from the time relations necessary for the action of these drugs that the cholinergic component of this humoral transmission precedes the adrenergic one. This suggests to these authors that the hypothalamic-hypophysial transmission follows the principle established for the liberation of adrenalin from the adrenal medulla. However, it is to be borne in mind that the neurohumoral transmission in the adrenal medulla has been proved by the direct assay of acetylcholine, whereas the assumption that cholinergic and adrenergic substances are responsible for hypothalamic-hypophysial effects rests on indirect evidence (the action of dibenamine and atropine) and the application of adrenalin to the hypophysis in unphysiological concentrations.

Although the nature of the neurohumors involved in these processes awaits further clarification, a neurohumoral transmission utilizing the hypophysial portal system seems fairly well established. Harris calls attention to the fact that the variability in the effects of stalk transection on gonadal functions may be related to the regeneration of this vascular system. In a recent study he found that in the rat estrus may recur after sectioning of the stalk (602, 603). However, when the regeneration of the blood vessels is prevented by the insertion of a piece of paper, the rats do not show any cycles, and partial regeneration of the portal system results in irregular cycles. The vascular hypothesis is further supported by the study of gonadotrophic functions in hypophysectomized rats with implants of the anterior hypophysis. If the implants were made into the subarachnoid space under the temporal lobe, sex behavior was disturbed, but in rats with grafts under the tuber cinereum normal estrous cycles and pregnancy and lactation occurred. Likewise the observation that hypophysectomy

performed within one hour after coitus prevents ovulation indicates that a slow non-nervous process is interposed between the central excitatory processes taking place during sexual intercourse and the activation of the anterior pituitary.

Only one or two disputed points should be mentioned. Harris's hypothesis presupposes that the blood flows through the portal system from the hypothalamus to the anterior hypophysis. Barrnett and Greep (75) succeeded through direct observation of the blood flow in the hypophysial stalk in verifying this assumption. This finding seems to make untenable the hypothesis of the Spatz school (978) that adenohypophysial hormones circulating in the portal system act via a chemoreceptor-like mechanism on the fine nerve plexuses of the median eminence* and thus regulate the flow of gonadotrophic hormones. This idea of a reflex activation of the medioventral parts of the tuber cinereum has been based on the assumption that the blood flows from the anterior hypophysis to the hypothalamus and not in the opposite direction.

The Relation of the Sympathetico-Adrenal System to the Adrenal Cortex

Although no evidence exists that the secretion from the adrenal cortex is influenced by nerves, there is a unique relation between the sympathetico-adrenal system and the internal secretion of the adrenal cortex, since increased discharges of the former seem to augment the hormonal release from the latter.

The first indication that adrenalin may lead to a secretion of adrenocortical hormones was presented by M. Vogt (1189). She showed that the injection of adrenalin in relatively small doses (from 7 gamma/Kg to more than 200 gamma/Kg) increased the amount of circulating adrenocortical hormones. Blood was obtained from the adrenal veins and assayed for cortical hormones by determining the effect of the injected blood on the survival time of adrenalectomized mice exposed to cold. This period was significantly increased when blood was injected which had been withdrawn during and for some time after the injection of adrenalin. Quantitative experiments suggested that under these conditions the amount of cortical hormones liberated was increased by several hundred per cent.

Vogt's experiments appear to be of a physiological as well as of a pharmacological significance because not only the injection of adrenalin but also electrical stimulation of the splanchnic nerves caused an increase in the concentration of cortical hormones in the blood of the

* Which is the infundibulum of the German investigators.

suprarenal vein. Whether the stimulation of autonomic centers directly or reflexly increases the liberation of cortical hormones through splanchnic impulses has apparently not been investigated by this method. No evidence was found for the assumption that the normal resting secretion of adrenalin caused a mobilization of adrenocortical hormones, since sectioning of the splanchnics did not seem to alter the concentration of cortical hormones in the adrenal vein. However, this conclusion cannot be considered final unless confirmed in experiments with chronic denervation of the adrenals.

Since acetylcholine is known to increase the secretion of adrenalin in the atropinized animal by its action on the adrenal medulla (346–348), Vogt studied the action of acetylcholine on the secretion of adrenocortical hormones and found effects similar to those seen in the experiments involving splanchnic stimulation or the injection of adrenalin. The similarity in the effect of the three procedures mentioned suggests that the increased secretion of adrenocortical hormones is in all cases initiated by adrenalin. This interpretation is supported by the fact that the splanchnics do not innervate the adrenal cortex. It is noteworthy that indirect signs of increased cortical activity under conditions which cause a sympathetico-adrenal discharge have been known for some time. Thus Sjöstrand (1117) described hyperemia of the adrenal cortex in asphyxia and upon the application of nociceptive stimuli.

These experiments were confirmed and extended by Paschkis *et al.* (993), who used dogs in which a London canula had been previously inserted so that blood from various arteries and the adrenal vein could be obtained without anesthesia. The assay of the blood was based on the effect of adrenocortical hormones on the glycogen synthesis in the liver. This effect is believed to be due to a hormone chemically different from that involved in the protection against cold. Nevertheless results similar to those in Vogt's observations were obtained in that adrenotrophic hormone (ACTH), adrenalin (20 gamma/Kg), and several conditions of stress such as insulin hypoglycemia and tissue injury resulting from the injection of formalin into the muscles increased the hormone content of the blood. The experiments seem to justify the conclusion that adrenocortical hormones in general are secreted in increasing amounts in stress and on direct stimulation of the sympathetico-adrenal system. In addition it was found that even in the resting animal, in contradistinction to Vogt's work, measurable quantities of adrenocortical hormones were present in the arterial blood. It is not unlikely that this difference is due to the absence of anesthesia in Paschkis's experiments. It appears probable that a

certain tonic innervation of the sympathetico-adrenal system leads to a steady secretion of the adrenocortical hormones even in the absence of environmental stress. However, the crucial experiment to determine whether splanchnicectomy will cause a disappearance of these hormones from the blood has not been performed using Paschkis's method.

Although the mechanism will presently be discussed by which increased adrenocortical secretion is induced when initiated by the secretion or injection of adrenalin, it may be said that, contrary to Vogt's original assumption, the effect of adrenalin on the cortex is not a direct one. Thus Pincus (1012) and Vogt (1192) failed to obtain evidence for any increased liberation of adrenocortical hormones in the isolated perfused adrenal gland upon the injection of adrenalin, although this organ increased its output of cortical hormones when ACTH was added to the perfusate.

THE ALARM REACTION

The experiments of Vogt and Paschkis seemed to throw a new light on the so-called alarm reaction. Selye (1104) had found that various conditions of stress, such as hemorrhage, anoxia, cold, and exercise, and stress induced by the injection of several toxic chemicals (arsenic, formaldehyde, etc.), produced functional and also anatomic changes in the rat. These alterations were particularly marked in the adrenal cortex, which showed hypertrophy, whereas the thymus and the lymph nodes became atrophic. This inverse relation between the adrenal cortex and the thymus and lymph nodes seems to depend on the quantities of adrenocortical hormones circulating in the blood. The secretion of these hormones in excessive amounts, as in conditions leading to hypertrophy of the adrenal cortex, or the injection of adrenocortical extracts causes involution of the thymus. On the other hand, patients with Addison's disease, a malady involving diminished adrenocortical secretion, show hypertrophy of the lymphatic tissue.

Studies on hypophysectomized animals have made it abundantly clear that the functional status as well as the size of the adrenal cortex depends on the hypophysis and particularly on the rate of secretion of the adrenotrophic hormone. The injection of purified ACTH results in adrenocortical hypertrophy and in involution of the thymus (Dougherty and White, 292). In view of the fact that stimulation of the splanchnics or the injection of small amounts of adrenalin leads to an increased secretion of adrenocortical hormones, it appeared probable that various conditions of stress which, as Cannon showed,

induce a secretion of adrenalin through central sympathetic excitation may subsequently activate the hormones of the adrenal cortex. The work described in the following pages seems to substantiate this interpretation and to elucidate in some detail the mechanism involved.

THE BIOCHEMICAL CHANGES OF THE ADRENAL CORTEX IN STRESS

Progress in science depends to a large extent on methodological advance. This is well illustrated in the field under discussion. Physiological indicators were needed to show changes in the functional state of the adrenal cortex. The assay of the adrenocortical hormones in the blood is very time-consuming and hardly suitable for extensive work. It was therefore of considerable importance when Long (860) discovered that increased adrenocortical activity is accompanied by a significant loss in both the cholesterol and ascorbic acid content of the adrenal gland. Later it was found that some of the circulating blood cells (lymphocytes, 293; eosinophils, 1128) suffer a considerable and reversible decline in conditions leading to an increased secretion of adrenocortical hormones. The last methods made it possible to follow up functional alterations in adrenocortical activity without sacrificing the animal. Their significance will be discussed later, but first the progress made by the utilization of the chemical analysis of the adrenal cortex will be reported.

It was shown, particularly by Long *et al.* (859, 861), that conditions of stress such as hemorrhage and trauma lead to a decrease in the cholesterol and ascorbic acid content of the adrenal cortex of normal rats. Severe burns cause similar changes (880). Cold, heat, fever resulting from the injection of foreign proteins (typhoid bacilli), and histamine likewise induced a marked diminution in the ascorbic acid content of the adrenal gland (1093). If the severity of the stress is graded by exposure to different degrees of temperature or by the injection of increasing amounts of histamine, the results show that the fall in ascorbic acid content parallels the intensity of the stress. Moreover these changes can be simulated by the injection of increasing amounts of ACTH.

It has been pointed out elsewhere* that a secretion of adrenalin not only results from conditions which cause a direct or a reflex excitation of autonomic centers but occurs also when as a consequence of diminished cerebral cortical activity the subcortical autonomic centers are released. There is evidence that in these circumstances the hormonal activity of the adrenal cortex is likewise increased. Thus it was found that anesthesia with sodium pentobarbital leads in a few

* See p. 296.

hours to a decrease in the cholesterol content of the adrenal glands (836) and also to a hypertrophy of its cortex. Similar effects are produced in anoxia through the lowering of the barometric pressure to 200–300 mm. Hg. Insulin hypoglycemia likewise gives evidence for adrenocortical activation as shown by the fact that the adrenal cortex is depleted of lipoids (1191). Moreover that a secretion of adrenocortical hormones occurs in insulin hypoglycemia is suggested by the fact that the blood sugar falls more rapidly in adrenalectomized than in normal and adrenodemedullated rats (40).

The temporary depletion of the adrenal cortex of cholesterol, ascorbic acid, and sudanophilic material under stress and the increased excretion of adrenocortical steroids in the human being (1013, 1014) under similar conditions appear to be due to an increased secretion of ACTH. This conclusion is supported by a number of facts. First, it should be mentioned that stress fails to elicit the signs mentioned in hypophysectomized animals. Second, the injection of purified ACTH duplicates the symptoms of stress in normal animals (1094); and last, the ACTH content of the anterior pituitary is decreased in animals subjected to harmful stimuli (222). The discussion of the mechanism by which the sympathetico-adrenal discharge is linked with hypophysial-adrenocortical activation will be postponed until the work dealing with lymphopenia and eosinopenia in stress has been dealt with.

LYMPHOPENIA AND EOSINOPENIA AND STRESS

Dougherty and White (292, 293) found in several species, including man, that the injection of ACTH leads to marked lymphopenia, associated with an increase in the number of the neutrophil leukocytes. This reaction is a specific effect of ACTH and is not produced by other proteins such as prolactin and gamma globulin. That ACTH affected the lymphatic tissue not directly but as the result of the mobilization of adrenocortical hormones was inferred from the fact that the effect was absent in adrenalectomized animals. The latter reacted to the injection of ACTH with a slight increase in the number of lymphocytes and polynuclear leukocytes and the total number of white blood corpuscles.

If the white cell count is altered when ACTH stimulates the adrenal cortex, it should be possible to elicit similar effects by an injection of adrenocortical hormones, and the action of these should be independent of the adrenal cortex. Indeed, it was found that the injection of specific cortical steroids such as corticosterone, compound E (cortisone), but not desoxycorticosterone (doca) evoked in the white

count of normal and adrenalectomized animals the same changes as were produced by ACTH in normals.

These findings made it desirable to study the action of various conditions of stress on the lymphocyte count. The conclusion drawn previously from the analysis of the chemical composition and anatomical structure of the adrenal cortex about the increased secretion of adrenocortical hormones in these conditions was confirmed in studies in which the lymphocyte count was taken as an indicator of adrenocortical functions. It was found that stress produced by chemicals (arsenite and benzene), cold, excitement, starvation, fever, and the injection of pitressin and histamine led to lymphopenia in normal but not in hypophysectomized or adrenalectomized animals (315).

Instead of lymphopenia a reduction in the number of circulating eosiniphils may be chosen as an indicator of increased adrenocortical secretion. Thorn (1038) found that ACTH markedly diminishes the eosinophil count in man, provided that the adrenal cortex is functioning (the test for Addison's disease). Experimental studies have shown that histamine, electroshock, and stress induced by surgical operations lead to eosinopenia in normal animals.

The reduction in lymphocytes following the injection of ACTH or adrenocortical hormones or the mobilization of the latter in conditions of stress appears to be due to an increased destruction of the lymphocytes in lymph nodes, as indicated by histological studies in which signs of degeneration in the lymphocytes were found in the above-mentioned conditions (1231). This interpretation is supported by the fact that the lymphocytes in the thoracic duct decline by 50 per cent following the injection of ACTH (1042). The effect of adrenocortical hormones on the lymphatic tissue also appears in gross changes in the weight of the tissue. Various conditions of stress or the injection of ACTH produces a diminution in the weight of the lymph nodes, spleen, and thymus, whereas an increase in the weight of lymphatic tissues occurs in adrenalectomized animals. It is of interest to mention that these reactions are modified quantitatively by other glands of internal secretion. Castrated animals show less change in the lymphatic tissue under conditions of stress.

Before we leave these problems, the general physiological significance of the alterations in the lymphatic tissue should be emphasized. As Dougherty and White point out, the marked and quick reduction in the lymphatic tissue furnishes an important source of nitrogen to the organism in starvation.* The disintegration of lymphocytes in

* Starvation is a condition of stress leading to a hypophysial-adrenocortical secretion.

fever is an important defensive reaction, since antibodies in great quantities are released under these conditions (291, 1232).

AGAIN THE ROLE OF SECRETED ADRENALIN IN THE ACTIVATION OF THE ADRENAL CORTEX

It was mentioned earlier that the injection of adrenalin leads to the occurrence of cortical hormones in the blood and that after repeated injections hypertrophy of the adrenal cortex results (Vogt, 1190). Other indicators likewise give evidence of an increased secretion of adrenocortical hormones after the injection of adrenalin. Thus Long and Fry (861) reported a marked decline in the cholesterol and ascorbic acid content of the adrenal gland after the injection of 20 gamma of adrenalin per 100 Gm. of body weight. Similar doses of adrenalin were found to cause lymphopenia in normal but not in adrenalectomized dogs (891).

Since the doses of adrenalin given are outside the physiological range, they illustrate the pharmacological effectiveness of adrenalin and certain related substances* in calling forth the secretion of adrenocortical hormones, but they do not prove that adrenalin when secreted under physiological conditions acts in a similar manner. The earlier work of Elmadjian and Pincus (315) and Dougherty and White (1232) showing that stress induces lymphopenia in normal but not in adrenalectomized animals fails likewise to clarify the role of the adrenal medulla. However, systematic studies have shown that adrenalin in very small doses (from 0.05 to 1 gamma per 100 Gm. of body weight) leads to a significant decrease in the number of lymphocytes and a relative increase in the number of neutrophils (486). This suggests that the amounts of adrenalin secreted in stress may be adequate to cause a fall in the number of lymphocytes and to produce the other changes indicative of increased adrenocortical secretion.

Hemorrhage, electrically induced convulsions, rage, and the action of histamine were indeed found to produce lymphopenia or eosinopenia in normal but not in adrenodemedullated animals (Table 15). Similar results were obtained by Malméjac and Gross (891), who observed that an adequate fall in the barometric pressure (anoxia) frequently leads to lymphopenia in normal dogs. However, this change in the number of circulating lymphocytes fails to appear after either adrenodemedullation or bilateral splanchnicotomy. This proves that the secretion of adrenalin is the first step in the chain of events leading to the increased secretion of adrenocortical hormones.

Long (860) reports that cold fails to activate the adrenal cortex

* For the similar action of nor-adrenalin see p. 325.

TABLE 15. The Effect of Rage on Lymphocytes in the Rat (Gellhorn and Frank, 487)

	Percentage of Lymphocytes				Probability Coefficient	Percentage of Red Blood Cells at 60 Minutes
	At Onset of Rage	After 20 Minutes	After 40 Minutes	After 60 Minutes		
10 normals	100	76	55	46	0.001	101
10 adrenodemedullated ...	100	91	84	82		98

after transection of the spinal cord at T_3 or T_4 or after adrenodemedullation. In our own work cold has been found to induce eosinopenia followed by eosinophilia in normal animals but only eosinophilia in adrenodemedullated and adrenalectomized rats. Apparently cold acts through the sympathetico-adrenal system on the hypophysis, and eosinophilia in cold is a reaction which is not related to the hypophysial-adrenocortical system. It was also noted that pain due to the subcutaneous injection of a hypertonic salt solution under the scalp fails to lower the number of eosinophils in animals with spinal transection at T_3, although the nociceptive impulses originating in segments above T_3 reached the brain (531). These experiments seem to show that the excitation of sympathetic centers through nociceptive impulses fails to induce an increased secretion of adrenocortical hormones if the activation of the adrenal medulla is prevented by transection of the spinal cord.

It may be concluded from these studies that in various forms of stress the secretion of adrenalin initiates adrenocortical secretion. However, two questions remain to be answered: first, do extramedullary factors lead likewise to adrenocortical secretion; second, how does the secretion of adrenalin activate the hypophysial-cortical mechanism?

With respect to the first question, Vogt (1191) found that the exposure of rats to 2°–4° C. for 16 hours as well as to high temperatures (39° C. for 2–6 hours), provided that fever results, causes a loss of adrenocortical lipids even after denervation of the adrenal glands. Hemorrhage to the extent of 2 per cent of the body weight had a similar effect, and insulin hypoglycemia induced in part of the denervated animals a loss of cortical hormones. Gellhorn and Frank (487) found that hemorrhage of a light degree (1 per cent of the body weight), rage, and electrically induced convulsions

caused lymphopenia in normal but not in adrenodemedullated rats. However, insulin hypoglycemia caused lymphopenia in normal and adrenodemedullated animals, although the effect was greater in the former; no changes occurred in adrenalectomized rats.*

Because the work of Meyer (1128) suggested that the eosinophil count was a finer indicator of adrenocortical secretion than the lymphocyte count, some of these experiments were repeated. It was found that electrically induced convulsions had a significant but lesser effect (eosinopenia) on adrenodemedullated than on normal rats. Histamine, however, induced eosinopenia only in normal, not in adrenodemedullated rats (464). From these data it may be inferred that moderate environmental stresses activate the adrenocortical hormones through a sympathetico-adrenal discharge. More severe stress (2 per cent hemorrhage, insulin hypoglycemia, etc.) causes mobilization of these hormones even in adrenodemedullated animals.

The new experiments of the Yale group (531) are in agreement with these conclusions. The action of cold on eosinophils is abolished by demedullation of the adrenals or by diencephalic lesions. However, more severe stress (laparotomy) calls forth eosinopenia in animals in which the sympathetico-adrenal discharge is impaired or abolished, as it does also in unoperated controls, but this effect is somewhat delayed. It seems to follow from our observations and those similar of Long and his collaborators that in the intact animal the liberation of adrenalin initiates adrenocortical secretion within a shorter latent period and in response to weaker stimuli than are required for the mechanism releasing adrenocortical hormones in the adrenodemedullated animals.†

More recently it has been found (561) that afferent impulses have an effect on the mobilization of adrenocortical hormones in normal

* This agrees with a recent finding of Vogt (1193) that hypoglycemia lowers the ascorbic acid of the adrenal cortex after inactivation of the adrenal medullae. In another study (1194) this author reports a lesser effect of emotional excitement in adrenodemedullated than in normal rats, while the action of β-tetrahydronaphthylamine on adrenocortical secretion is not altered by denervation of the adrenal medulla.

† According to Colfer, de Groot, and Harris (237) restraint and pain elicit lymphopenia in rabbits regardless of the integrity of the innervation of the adrenal medulla. It appears not unlikely that the importance of the sympathetico-adrenal system for the increased secretion of adrenocortical hormones shows considerable variations in different species. This is borne out by the work of Porter (1024), according to which stimulation of the posterior hypothalamus causes eosinopenia in the cat. These experiments lend strong support to our interpretation of the role of central sympathetic discharges in initiating increased adrenocortical secretions.

rats, since trauma (fracture of the tibia) and a mild scald induced a greater reduction in adrenal ascorbic acid when they were applied to the innervated than to the denervated leg. This observation is in harmony with our general idea according to which it is assumed that the activation of the sympathetico-adrenal system represents a particularly effective mechanism by which the hormones of the adrenal cortex can be mobilized. The necessary link between the nociceptive impulses and the secretion of adrenocortical hormones is, of course, the secretion of adrenalin, as established by Cannon and Hoskins (199) for these conditions.

Several investigators report experiments which are pertinent to the question of the site of the action of adrenalin in relation to the hypophysial-adrenocortical mechanism. There are obviously three possibilities: either the adrenalin acts on the periphery, i.e., on the tissues; or it elicits the secretion of ACTH by its direct action on the anterior pituitary; or it elicits this through the intermediation of the nervous hypothalamic centers which are known to regulate the rate of secretion of the hormones of the adenohypophysis.

The reactivity to stress of animals in which the hypophysial stalk had been transected was studied in several investigations. Selye (377) destroyed hypothalamic-hypophysial connections in the rat. In spite of an incidental partial hypophysectomy a significant loss in the adrenocortical ascorbic acid content occurred on exposure to cold. This loss was absent in completely hypophysectomized animals. These results were confirmed in experiments in which after hypophysectomy hypophysial tissue was transplanted into the anterior chamber of the eye. Exposure to cold induced in these animals as big a fall in the ascorbic acid of the adrenal cortex as it did in unoperated controls. There seemed to be a positive correlation between the physiological state of the transplant and the degree of the fall in the ascorbic acid concentration.

Similar experiments were performed by Long *et al.* (916), who likewise used hypophysectomized rats with transplants of pituitary tissue in the anterior chamber of the eye. They used the eosinophil count as an indicator of the release of ACTH and found that painful stimulation as well as the injection of adrenalin evoked marked eosinopenia. After removal of the graft the injection of adrenalin failed to reduce the eosinophil count. Finally Cheng and his collaborators (222) investigated this problem by using stalk-transected rats. They studied the action of histamine on the ascorbic acid of the adrenal cortex and found in the operated animals a reduction similar to that in the controls, whereas hypophysectomized animals did not

show any change. That the operations were successful was ascertained by the occurrence of diabetes insipidus and the degeneration and reduction in the cell count in the supraoptic nuclei.*

These experiments suggest strongly that the release of ACTH under stress is not the direct effect of nervous or humoral impulses originating in the hypothalamus. Consequently it may be thought that adrenalin acts either directly on the anterior hypophysis or indirectly by affecting the balance between the production and utilization of adrenocortical hormones in the tissues. That adrenalin can act on the adenohypophysis directly was shown by Long *et al.* (915), who found that the injection of this drug into the anterior chamber of the eye in which a hypophysis had been transplanted released ACTH from this tissue successfully. The injection, however, of the same quantity of adrenalin into the anterior chamber of the contralateral control eye was ineffective. Adrenalin was highly effective since 0.2 gamma reduced the eosinophil count by 44 per cent. Nevertheless it remains doubtful whether these experiments prove the action of adrenalin on the hypophysis in physiological conditions. Adrenalin was injected in Long's experiments in a concentration of 1:250,000 into the anterior chamber of the eye, and it seems unlikely that such a concentration can ever be reached as the result of adrenomedullary secretion.

An alternative explanation of the mechanism by which adrenalin causes a release of ACTH was presented by Sayers and Sayers (1093). It is based on the general fact that the secretion of the trophic hormones of the anterior pituitary seems to be regulated by the degree of activity of their target organs. Applied specifically to ACTH, it is assumed that its secretion depends on the degree of adrenocortical secretion and the level of these hormones in the tissues. Thus Ingle (724) showed that exercise no longer produces adrenocortical hypertrophy if the rats are injected with cortical hormones during the experimental period. Apparently in normal animals the cortical hormone level is decreased during exercise, an effect that stimulates the adenohypophysis to replenish the deficiency by an additional secretion of ACTH. If the injection of adrenocortical extracts prevents this fall in the peripheral hormone level, no pituitary secretion occurs.

Instead of using the hypertrophy of the adrenal cortex as an indicator of increased ACTH secretion, Sayers and Sayers studied the ascorbic acid depletion of the adrenal cortex in stress and the influence of adrenal extracts and steroids on this phenomenon. It

* See pp. 297ff.

was found that pretreatment with extracts of the adrenal cortex abolished the effect of various forms of stress on the ascorbic acid concentration of the adrenal gland. If the injection of adrenocortical extracts was combined with that of ACTH, the ascorbic acid concentration of the adrenal cortex was lowered to the same degree as in the absence of adrenal cortex extract (Table 16). This observation indicates that the cortical extracts which prevent the ascorbic acid changes under stress do not act on the adrenal cortex but on the adenohypophysis and inhibit the secretion of ACTH. Quantitative experiments show that increased amounts of cortical extracts diminish *pari passu* the ascorbic acid depletion (Table 17). Since the latter, as was shown earlier, is directly related to the amount of ACTH secreted, it may be said that the adrenocortical hormone level in the blood and tissues is indirectly related to the secretion of ACTH. This relation was confirmed by Gellhorn and Frank (487), who showed that the effect of adrenalin on the lymphocytes in normal rats could be prevented by pretreatment with cortical extracts.

More recently Sayers and Cheng (1092) furnished direct evidence for the action on the adenohypophysis of the adrenocortical hormone level in the tissues. They assayed the ACTH content of the anterior pituitary in normal rats under conditions of stress (trauma) and after adrenalectomy by injecting this organ into hypophysectomized rats and determining the reduction of the ascorbic acid content of the adrenals. After stress the ACTH content of the pituitary gland

TABLE 16. The Inhibition of Pituitary Adrenocorticotrophic Activity by the Adrenal Cortex Hormone, Following the Subjection of Rats to a Variety of Stresses (after Sayers and Sayers, 1093)

	Ascorbic Acid Concentration of Adrenal Gland, mg/100 Gm of Fresh Tissue		In Pretreated Rats, Amount of Adrenal Cortex Extract Injected Subcutaneously, ml/100 Gm of Body Weight
	Not Pretreated	Pretreated	
Controls	419	423	1.1
Subjected to stress			
Cold	314	415	1.4
Heat	277	405	1.0
Histamine	265	422	0.1 mg.
Epinephrine	308	419	0.1 mg.
Typhoid organisms	305	441	0.5
Injected with adrenocorticotrophic hormone	314	310	1.5

TABLE 17. Quantitative Aspects of the Inhibition of Pituitary Adrenocorticotrophic Activity (after Sayers and Sayers, 1093)

	Amount of Adrenal Cortex Extract Injected Subcutaneously in Pretreatment, ml/100 Gm of Body Weight	Ascorbic Acid Concentration of Adrenal Gland, mg/100 Gm of Fresh Tissue
Unexposed controls	None	419
Rats exposed for 1 hour to temperature of		
7° ± 1° C.	None	365
4° ± 1° C.	None	273
4° ± 1° C.	0.01	287
4° ± 1° C.	0.1	354
4° ± 1° C.	0.2	406
4° ± 1° C.	0.3	404

was reduced by 35 per cent, but after adrenalectomy by 80 per cent. Apparently a maximal discharge of ACTH takes place when the adrenocortical hormones are no longer present in the tissues. In Addison's disease ACTH could be assayed in the blood but not in normals or under conditions leading to adrenal hypertrophy (Taylor, 1148). It is interesting that the normal anterior pituitary of the rat has a store of ACTH sufficient to reduce the ascorbic acid in the adrenal gland by 50 per cent in 100 animals.

We come, therefore, to the conclusion that various forms of stress lead to a sympathetico-adrenal discharge which increases the consumption of adrenocortical hormones in the blood and tissues. The lowered concentration of these hormones acts as a stimulus to the adenohypophysis which causes it to increase its secretion of ACTH. Through this substance the adrenal cortex is stimulated and the level of the adrenocortical hormones is restored in the blood and tissues. There is evidence that in severe forms of stress the hypophysial-adrenocortical mechanism may be activated even after the elimination of the adrenal medulla (487, 560, 1193, 1194). In addition Gordon (561) has shown that the greater sensitivity of innervated than of denervated tissues to trauma, as indicated by the subsequent mobilization of adrenocortical hormones, is present even in adrenodemedullated animals. Although adrenalin can no longer be held responsible for the initiation of the hypophysial-adrenocortical secretion under these conditions, the experiments do not require a fundamentally different explanation. The activation of the adrenal medulla as the result of nociceptive stimulation represents only a part of the reflex excitation of the sympathetic nervous system, and nor-adrenalin is liberated from many adrenergic nerves and blood

vessels* even in adrenodemedullated animals. In contradistinction to the lesser sensitivity of man (714, 998) to nor-adrenalin than to adrenalin, it was found that the rat responded to minimal doses of nor-adrenalin with eosinopenia (464). It seems therefore justified to assume that certainly in the normal organism and probably after adrenodemedullation, adrenalin and/or nor-adrenalin initiate the activation of the hypophysis leading to adrenocortical secretion. However, the observation that severe trauma applied to denervated tissue may result in a maximal decrease of the ascorbic acid in the adrenal cortex even in adrenodemedullated animals shows clearly that these nervous factors are dispensable. Apparently the various conditions of "stress" may, as the result of tissue destruction, increase metabolism (as on exposure to cold), and possibly other factors cause a lowering in the concentration of the adrenocortical hormones in the blood and tissues and thereby bring about a release of ACTH from the anterior hypophysis.

In spite of the complexity of these processes it is very probable that in addition a direct action of the hypothalamus on the anterior hypophysis and consequently on the release of ACTH plays an important role. The preservation of the secretion of ACTH in stress after stalk transection and particularly after hypophysectomy and implantation of the pituitary into the eye seemed to eliminate the possibility that hypothalamic-hypophysial impulses are involved. On the other hand, Harris (268) showed that stimulation of the tuber cinereum or of the mammillary bodies elicits lymphopenia and that lesions in these structures abolish lymphopenia in response to stress. Moreover the reduction in the number of lymphocytes in stress seemed to be independent of the adrenal medullae, nor could it be produced by the injection of adrenalin.

What is the cause of this discrepancy? One might think of differences between species,† since the former investigations were performed on the rat and Harris's work was on the rabbit. The great sensitivity of the hypothalamic-hypophysial system of the rabbit to afferent stimuli is obvious from the work on gonadotrophic hormones. On the other hand, it may be worthy of emphasis that, depending on the degree of excitation, different mechanisms may lead to the release of ACTH. The experiments showing that removal of the hypophysis and its implantation elsewhere do not abolish the release of ACTH to stress or injected adrenalin prove only that in the

* See p. 320.

† See Gellhorn's discussion (461) at the adrenal conference of the Macy Foundation.

rat the hypothalamus does not play an indispensable part in this reaction. However, this work does not exclude the possibility that in the normal organism reflex activation of the hypothalamus may take place. As a matter of fact, the just published work of Porter (1024) according to which stress-induced eosinopenia is abolished by lesions in the posterior hypothalamus proves, at least for the cat, that the excitation of sympathetic diencephalic structures is a prerequisite for initiating the hypophysial adrenocortical secretions. In addition hypothalamic-hypophysial discharges involving the neurohumoral mechanism which has been found to be operative in the liberation of the gonadotrophic hormones may be of secondary importance.

It is concluded from this work that the release of ACTH which activates the adrenal cortex is based on: (1) the secretion of adrenalin, causing a lowering of the adrenocortical hormone level in the blood and tissues and thereby a release of ACTH from the anterior pituitary; (2) hypothalamic-hypophysial discharges causing the secretion of ACTH.

Both mechanisms involve the hypothalamus, whose rate of discharge is increased in conditions of stress either by direct or reflex excitation or by release from cortical control (as in anoxia). The first mechanism seems to be more sensitive than the second, since mild stimuli (pain, excitement) do not cause adrenocortical secretion in adrenodemedullated animals. On the other hand, it would be erroneous to conclude from the marked reduction of ascorbic acid in adrenodemedullated rats in severe stress that the sympathetico-adrenal mechanism is not involved in the mobilization of adrenocortical hormones. As Barcroft (64) points out, processes of vital importance to the organism are frequently regulated by more than one mechanism. Carbon dioxide continues to stimulate respiration after the removal of the sino-aortic chemoreceptors, and sympathectomy does not grossly interfere with the maintenance of circulation and temperature; but it would be illogical and also contrary to the facts to conclude that the sino-aortic receptors and the sympathetic nervous system have no effect on these functions.

THE SIGNIFICANCE FOR NEUROPSYCHIATRY AND MEDICINE OF THE RELATION BETWEEN THE SYMPATHETICO-ADRENAL SYSTEM AND THE ADRENAL CORTEX

Studies showing that conditions associated with a sympathetico-adrenal discharge involve important parts of the endocrine system are not only of theoretical interest but also of practical importance. One thinks primarily of psychotics who are subjected to shock treat-

ment; under these conditions one would assume that not only the sympathetico-adrenal system but also the activation of the adrenal cortex is involved. As a matter of fact, extensive studies have been made on schizophrenes, psychoneurotics, and patients with involutional depression by Hoagland, Pincus, and their collaborators (668, 670, 673, 1013–1015) on these questions.

It was found that schizophrenes do not show any significant deviation in adrenocortical activity, as indicated by the excretion of 17-ketosteroids (562) and uric acid during rest, but that the response of the adrenal cortex to conditions of stress is greatly diminished. Exposure to a hot environment of high humidity elicited in normals a decrease in the number of lymphocytes but in schizophrenes an increase. Psychic stress (tests on a pursuit meter involving psychomotor coordination and similar procedures) resulted in a diminished response of the adrenocortical system. The increase in adrenocortical activity after awakening, as indicated by the urinary excretion of steroids, amounts to about 50 per cent in normal persons but only 3 per cent in psychotics. Finally, these authors observed that the responsiveness to ACTH, particularly as indicated by the excretion of 17-ketosteroids and sodium, was greatly reduced in 72 per cent of their patients hospitalized for an average of two years and was diminished in 50 per cent of schizophrenes hospitalized for a shorter period. These alterations are apparently not due to nutritional defects, since a diet rich in vitamins and proteins did not influence the responsiveness of these patients to ACTH.

Hoagland *et al.* (668) also reported that those patients who improve under either insulin or electroshock treatment responded to ACTH-injection before the treatment whereas refractoriness to this hormone indicated a poor prognosis. In view of these findings it is of interest to point out that in man electroshock and insulin coma likewise stimulate adrenocortical function, as indicated by an increased excretion of 17-ketosteroids (Hoagland, Malamud and Kaufman, 673), lymphopenia (Parsons *et al.*, 991; Mikkelsen and Hutchens, 929) and eosinopenia (Tsai, 1171; Altschule, 28; and their collaborators).

There is a discrepancy in the literature concerning the site at which a disturbance of adrenocortical secretion exists in psychotic patients. The tests with ACTH suggested to Hoagland, Pincus, and their collaborators that the reactivity of the adrenal cortex to hypophysial stimulation is deficient. On the other hand, Parsons *et al.* deny a deficiency of the hypophysial-adrenocortical system, since in their patients the injection of adrenalin induced lymphopenia as in normal persons. In addition the course of lymphopenia induced by adrenalin

was similar to that seen after electroshock and insulin coma. On the other hand, these authors noted likewise a deficient reactivity of the schizophrenes to "psychological stress," since excited patients failed to show lymphopenia and the preparation for electroshock treatment showed no influence on the lymphocytes.

From the previous discussion it follows that the various forms of stress involve a sympathetico-adrenal discharge which leads to an increased secretion of ACTH with consequent augmented adrenocortical secretion. The clinical data seem to show that at least some forms of stress are relatively or absolutely ineffective in psychotics whereas others, at least in the observations of Parsons and Mikkelsen, cause changes like those seen in normal persons. It seems logical to conclude from these data that the difference in reactivity between normals and psychotics is not primarily based on changes in the endocrine system but rather in the reactivity of the sympathetico-adrenal *centers* which initiate the reactions in the adrenal medulla, adenohypophysis, and adrenal cortex. There seems to be little doubt that the sympathetico-adrenal system may be activated from different levels of the central nervous system. Diminished reactivity of the sympathetic divisions of the autonomic centers probably at the cortical and hypothalamic level frequently occurs in schizophrenes.* On the other hand, sympathetic reflexes involving the medulla oblongata and spinal cord are apparently not changed in these patients. This would make it understandable that electroshock, which undoubtedly acts also on medullary autonomic centers, should activate the sympathetico-adrenal system (and consequently adrenocortical secretion) while "psychological stress" should fail to do so.

There are physiological analogues for this interpretation. Histamine causes a sympathetico-adrenal discharge leading to activation of the adrenal cortex, which is not interfered with by pentothal anesthesia (Cheng *et al.*, 222). Cold, however, fails to induce increased adrenocortical secretion in anesthesia.† Histamine seems to elicit the secretion of adrenalin via carotid sinus reflexes which act on the medulla oblongata, whereas cold is known to act on the hypothalamus (Ranson, 1033).

Although in the writer's opinion the chief physiological difference between normals and psychotics lies in the reactivity of higher sympathetic centers, the lesser responsiveness of the adrenal cortex of psychotics to ACTH should not be neglected. These two facts are possibly interrelated. It was shown that adrenocortical activation is

* See Chapters 18 and 20.

† Unpublished observations.

initiated by a sympathetico-adrenal discharge. In normal man living under the conditions prevalent in civilized society this mechanism is not often activated by gross alterations in the internal environment, such as a fall in the blood sugar or a change in the oxygen content, but as the result of psychic stress. Failure in the reactivity of the cortex and hypothalamus to such stimuli may gradually lead to a lessened responsiveness of the adrenal cortex. This would explain why schizophrenes respond less to ACTH the longer the disease lasts, and it would account for the fact that the prognosis is better in those patients who react to ACTH. According to this interpretation the test with ACTH is valuable because it reflects the duration and severity of the central autonomic deficiency, but it appears doubtful whether, as Pincus, Hoagland, and their collaborators assume, the psychosis is related to a defect in the reactivity of the adrenal cortex. That ACTH is without therapeutic value in schizophrenia is in line with this argument.

Thorn and his collaborators (1038) have made an important application to clinical medicine of their adrenalin test. In physiological experiments they found that various conditions of stress led to eosinopenia in the normal animal but were ineffective after either adrenalectomy or hypophysectomy. Clinical stress or the injection of relatively large quantities of adrenalin resulted in marked eosinopenia in man provided that the hypophysial-adrenocortical system was intact. But in hypopituitarism and in Addison's disease the test was negative. Similarly it was found that ACTH, which for its action needs a functioning adrenal cortex, fails to produce eosinopenia in patients with Addison's disease.

Can Thyroid Secretion Be Modified by Neurogenic Discharges?

Numerous attempts have been made to demonstrate the action of autonomic nerves on the secretion of thyroxin and thyroglobulin, but the results have largely been negative. Stimulation of the cervical sympathetic trunk furnished no evidence for the presence of secretory nerves of the thyroid gland, since the thyroid hormones in the blood were not increased (1060). The attempt of Cannon *et al.* (196, 391) to enhance the sympathetic discharges to the thyroid gland, by anastomosing the phrenic nerve with the peripheral fibers innervating the thyroid gland, produced signs of heightened thyroid activity only in a small percentage of cases and negative results in the hands of other investigators (187, 895). Experiments with prolonged stimulation of the cervical sympathetic also have led to conflicting results (590). The fact that the whole sympathetic chain can be removed without

significantly altering the metabolic rate (827) suggests that the sympathetic fibers supplying the thyroid do not modify the secretion of the thyroid hormones under physiological conditions. Apparently the sympathetic nerves do not carry secretory fibers to the thyroid gland. Moreover the experiments seem to indicate that the secretion of the thyroid hormones is largely independent of wide variations of the autonomically controlled blood supply. However, it should not be inferred that the nervous system is without influence on the thyroid gland. Clinical experience shows that the opposite is true, but the influence of the central nervous system is brought to bear on the thyroid in an indirect manner through the thyrotrophic hormone.

Before this topic is discussed in the next section, the influences exerted by the peripheral nerves on several glands of internal secretion may be compared. As was mentioned earlier, denervation of the adrenal medullae abolishes the secretion of adrenalin under physiological conditions, whereas elimination of the peripheral nerves supplying the thyroid, the gonads, and the pituitary is without noticeable effect on the internal secretion of these glands. The pancreas is in an intermediate position: the vagus influences the rate of insulin secretion, but the chief regulator, the level of the blood sugar, remains effective after vagotomy. No peripheral nerves supply the adrenal cortex, and the discharges of adrenalin induced by excitation of the splanchnic nerves and the secretions of the adrenal cortex are indirectly related.

The Neural Control of the Secretion of the Thyrotrophic Hormone

That the secretion of thyrotrophin from the anterior pituitary is essential for the structural and functional integrity of the thyroid gland needs no further elaboration. Its rate of secretion increases as the level of thyroxin falls in the blood. In this respect its behavior is similar to that of other trophic hormones of the anterior pituitary. As to the dependence of the secretion of the thyrotrophic hormone on the hypothalamus, only a few investigations are available (1178). Several authors failed to observe any change in the structure of the thyroid gland after severance of the pituitary stalk. Mahoney and Sheehan (890) found the basal metabolism after this operation to be normal, which seems to indicate that the chief function of the gland is not altered. However, recent work (Brolin, 139) with improved operative technique suggests that complete transection of the stalk is accompanied by reduced thyroid activity. The acinar epithelium is lower than in unoperated controls, and the nuclei are oval instead of

round. Exposure to cold, which in normal animals increases not only the secretion of the adrenotrophic but that of the thyrotrophic hormone as well, fails to increase the activity of the thyroid after transection of the hypophysial stalk. These observations imply that the normal level of thyroid activity and the augmented function of this gland on exposure to cold depend on impulses originating in the hypothalamus. Since histological changes in the thyroid gland are by no means as severe in stalk-transected animals as they are after hypophysectomy, it may be inferred that a partial thyrotrophic secretion persists after stalk transection.

Further evidence of the significance of hypothalamic-hypophysial relations for thyrotrophic activity comes from new experiments by Brolin (140), who studied the influence of thyroidectomy on the histological structure of the anterior pituitary in normal and stalk-transected rats. It has been shown that the basophilic cells in this gland represent a good indicator of the degree of thyrotrophic hormone secretion. Vacuolization and hypertrophy of these cells occur when thyrotrophic secretion is increased experimentally – for example, by exposure of the animals to cold or by thyroidectomy. In both conditions no such reaction occurs if adequate amounts of thyroxin are injected. Apparently thyroidectomy leads to a depletion and exposure to cold to an increased consumption of the thyroid hormones in the blood and tissues, so that both induce a release of thyrotrophic hormone from the anterior pituitary. If thyroidectomy is performed on animals with a complete transection of the stalk, the basophil cells in the anterior hypophysis fail to show signs of increased activity. In view of the fact that a reduction of the thyroid hormone level in the blood and tissues to zero through thyroidectomy represents a very strong stimulus to the cells which regulate thyrotrophic secretion, the absence of changes in the basophil cells is strong evidence in favor of a hypothalamically controlled thyrotrophic secretion.

Studies on rats with hypothalamic lesions between the optic chiasma and the infundibulum have confirmed these results. Greer (576) produced a maximal stimulus for the secretion of the thyrotrophic hormone by the injection of thiouracil. In unoperated control animals the thyroid glands showed hyperplasia, whereas they were atrophic in animals with hypothalamic lesions, and these fundamental changes were likewise reflected in the weights of the thyroid glands. However, thyrotrophin secretion is not abolished through these lesions, since the iodide-concentrating ability of the thyroid gland is preserved. Whether these results indicate that hypothalamic lesions only reduce thyrotrophic secretion or that two thyrotrophic hormones are elabo-

rated with different degrees of dependence on the hypothalamus is not yet known.

Conclusions

The secretion of trophic hormones from the adenohypophysis depends less on the hypothalamus than does the internal secretion released from the posterior pituitary gland. However, experiments performed with increasingly refined techniques have furnished growing evidence that the hypothalamus influences the rate of secretion of the gonadotrophic, thyrotrophic, and, to a lesser degree, adrenotrophic hormones. Differences between species and the intensity of stimulation and stress play an important part, since obviously several mechanisms are employed for the same final goal, the increased secretion of hormones in target organs. The persistence of secretions from the anterior pituitary even after its dissociation from the central nervous system is obvious from the comparison of structure and function of endocrine glands in hypophysectomized animals with and without implantation of the hypophysis. However, the final evaluation of the role of the nervous system (the hypothalamus and sympathetico-adrenal system) for the trophic hormones will have to wait for the development of methods for a quantitative determination of hormones in the blood.

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The Physiological Basis of Emotion

If a physiologist discusses the problem of emotion today, he will quite naturally take as his point of departure the ideas which Walter B. Cannon (190–192) developed a number of years ago. In attempting to refute the James-Lange theory, Cannon reached the conclusion that in emotion it is the thalamus which is excited through afferent stimuli. These impulses appear to be relayed to other parts of the diencephalon and result in a "downward discharge" activating viscera and skeletal muscle. In addition they elicit an "upward discharge" constituting the equivalent of the "feeling tone" of the emotion. Cannon further assumed that an "upward discharge" to the cortex of the brain diminishes the inhibitory action of this structure on the thalamus or hypothalamus. In the following discussion an attempt will be made to evaluate, within the framework of Cannon's thalamic theory, some of the pertinent investigations which have been performed in the intervening years (459).

The Sympathetic Discharge in Emotion

Cannon's finding that the "downward discharge" involves the sympathetico-adrenal system is common knowledge today. Consequently a brief summary of his work will suffice. He showed that in cats the sympathetico-adrenal system as a whole is involved in emotional excitement. In addition to hyperglycemia, piloerection and sweating are observed; these symptoms clearly indicate a sympathetic discharge. The number of red blood corpuscles increases as the result of sympathetic excitation of the splenic nerves (Izquierdo and Cannon, 729). Gastrointestinal activity as revealed by X-ray studies is inhibited. A rise in the blood pressure and a faster pulse rate are further symptoms of sympathetic excitation in emotion. Cannon's discovery (206) that

chronically denervated structures, such as the nictitating membrane and the dilator of the pupil, become highly sensitive indicators of the action of adrenalin has added a powerful tool for studies in this field. Thus contraction of the denervated nictitating membrane and dilatation of the denervated pupil reveal a discharge of adrenalin in states of emotional excitation. The pulse rate of the denervated heart increases through the same mechanism. Even in animals without adrenal glands or so operated that the nervous control of adrenalin secretion is eliminated, neurohumors of the sympathetic system appear in the blood. Bodo and Benaglia (109) showed that sympathin released in emotional excitement from the endings of sympathetic nerves accounts for the contraction of the denervated nictitating membrane in such animals.

The Parasympathetic Discharge in Emotion

It was mentioned earlier that conditions such as anoxia or cold which, according to Cannon and others, initiate a sympathetico-adrenal discharge also lead to parasympathetic activity involving the vago-insulin system. Similarly the visceral discharge during emotion is not restricted to the sympathetico-adrenal system but concerns the vago-insulin system as well. This was shown in two groups of experiments (476). In the first, normal, adrenodemedullated, and adrenodemedullated-vagotomized rats were exposed to noise, the effect of which on the blood sugar was determined (Fig. 79). Under these conditions the blood sugar of normal rats increased, but that of adrenodemedullated animals decreased. The latter result suggested an activation of the internal secretion of the pancreas via the vagus. Consequently adrenodemedullated rats in which the vagi had been sectioned below the diaphragm were tested and were found to show no changes in the blood sugar under conditions of emotional excitement. If the rats were tied to an animal board, the emotional excitement resulting from struggle provided likewise evidence for a sympathetico-adrenal and vago-insulin discharge.

In the second group of experiments, cats were used in which the effect of the sympathetico-adrenal discharge on the blood sugar was prevented by transection of the spinal cord at the cervical level. Under conditions of emotional excitement such animals showed a fall in the blood sugar, which could be eliminated by vagotomy. Thus these experiments too indicate that emotional excitement induces vago-insulin and sympathetico-adrenal discharges. Since in normal animals the blood sugar rises under these conditions, it may be said that the sympathetico-adrenal system predominates over the vago-insulin

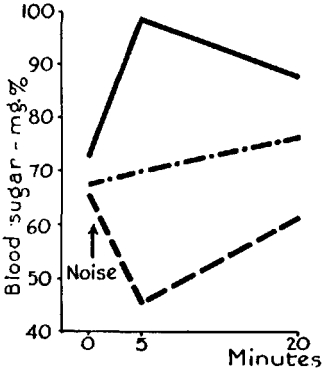

FIGURE 79. The influence of noise on the blood sugar of normal rats (solid line), adrenalectomized rats (broken line), and adrenalectomized-vagotomized rats (dotted broken line). The experiment indicates that emotional excitement causes a discharge over the sympathetico-adrenal and vago-insulin system, with the former predominating. (Gellhorn, Cortell, and Feldman, 476.)

discharge if changes in the blood sugar are taken as an indicator of the central autonomic balance.

Cannon has repeatedly emphasized the great physiological significance of the increased blood sugar level for conditions of fighting associated with emotional excitement. If we consider the blood sugar level alone, the activation of both vago-insulin and sympathetico-adrenal systems might appear as a disadvantageous reaction in view of the fact that the insulin secretion must have a tendency to counteract the rise in the blood sugar. It must be remembered, however, that the utilization of glucose depends not only on the blood sugar level but also on the amount of insulin present (Soskin, 1127). Consequently a hyperglycemic reaction combined with an increased insulin secretion creates optimal conditions for the utilization of glucose. The vago-insulin and the sympathetico-adrenal systems act as synergists as far as the utilization of glucose is concerned. This synergistic action under conditions of emotional excitement is based on the greater reactivity of the sympathetico-adrenal system; the result is a hyperglycemia maintained in the presence of an increased secretion of insulin.

It should be added that other signs of parasympathetic excitation are likewise present in emotion. If sympathetic effects originating in the brain are blocked through high transection of the spinal cord, excitement induced by a slight noise causes a marked fall in the pulse rate (1107). Contraction of the bladder, defecation, and erection of the penis are further symptoms of parasympathetic discharge noted in animals during emotional excitement (716). In the rabbit this condition leads to hypothermia through hyperventilation and vasodilatation and at the same time inhibits shivering (568). This interesting observation suggests that in some emotional states parasympathetic

excitation is associated with inhibition of the sympathetic and somatic reactions which maintain the temperature of the body.

Pleasurable emotions induced by gustatory and olfactory stimuli cause parasympathetic excitation. This mechanism underlies the psychic secretion of gastric juice, since it is abolished by vagotomy. The motor activity is likewise increased in the gastrointestinal tract under these conditions. Sexual excitement is known to induce vasodilatation in the sex organs, but it is of interest that the parasympathetic excitation may also appear in the form of increased gastric secretion (301).

Autonomic Discharges in Human Emotion

Many observations of Cannon on the sympathetic effects of emotion have been confirmed in man. Here again a brief résumé of relevant findings must suffice. Todd (1160) reported that anxiety and tenseness cause a loss in tone and a decrease in the amplitude of the contractions as well as a prolongation of the emptying time of the stomach. In patients with fistulae an inhibition of peristalsis was noted in many parts of the gastrointestinal tract. Augmentation of the blood pressure, pulse rate, and palmar sweating (galvanic reflex) (252), and dryness in the mouth due to viscous, "sympathetic" salivary secretion are familiar indicators of sympathetic discharges in human emotion. Hyperthermia of neurogenic (diencephalic?) origin has also been reported in situations of stress.

Parasympathetic symptoms are likewise well established in human emotion. Increased frequency of urination with or without emptying of the rectum occurs in slight and severe emotional disturbances (29, 301, 732). Weeping, which may be abolished by sectioning of the facial nerve, is another symptom of parasympathetic excitation (881). A startle produces a fall in the pulse rate, probably of vagal origin (1163). As in chimpanzees, excitement induced by a sudden noise causes in infants parasympathetic effects such as erection of the penis and defecation (716).

That pleasurable emotion aroused by eating or the sight or smell of food and conditions related to it induces parasympathetic effects has frequently been observed. These effects appear not only in the form of increased secretion of the intestinal juices but also as augmented motor activity of the gastrointestinal tract. Brunswick (167) noted that the type of emotional disturbance is related to the form of autonomic discharge, as revealed by the motor functions of the gastrointestinal tract. Pleasant as well as unpleasant emotions may induce parasympathetic discharges: the smell or the expectancy of food may lead to an increased secretion of saliva and gastric juice,

and an unpleasant odor may produce excessive salivary secretion before vomiting.

Vago-insulin discharges in emotional stress have been observed in man (1026, 1043) – a fact confirming the previously described animal experiments. The glucose tolerance curve and the blood sugar are low in such patients, but vagotomy, atropine, or psychotherapy restores them to normality. The emotional disturbance is apparently associated with an imbalance in the reactivity of the autonomic centers.

This brief survey shows that both branches of the autonomic nervous system are activated in emotion. That the type of emotional disturbance determines at least to a certain degree whether the discharge is predominantly parasympathetic or sympathetic may be inferred from the observation that different forms of emotion are accompanied by pallor or increased vascularity of the face and by corresponding sympathetic and parasympathetic effects appearing in the arm, as disclosed by plethysmographic experiments (Weber, 1213). However, the problem of the relation between emotion and autonomic discharge is complicated by the fact that different persons may react differently in situations presumably eliciting the same kind of emotional disturbance. Thus Richter's observation (1051) that during the air raids in London some persons turned white while others flushed in the face suggests a sympathetic dominance in the first and a parasympathetic dominance in the second group.

The relation between the kind of autonomic discharge and the form of emotional disturbance as well as type of personality is an important question the answer to which has been greatly advanced in recent years by the extensive work of Wolff and his collaborators (1238, 1240–1243). Their studies on patients with gastric fistulae allowing the direct observation of vascular, motor, and secretory changes are particularly significant and impressive. The results of this work may be summarized by stating that motor activity, vascularity, and the secretion of hydrochloric acid were increased not only under conditions of "pleasurable thoughts of eating" but also in situations calling forth "aggressive feelings including resentment, hostility, and anxiety." At the same time a flushing of the face and an increased secretion and hyperemia of the mucous membrane of the nose could be observed (698).

In contradistinction to these signs of parasympathetic excitation, conditions of fear exerted the opposite effects on the gastric mucosa and the motility of the stomach in the same person. These studies suggest that fear causes reactions predominantly sympathetic, and

feelings of hostility and anxiety predominantly parasympathetic discharges. In line with this interpretation is the interesting observation of Wolf and Wolff that anxiety fails to produce the described effects on the stomach after vagotomy (1238).

Further studies of these authors showed that resentment and anxiety produced parasympathetic symptoms in other organs as well. Under the influence of these emotions hyperemia of the vagina and increased vaginal discharge occurred, and increased vascularity appeared in the bladder and colon under direct inspection. Under these circumstances the increased parasympathetic tone accounts for the diminished capacity of the bladder. Assuming that such functional changes persist long enough, they may lead to edema of the mucous membranes and hemorrhages (observed in the stomach, bowel, and nasal mucosa).

Specific differences between the effects of emotion on the autonomic nervous system can also be demonstrated through circulatory studies. A situation evoking an aggressive attitude on the part of the patient may produce a sympathetic response characterized by an increase in the heart rate, cardiac output, and peripheral resistance and is consequently followed by an elevation of the diastolic and systolic blood pressure. At the same time the renal blood flow is markedly reduced, an effect abolished by sympathectomy. On the other hand, the same person may show a depressor response if the emotional picture is dominated by feelings of dejection and defeat. Under these conditions the cold pressor test (immersion of the hand in cold water) results in a fall in the blood pressure, whereas a pressor reaction occurs in the normal person.*

Apparently certain forms of emotion affect primarily the sympathetic and others chiefly the parasympathetic division of the autonomic nervous system,† although individual variations are common.

* Hickam *et al.* (647) found that "anxiety" produced different cardiovascular effects in different persons. In the majority the cardiac output, oxygen consumption, and heart rate were increased while the peripheral resistance was diminished. In others the resistance was decreased, but the heart rate was diminished (vagal impulses) and the blood pressure lowered. In a small group the blood pressure and peripheral resistance were increased. It seems that the first group showed predominantly a sympathetico-adrenalin discharge, the second group signs of a parasympathetic activation, and the third symptoms suggesting the liberation of nor-adrenalin. It would be important to determine whether in different persons different forms of adrenalin are secreted in the same type of emotional excitement or whether adrenalin and nor-adrenalin respectively can be correlated with different forms of emotion (see also Schneider *et al.*, 1098).

† Diethhelm's claim (288) that depending on the type of emotion produced, "acetylcholine-like" or "epinephrine-like" substances appear in the blood needs confirmation.

A given situation may provoke in one person a considerable increase in the pulse rate and no increase in the blood pressure and in another person a marked effect on the blood pressure and practically no change in the pulse rate (1242). Wolff points out that certain persons react preferentially in a certain area of the autonomic nervous system, and he speaks therefore of "stomach reactors," "nose reactors," "pulse reactors," etc. Well-defined emotional conditions seem to induce specific autonomic "downward" discharges which, within certain limits, appear to be modified by inherent individual characteristics based on changes in the autonomic balance or on a preferential susceptibility of a certain branch of the parasympathetic or sympathetic autonomic nervous system.

The Hypothalamus and Autonomic Discharges in Emotion

The characteristic autonomic discharges which regularly accompany human emotion and which in animals appear to the observer as significant indicators of disturbances in the emotional sphere suggest the involvement of some central structure. This structure is thought to be responsible for the integration of those autonomic and somatic changes which since Darwin's classical description have been considered the expression of emotion in man and animals.

That the cortex is not required for the expression of emotion has been known since Goltz's description (557) of the decorticate dog, which has been confirmed on this and other species by numerous investigators.* It has been demonstrated not only that decorticate animals are capable of expressing emotion but also that rather insignificant stimuli frequently arouse reactions of rage. On the other hand, decerebrate animals show pseudoaffective reactions only to a rudimentary degree (67, 1107). Consequently some part of the diencephalon or midbrain seems to be responsible for the integration of these responses. This conclusion appears justified by Bard's discovery (67) that the emotional hyperreactivity so prominently displayed in decorticate animals on the slightest sensory stimulation is lost after the elimination of the posterior one-fifth of the diencephalon. Cats in which the brain anterior to the midbrain or pons has been destroyed still show somatic and autonomic components of the sham rage response, but the integration is lacking and the threshold to sensory stimulation is greatly raised.

The logical procedure for a further investigation of the physiological basis of emotion was to stimulate or to destroy various parts of the diencephalon and particularly of the hypothalamus, the close relation

* See Gellhorn, *Autonomic Regulations* (446).

of which to the emotional process was evident from experimental work on animals (Bard) and from clinical observations.

After the classic work of Karplus and Kreidl (755, 756) the hypothalamus was subjected to an extensive experimental analysis. Ranson and his school demonstrated various effects of stimulating the hypothalamus. Most important was the observation that electrical stimulation of it elicited in unanesthetized or anesthetized animals a typical motor pattern and autonomic discharges closely resembling the rage complex in the normal animal (1031). The reactions apparently were specific for the hypothalamus, since they could not be elicited from neighboring structures such as the thalamus or the internal capsule. In order to convey an adequate picture of the behavior of these cats and to show how close is the resemblance to the behavior of a normal cat under conditions of rage, Ranson's description may be quoted:

"In cats under ether anesthesia a bipolar needle electrode was inserted into the brain so that the bare tips of the constituent wires were in the hypothalamus and the electrode was then immovably fixed to the skull. After the animal had recovered from the anesthesia and was resting quietly, a faradic stimulus near threshold strength was applied through the buried electrode. At the onset of stimulation the animal became alert, raising its head and opening its eyes, disclosing dilated pupils. The respiration increased in rate and depth and the animal soon began to struggle, clawing, biting and trying to free itself from the hammock in which it was restrained. If the stimulus was continued the hair on the back and tail began to bristle, sweat appeared on the pads of the feet, and saliva ran from the mouth. When such an animal was given a barium meal and examined under a fluoroscope, it was seen that stimulation of the hypothalamus caused an immediate cessation of the gastrointestinal peristalsis due to inhibition of the gut through the sympathetic system. In all these respects the cats behaved as they would had they been threatened by a barking dog." These observations obviously indicate that those somatic and autonomic responses which are the overt signs of emotional display are integrated in the hypothalamus.

Hess (637), performing similar experiments on cats with aseptically inserted electrodes, confirmed the autonomic-somatic integration in this emotional display and added some important features. Cannon and his students designated the emotional reactions seen in decorticate animals as "sham" rage, and Masserman (906) gave further evidence for a fundamental difference between natural emotion and the pseudoemotion elicited by hypothalamic stimulation. He noted that a feeding cat whose hypothalamus was stimulated showed

the typical signs of sympathetic excitation (pupillary dilatation, piloerection, etc.) but continued to eat. From this observation and also from his inability to use the hypothalamic stimulus as a conditioned stimulus for the establishment of conditioned reflexes, Masserman concluded that the hypothalamus represented a motor center only and that its excitation seemed to lead solely to a pseudoemotional behavior but not to emotion.

We have shown that this concept of the hypothalamus as an exclusively motor center is no longer valid, since hypothalamic stimulation leads to definite cortical changes. If it is not valid, hypothalamic stimulation under proper conditions should elicit both a "downward" and an "upward discharge" and consequently lead to a state in which the experimental animal would not only *show* emotion but *experience* it. Obviously only indirect criteria are available for such an interpretation. Hess (637) mentions that if a stimulation leading to the typical autonomic-somatic discharge which he characterizes as a defensive reaction is continued or intensified, the cat may actually attack a person standing nearby. This attitude of directed attack may change into one of flight. Although in general the signs of emotional disturbance cease with the cessation of stimulation, as seen by earlier observers, he also found that a marked emotional discharge was followed for minutes by an altered behavior of the cat, indicating increased irritability. These observations strongly suggest that the whole complex of emotion may be elicited by electrical stimulation of the hypothalamus.

Systematic exploration of the diencephalon with simultaneous recordings of various autonomic responses showed that particularly the area of the mammillary body and the posterior hypothalamus give rise to sympathetic effects, such as an increase in the blood pressure, pupillary dilatation, contraction of the nictitating membrane, sweat secretion (209), and the inhibition of gastrointestinal activity (Beattie, 78).

Parasympathetic effects are likewise produced by hypothalamic stimulation, but these effects are in general more easily obtained from the anterior part of the diencephalon. This was clearly brought out by the studies of the Ranson school on temperature regulation (1033). The release of heat (vasodilatation and increased respiration [panting]) was found to be regulated by the anterior part of the diencephalon, particularly the area between the optic chiasma and the anterior commissure, while the conservation of heat (vasoconstriction, increased heat production through the liberation of adrenalin) was a function of the caudal part of the lateral hypothalamus.

Increased peristalsis and slowing of the pulse rate due to vagal impulses have also been noted on stimulation of the anterior hypothalamus. Hess confirmed and extended the work of the Ranson school and found a similar fairly sharp division between the parasympathetic and sympathetic effects resulting from the stimulation of anterior and posterior parts of the hypothalamus. The former resulted in pupillary constriction, urination, and defecation. Here again, the effects are not restricted to the autonomic nervous system but involve the somatic nervous system as well. Stimulation of the posterior part of the hypothalamus leads to an increased motor excitability culminating in an attack of rage; excitation of the anterior part causes a diminution of muscle tone and diminished motor excitability (Fig. 80).

One gets the impression from these investigations that the posterior hypothalamus, and particularly the area of the mammillary bodies, is primarily involved in aggressive or defensive reactions similar to

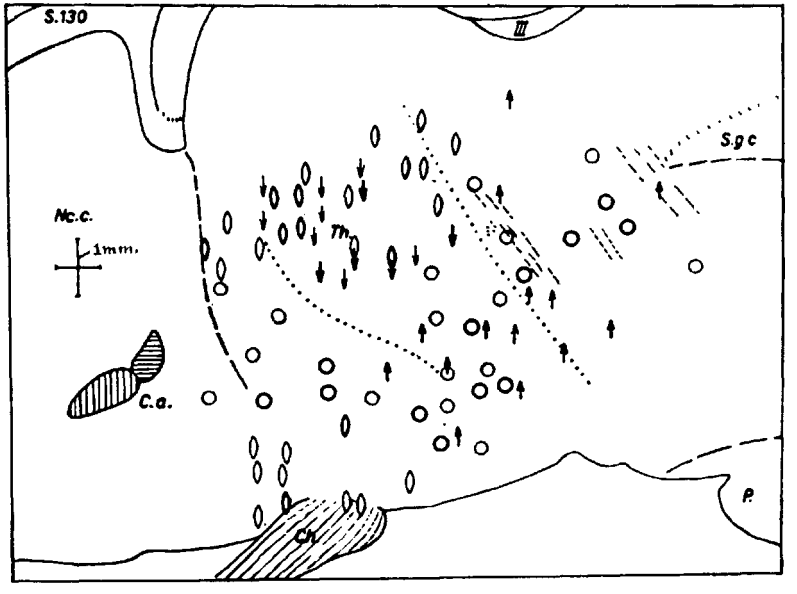

FIGURE 80. Autonomic-somatic integration in the diencephalon. Sagittal section through the brain of a cat. Pupillary dilatation indicated by circles; pupillary constriction, by ovals; increased motor excitability, by upward-pointing arrows; decreased motor excitability, by downward-pointing arrows. The experiment indicates that motor excitation is associated with sympathetic discharges, whereas diminished excitability of the somatic nervous system is associated with parasympathetic discharges. (Hess, 637.)

TABLE 18. The Effect of Hypothalamic Stimulation on Autonomic Effectors of the Cat before and after Vagotomy (Gellhorn, Cortell, and Murphy, 477)

Intensity and Frequency of Hypothalamic Stimulation	Pupil	Nictitating Membrane	Pulse Rate per Minute			
			Before Stim.	During Stim.	Immediately after Stim.	2 Minutes after Stim.
2.1 volts, 90 per sec.						
Vagi intact	+++	+++	159	78	138	160
After vagotomy ..	+++	++	156	159	159	156
2.3 volts, 90 per sec.						
Vagi intact	+++	++++	143	115	130	141
After vagotomy ..	++	++++	152	158	160	152
2.3 volts, 21 per sec.						
Vagi intact	++++	++++	142	133	112	138
After vagotomy ..	++++	+++	152	158	160	150

those seen in emotional excitement, which are characterized by an integration of predominantly sympathetic reactions with complex patterns of movements. The anterior hypothalamus, on the other hand, regulates trophic processes dealing with secretion, absorption, and excretion. The last functions are aided by typical postural attitudes, as seen in the normal animal during urination and defecation (637). However, it should be borne in mind that under certain conditions parasympathetic effects are obtained even from the posterior hypothalamus. With low frequency of electrical stimulation parasympathetic signs appear there, though with higher frequencies they are replaced by sympathetic effects (591). Also, as in emotion, sympathetic effects often predominate on hypothalamic stimulation and reveal the simultaneous activation of the parasympathetic system only after the sympathetic effects have been excluded. Thus stimulation of the posterior hypothalamus causes a fall in the blood sugar through the vago-insulin system after the adrenals and the liver have been denervated or the action on the sympathetic system has been eliminated by section of the cervical spinal cord (476). Furthermore parasympathetic as well as sympathetic effects may be elicited at the same time by hypothalamic stimulation (477). As Table 18 shows, maximal pupillary dilatation and contraction of the nictitating membrane may be combined with a distinct vagal slowing of the heart. Consequently there is no fundamental difference between the somatic and autonomic effects of hypothalamic stimulation and those seen in an emotional situation in man and animals.

Stimulation of the anterior and posterior parts of the hypothalamus influences the autonomic nervous system in man as in animals.

Mechanical manipulation of this area may give rise to great excitement and symptoms of mania (368). The destruction of the hypothalamus tends to produce stuporous conditions at least for a period of time (1032).

On the basis of this information it appears probable that emotion is associated with an excitation of the hypothalamus and particularly its posterior part. Depending on the form of excitation and the relative balance of parasympathetic and sympathetic neurons in this area, there may be considerable variations in the type and balance of the autonomic discharges.

The Somatic Discharge in Emotion

Not only the autonomic but also the somatic part of the "downward discharge" may show some degree of specificity. The rage reaction of the normal or decorticate cat as well as the manifestations of rage following hypothalamic stimulation is accompanied by motor discharges which seem to prepare the animal for fight through unsheathing of the claws, growling, hissing, attempts to bite, etc. Quite different is the motor behavior of the decorticate cat on exposure to a loud noise, as described by Bard: "The moment the noise was heard the cat abruptly retracted and lowered its head, crouched, mewed, and then dashed off running rapidly in a slinking manner with head, chest, belly, and tail close to the floor. After blindly colliding with several objects in her path, she came to rest in a corner, where she crouched mewing plaintively with eyes and pupils wide and the hair of back and tail erected." This behavior was interpreted by Bard (67, 69) as indicating that the animal made "wild attempts to escape, as if possessed by the most profound terror." In both instances the autonomic discharge appears to be predominantly sympathetic in nature, suggesting that the motor patterns expressing emotion are more varied than the types of autonomic discharges which appear at the same time.

It is also known that under conditions of extreme fear an entirely different reaction may be observed. In terror a person may feel unable to move, although sympathetic excitation persists as in rage. It is interesting to relate these psychophysiological experiences to the experiments of W. Smith (1123), who on stimulation of Brodman's area 24 (located on the medial side of the brain in the anterior part of the gyrus cinguli) obtained sympathetic discharges such as pupillary dilatation, a rise in the blood pressure, and piloerection. These autonomic effects were accompanied by a complete relaxation of all extremities. At that time I suggested to Dr. Smith that the reaction

he had been studying may underlie the emotional experience of extreme fear and terror. This interpretation appears to be confirmed by the recent work of Ward (1208), who removed area 24 bilaterally in monkeys with the result that these animals no longer showed any fear reactions (551a). It seems likely that in a state of terror this sup-

TABLE 19. The Specificity of the Somatic Discharge in Emotion, Based on Duchenne's Stimulation of Facial Muscles (Duchenne, 298)

Facial Muscle	Emotion
M. corrugator supercilii	Anguish
M. zygomaticus	Joy
M. triangularis	Grief
M. zygomaticus and *M. corrugator supercilii*	Compassion

pression of movement is accomplished by discharges which originate in the hypothalamus and activate the gyrus cinguli through the Vicq d'Azyr bundle via the anterior thalamic nuclei (989).

The greatest variations in the motor patterns which accompany emotions are seen in the face. As is well known, they may be accompanied by different forms of autonomic excitation, as seen in the blushing of shame and the pallor of fear,* but the specificity of autonomic reactions in different forms of emotion appears very limited when compared to the innumerable shades in the motor expression of emotions. The anatomic basis of the latter has been elucidated by Duchenne's classical work (298), recently made accessible to the English-speaking world in a fine translation and beautiful edition. Duchenne showed by stimulation of the muscles of the face that facial expressions accompanying different moods and feelings are the result of the excitation of different muscles or groups of muscles (Table 19). It is interesting to note that persistent contractions of striated muscles in anxious persons may lead to muscle spasms and give rise to pain (Wolff, 1239a).

Some further remarks on the nature and origin of the somatic discharge may be in order. It is well known that in lesions of the cerebral cortex or of the internal capsule the voluntary execution of facial movements is impaired or abolished whereas apparently paralyzed muscles can be activated in the mimic expression of emotion. Martin (903) mentions that even in bilateral cortical lesions laughing

* These reactions are measurable through plethysmography of the ear (Weber, 1213).

remains normal in spite of a paralysis of the face muscles to voluntary innervation. As a matter of fact, excessive and uncontrollable laughter is seen in organic brain disease in which the function of both pyramidal tracts is impaired. Through a careful analysis of his own cases and those reported in the literature Martin reached the conclusion that "in everyone of these cases (involving fits of laughter) in which there were indications of the sites of the lesions, the latter, though of different natures, were so placed as to affect the hypothalamus." The observation of Dott (290) that a hypophysial cyst abolished the expression of laughter and crying seems to indicate that in pleasant and unpleasant emotions somatic and autonomic expressions are integrated in or near the hypothalamus. This clinical material is of great value, since our information about pleasant emotions obtained in animal experiments is scarce, though in general agreement with these findings. The subcortical origin of the somatic expression of these states is supported by the observation that pleasant emotions may be observed in cats even after decortication (1056), and purring is said to occur on hypothalamic stimulation (538). The masklike facial expression in Parkinsonism, in which voluntary innervation is intact, points likewise to the subcortical origin of facial expression in emotion.

Hinsey (664) showed that weeks after the cortex had been removed and the pyramidal system had degenerated, the stimulation of the hypothalamus elicited ipsilateral and contralateral movements of a phasic as well as of a postural character. This subcortical extrapyramidal motor system is obviously activated in the hypothalamus under conditions of emotion and integrated with the autonomic discharges. Apparently stimulation of the motor cortex as well as of the hypothalamus leads to integrated autonomic and somatic effects. The autonomic effects are more prominent and have a greater tendency to be generalized after hypothalamic than after cortical stimulation.

The study of somatic discharges in emotion must take into consideration the integration of cortically and hypothalamically induced movements. Subthreshold stimulation of the hypothalamus combined with suprathreshold excitation of the motor cortex leads to greatly increased movements. These retain the character of cortically induced movements and are independent of sympathetic effects on the cerebral blood vessels, since this facilitation persists and is often increased after bilateral cervical sympathectomy (Murphy and Gellhorn, 957). The facilitatory action of the hypothalamic "upward discharge" may at least in part explain the increase in muscle strength seen in emotion.

This phenomenon is not only a common experience in man and animals but also appears under pathological conditions. Denny-Brown

(280) observed in monkeys with lesions of the motor cortex that the residual deficit appeared least when the animals were tested in a state of emotional excitement. That hemiplegics with aphasia may show ejaculatory speech suggests a similar basic mechanism.*

From these studies it may be concluded that subcortical discharges constitute the chief somatic component activated in emotion. They may be reinforced under certain conditions by cortically induced movements, but the typical emotional expressions of the face are retained under conditions in which the cortical motor areas are no longer functioning.

Hypothalamic-Endocrine Relations in Emotion

The "downward discharge" is only inadequately described when it is stated that it involves the two divisions of the autonomic nervous system as well as striated muscles brought into specific patterns of expression through diencephalic coordinating centers. It was previously mentioned that autonomic activity leads to changes in the endocrines through an increased secretion of insulin and adrenalin. It was further shown that adrenalin in turn leads to the secretion of adrenocortical hormones via the anterior hypophysis. The validity of these findings for the neuro-endocrine balance in emotion is evident from the following observations. Emotional excitement (rage) induced in rats by a slight shock – not a convulsive shock – is accompanied by lymphopenia in normal but not in adrenodemedullated rats (487). Since adrenodemedullated rats react to the injection of minute quantities of adrenalin with lymphopenia as promptly as do normal rats, their failure to show lymphopenia in emotional excitation and under other conditions inducing a sympathetico-adrenal discharge appears to be due to the removal of the adrenal medullae. Similar results were obtained with the eosinophils as indicator of a hypophysial-adrenocortical discharge. Apparently the discharge of adrenalin through sympathetic impulses originating in the hypothalamus represents the first link in a chain of events leading to the activation of the adrenal cortex through the anterior lobe of the hypophysis.†

* Hypothalamic and cortical stimulation may also cause facilitation at the spinal level, as shown by Rhines and Magoun (1045). However, it seems not correct to explain the hypothalamic–motor cortex interaction solely by changes at the spinal level. In addition to the arguments cited by Murphy and Gellhorn, it should be mentioned that activation of the motor cortex through afferent impulses originating in the hypothalamus leads, according to unpublished experiments with M. Bernhaut, to an actual discharge in the pyramidal tracts. It is this discharge which, in my opinion, greatly contributes to the striking somatic facilitation.

† See p. 318.

Conditions of stress such as cold or emotional excitement are sometimes accompanied by eosinophilia rather than eosinopenia (1241). Exposure to cold causes this effect only after the sympathetico-adrenal system has been eliminated surgically or pharmacologically (464). Since stress acts on both divisions of the involuntary nervous system, this suggests that eosinophilia is the expression of the action of the parasympathetic unopposed by the sympathetic nervous system. Such a view is supported by the fact that anxiety is accompanied by eosinophilia in addition to the many signs of parasympathetic hyperactivity which were described earlier. It would be interesting to determine whether the eosinophilia following stress in adrenodemedullated animals was abolished by subdiaphragmatic vagotomy and would disappear also in human anxiety after vagotomy had eliminated the increased secretory and motor activity of the gastrointestinal tract commonly associated with this emotional state.

These findings clearly show that the changes occurring in the endocrine system in emotion are more profound than was formerly assumed. There is additional evidence for changes in the secretory activity of the hypophysis. Emotional excitement induced by nociceptive impulses or by noise leads to an increased secretion of the antidiuretic hormone from the posterior lobe of the hypophysis (1185). This effect persists after denervation of the kidneys and the adrenals and after removal of the abdominal sympathetic chains. The reduction of urinary flow seen in hydrated animals in excitement can be matched by the injection of posterior pituitary extracts but not by adrenalin, and these results have been shown to be valid in man. Kelsall (762, 763) found that pain induced by voluntary contractions of ischemic muscles inhibited diuresis but left the rate of glomerular filtration unchanged, and Noble (973) observed that patients fainting after a venous puncture showed a significantly increased excretion of the antidiuretic hormone in the urine. Since this phenomenon did not occur in the absence of fainting, its relation to emotional disturbance appears quite probable.

These data support the interpretation that emotion in man may increase the secretion of posterior pituitary hormones, the relation of which to the supraoptic nuclei of the diencephalon was discussed earlier. Since the different posterior pituitary hormones frequently show parallel changes under various experimental conditions, it is not unlikely that sexual excitement is accompanied by an increased secretion of the oxytocic hormone. The latter may account for the augmented activity of the uterus in coitu (Reynolds, 1043a) which furthers the movements of the spermatozoa in utero. Harris (603)

mentions that in the rabbit sexual intercourse does not result in the liberation of the antidiuretic hormone from the posterior pituitary. It seems possible, therefore, that sexual excitement may release sufficient quantities of the oxytocic hormone to increase the activity of the uterus without influencing the rate of secretion of other hormones of the neurohypophysis. This is at least a suggestion, although not a proof, that the hormonal discharge initiated by the hypothalamus may show characteristics which are specific for different forms of emotion.

It was pointed out that emotional excitement leads to the liberation of the adrenotrophic hormone from the anterior pituitary and that the secretion of adrenalin initiates this chain of reactions. In addition it was shown earlier that sexual excitement augments the rate of secretion of the gonadotrophic hormones and in this reaction the site of excitation is the hypothalamus, the sympathetico-adrenal system not being involved. Whether emotional excitement leads to an increased secretion of the thyrotrophic hormone is not known. Since at least in some species hypothalamic stimulation leads to lymphopenia without the intervention of adrenalin, it appears not unlikely that the hypothalamic-anterior pituitary system may be directly activated in emotion and may enhance the rate of secretion of ACTH (237).

It is clear from this discussion and the experiments described in Chapter 13 that various forms of stress and emotional excitement activate both branches of the autonomic nervous system and fundamentally alter the balance in the endocrine system through changes in the rate of secretion of adrenalin, insulin, the posterior pituitary hormones, and the trophic hormones of the anterior hypophysis. These facts are of importance inasmuch as they show how much more complex the "downward discharge" is than Cannon assumed it to be. Indeed there are few physiological – i.e., reversible – reactions of the organism which involve as many organs and systems and as profound changes as are seen in emotion. No wonder that repeated exposures to these effects are apt to alter the reactivity of the person (neurosis, etc.) and even induce permanent anatomical damage in various organs.

The endocrine changes observed in emotional excitement suggest some interesting problems. It was emphasized in this discussion that the autonomic and somatic "downward discharges" show a high degree of specificity related to the type of emotion involved. Does a similar specificity exist with respect to the endocrine changes? Does sexual excitement involve primarily the hypothalamic-gonadotrophic system or does it activate the supraoptic-posterior pituitary unit and thereby the oxytocic hormone as well? Does the hypothalamus act

as a unit in emotion, or can different parts of this structure be activated directly or indirectly under these conditions, and does the form and degree of the excitation determine the extent to which the anterior and posterior hypophysis may be activated in part or as a whole? These and related questions cannot be answered at present, but the methods for a quantitative study of these problems are available.

A final remark on these endocrine changes may not be superfluous. Hormones affect the excitability of neurons* directly or indirectly – i.e., through changes in the ion concentration in the blood and tissues. They may thereby contribute to homeostasis† and at the same time be responsible for the change in sensation and perception observed in emotional excitement.

The Hypothalamic-Cortical Discharge in Emotion

The next phase of the problem which Cannon envisaged, the "upward discharge" from the hypothalamus to the cortex, may be demonstrated by several methods. In cats anesthetized with "Dial"-urethane, potentials recorded from various cortical areas appear largely in the form of grouped potentials similar to those seen in sleep. If a certain part of the cortex is excited, the grouped potentials disappear in this area and are replaced by potentials of smaller amplitude and higher frequency; on cessation of the stimulation the grouped "Dial" potentials reappear. Whereas the excitation of a specific sense organ produces signs of excitation confined to its specific cortical projection area, the stimulation of the hypothalamus induces excitation in all cortical areas (957). The effects are bilateral, but the action on the ipsilateral side is stronger. Similar results are obtained when the effect of hypothalamic stimulation on the cortex is studied after various cortical areas have been strychninized by the topical application of minute pledgets soaked in strychnine solution. The increase in the number of strychnine spikes and the disappearance of grouped spikes on hypothalamic stimulation again indicate cortical excitation in all cortical areas (Fig. 81).

The effect of this "upward discharge" can be studied in man through the EEG. Hyperemotional states are characterized by potentials of low amplitude and relatively high frequency (20 per second) which may replace the alpha potentials in frontal, parietal, and even occipital parts of the skull (Cohn, 235). These changes are probably

* See pp. 52–53 concerning the effect of adrenalin, ACTH, the adrenocortical hormones, and thyroxin on the central nervous system.

† See p. 390.

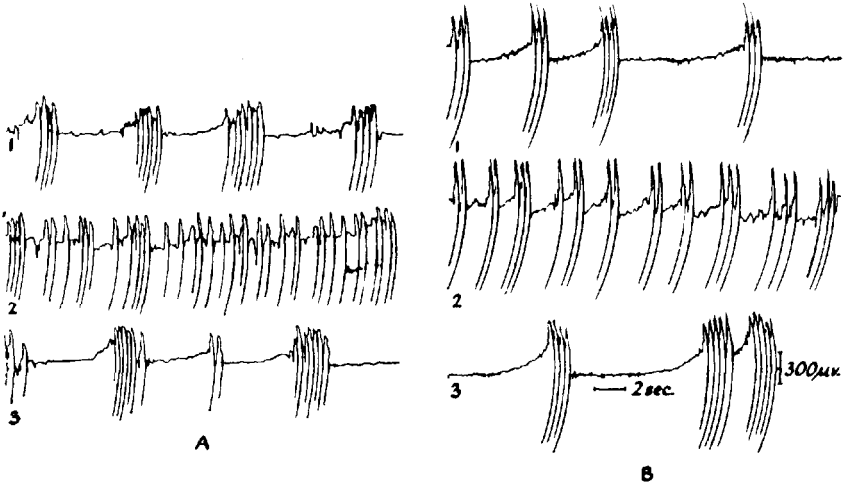

FIGURE 81. The effect of stimulation of the mammillary nuclear group on locally induced cortical strychnine spikes after acute section of the cervical sympathetics. Records A are from the ipsilateral posterior sigmoid gyrus; records B, from the ipsilateral occipital lobe. *Records 1:* control. *Records 2:* after hypothalamic stimulation. *Records 3:* control, 3 minutes later. (Murphy and Gellhorn, 957.)

due to diffuse cortical excitation originating in subcortical nuclei (hypothalamus?). But it is not necessary to refer here to pathological emotional states. Every electroencephalographer is familiar with the fact that apprehension during the taking of the EEG may cause a disappearance of the alpha potentials or a reduction in their amplitude. When the subject has been reassured, the potentials may reappear.

That a simple arousal reaction which activates the whole cortex of the brain is mediated through hypothalamic-cortical discharges was indicated earlier in connection with the discussion of the physiological basis of consciousness. The problem of consciousness and that of emotion are intimately interrelated. A sensory stimulus when applied for the first time induces, as mentioned before, a generalized cortical reaction. The alpha potentials are blocked and a galvanic reflex (palmar sweating) appears. On repetition of the sensory stimulus the blocking of the alpha potentials becomes confined to the specific sensory projection area and the galvanic reflex disappears (Lindsley, 846). Apparently it is the newness of the stimulus which elicits a startle-like reaction. The latter seems to be akin to emotion both from the psychological point of view – there is obviously a transition

from startle to fright – and with respect to underlying physiological mechanisms.*

The Influence of the Cortex on the Hypothalamus

The inhibitory action of the cortex on the subcortical structures remains to be discussed. Since the memorable work of Goltz (557) it has been known that removal of the cortex greatly increases emotional reactivity in experimental animals. These investigations have been confirmed and extended by Cannon and Bard, who showed that the center of autonomic and somatic reactions elicited under conditions of emotional excitement is located in the posterior part of the diencephalon and that this region is normally inhibited by the cortex. As mentioned earlier, Cannon assumed that this inhibitory action is diminished as a result of cortical excitation. In other words, he believed that two types of "upward discharges" are present, the first representing the physiological basis of the alteration in the "feeling tone" of perceptions under conditions of emotion, and the second causing a diminution in the degree of inhibition which normally is exerted by the cortex on subcortical structures and particularly on the hypothalamus. Our investigations have given no evidence that would support such a division of the "upward discharges," since hypothalamic stimulation appears to produce only an excitatory action on the cortex (957).

The degree of the restricting power of the cortex over subcortical structures in general and the hypothalamus in particular seems to be directly related to the state of cortical excitation. This is proved not only by the diencephalic release in decorticate animals, to which reference has been made frequently, but also by the fact that the autonomic centers in the diencephalon show increased reactivity when cortical functions are depressed as in anoxia. In both instances evidence was obtained showing that the hypothalamic "downward discharge" is increased. But, as discussed elsewhere,† recent investigations have shown that the inhibition of the hypothalamus produced by the normal activity of the cerebral cortex concerns not only the hypothalamic "downward" but also the hypothalamic-cortical "upward discharge" which affects the cortex of the brain as a whole. The inhibitory power of the brain appears to be a function of cortical excitability: as the activity of the cortex decreases, this influence on the diencephalon is diminished. The increased emotional reactivity in various forms

* Concerning the pathways involved in the hypothalamic-cortical discharge see Chapter 9 and bibliographical entry 230a.

† See p. 152.

of anoxia and in the precomatose stages of hypoglycemia may be interpreted on this basis.

The mechanism through which the diencephalon is released is not well understood. Specific inhibitory neurons residing in definite parts of the cortex are probably not involved. Stimulation of various parts of the cortex either electrically or by means of strychnine does not cause inhibition of the hypothalamus (958). Whether stimulation of the cortical suppressor areas inhibits the hypothalamus does not seem to have been investigated, but such a result appears to be unlikely, since suppression of the cortex no matter of what origin is accompanied by hypothalamic release. Of importance seem to be the quantity and in part the location of the cortical tissue which is eliminated. The removal of one cortical lobe is not accompanied by increased pseudoaffective behavior. On the other hand, hemiplegia results in a more marked facial expression of emotions on the paralyzed side.

An interesting contribution to this problem is a study by Bard and Mountcastle (70), who showed that removal of the neocortex produces not a hyperexcitable state but rather a condition of placidity in cats. Such animals can be handled very roughly without eliciting signs of anger. Severe nociceptive stimuli result at most in crying and attempts to escape, but the autonomic-somatic syndrome which is generally interpreted as anger or sham rage never occurs. However, the additional ablation of the midline cortex (gyrus cinguli) or various parts of the rhinencephalon (pyriform lobe, amygdala, hippocampus) converts these placid animals into ferocious ones. The experiments indicate that the restraining influence on the hypothalamus is exerted in the cat through the phylogenetically oldest parts of the cortex (rhinencephalon). Their action is apparently opposed to that exerted by the neocortex, since the removal of just the neocortex increases the restraining power of the rhinencephalon. It should, however, be said that impressive as these results are, they leave many questions still unanswered, especially those concerning the cause of the fundamental difference between the behavior changes in monkeys and the changes in dogs and cats subjected to similar cortical lesions (69, 1132, 1157a).

The investigations of Bard and Mountcastle constitute an extension of a line of researches initiated by Klüver (784–786) and Bucy (175), who were concerned with determining the functional significance of rhinencephalic structures. These investigators, upon removing the major portions of the rhinencephalon (hippocampus, uncus, amygdala) in addition to the temporal neocortex, analyzed the behavior

changes following the bilateral removal of these structures in monkeys and found that such extirpations lead not only to a disappearance of the expressions of emotions but also to a complete loss of anger and fear reactions or at least to a profound modification of all responses to stimuli normally eliciting various forms of emotional behavior. It should be emphasized that Klüver and Bucy found not only striking changes in emotional reactions and expressions but also other profound behavior alterations possibly related to the emotional changes, such as hypersexed behavior, a greatly increased tendency to attend and react to every stimulus, and an apparent inability to recognize animate and inanimate objects on the basis of visual or auditory criteria.

The intimate interrelation of the hippocampal formation with the hypothalamus (mammillary body) and the gyrus cinguli, which is considered the "receptive region for the experience of emotion," was first emphasized by Papez in 1937 (989). Since this time his general concept has been confirmed and elaborated on the basis of anatomical, physiological, and clinical studies. Recent work (918) suggests dividing the hippocampus into two parts: the sensory section, serving as a "visceral" correlation center where impulses from practically all sense organs are received, and the motor section, which transmits these impulses via the hypothalamus and anterior thalamic nuclei to the gyrus cinguli. For this reason attention is again called to experiments involving the gyrus cinguli.* It should also be mentioned that the stimulation of rhinencephalic structures such as the amygdala inhibits spontaneous movements, lowers the blood pressure, and causes a cessation of respiration (743). These effects are obviously similar to those obtained on stimulation of the anterior portion of the cingular gyrus.

* Bilateral removal of this area makes the monkey fearless and greatly alters its social behavior, as the following quotation from Ward's work (1208) indicates. "The monkey loses its preoperative shyness and is less fearful of man. It appears more inquisitive than the normal monkey of the same age. In a large cage with other monkeys of the same size, such an animal shows no grooming behavior or acts of affection toward its companions. In fact, it treats them as it treats inanimate objects and will walk on them, bump into them if they happen to be in the way and will even sit on them. It will openly eat food in the hand of a companion without being prepared to do battle and appears surprised when it is rebuffed. Such an animal never shows actual hostility to its fellows. It neither fights nor tries to escape when removed from a cage. It acts under all circumstances as though it had lost its social conscience. This is probably what Smith saw and called tameness. It is thus evident that following removal of the anterior limbic area, such monkeys lose some of the social fear and anxiety which normally governs their activity and thus lose the ability to forecast accurately the social repercussions of their own actions."

Hypothalamic Lesions and Emotion

It appears that the hypothalamus occupies a central place in the neurophysiology of emotion through the integration of the viscero-somatic behavior accompanying this condition and through the complex and mutual influences which exist between cortex and diencephalon. Studies on the effect of bilateral hypothalamic lesions support these conclusions. A striking change in the behavior of cats and monkeys was seen following such lesions (604, 725, 1032, 1034). For a number of days these animals were in a somnolent state from which they could easily be aroused and to which they returned in the absence of outside stimuli. They often showed signs of catalepsy and could be placed in awkward positions without making attempts at correction. Chronic animals surviving the lesions for a number of days or weeks showed a gradual diminution of the changes induced by the operations. The faces of these animals were masklike, in contradistinction to the well-known facial expressions of normal monkeys, and remained so for some time. Wild rhesus monkeys became tame on bilateral destruction of the mammillary bodies.

Ranson stresses the fact that interruption of the pathways from the hypothalamus to the thalamus and cortex does not lead to catalepsy and emotional hyporeactivity and believes that the state of somnolence is due to the elimination of the "downward discharge" from the hypothalamus. With this interpretation we cannot agree. Important as the "downward discharge" is for many functions, the elimination of the hypothalamic-cortical discharge is probably the most important factor in the production of abnormal behavior in animals with large bilateral hypothalamic lesions.*

Recent work indicates that the reactivity of the hypothalamus is not solely determined by hypothalamic-cortical relations. With the cortex intact a rage reaction can be elicited not only by stimulation of the mammillary bodies and closely adjacent areas, as reported earlier, but also by destructive lesions of the ventromedial hypothalamic nuclei in the cat (Wheatley, 1230). Apparently these nuclei exert an inhibitory action on the caudal part of the hypothalamus. Upon release of the hypothalamus from these nuclei a minute stimulus produces, as in the decorticate animal, a characteristic rage reaction.

The Arousal of Emotion

The question remains to be discussed how emotional excitation can be aroused. Cannon suggested that impulses from peripheral receptors

* See also Chapter 9.

are relayed in the thalamus and cause excitation of the diencephalon. This is indeed the case, as can be shown by the study of hypothalamic action potentials under the influence of nociceptive stimuli. Mechanical or electrical stimulation of the sciatic nerve will produce in hypothalamic action potentials distinct changes indicative of excitation (466).

It should be added that excitation of the higher senses (eye, ear) may likewise arouse emotional excitation. Thus it is found in cats made hyperreactive as the result of elimination of the rhinencephalon that optic or acoustic stimuli elicit a well-directed rage reaction, although these stimuli may be ineffective after complete decortication (69). The physiological basis of this phenomenon seems to lie in cortico-hypothalamic connections which can be demonstrated with the strychnine method. Strychninization of cortical projection and association areas may cause a firing of the hypothalamus. The appearance of strychnine spikes in the dorsomedial and the ventrolateral nuclei suggests that these parts of the thalamus furnish an intermediary station in the transmission of cortico-hypothalamic impulses (958).

According to Ward and McCulloch (1210) cortico-hypothalamic connections are restricted to the frontal lobe. If this is the case, it must be assumed that the transmission of impulses from the primary sensory projection areas to the frontal lobes precedes emotional excitement based on a sensory impression; or, to express this matter in simple psychological terms, the evaluation of sensory experience by the frontal lobes is a prerequisite of an emotional arousal on a sensory basis. Such an interpretation is not without experimental foundation. The separation of connections between the frontal lobe and the thalamus and hypothalamus as practiced in frontal lobotomy has been shown to decrease or eliminate the emotional reactivity to severe pain (Freeman and Watts, 388; Falconer, 334). However, it is likely that the activation of the hypothalamus from sensory projection areas via the frontal lobes plays a role only in primates. In lower forms like the cat emotional behavior is not abolished by bilateral removal of the frontal lobes. Since in such animals a rage reaction may be brought about by sensory stimuli, cortico-hypothalamic pathways which do not involve the frontal lobes may be involved. The relay over the frontal cortex is perhaps only an additional reinforcing link.

A similar mechanism is probably operative when emotion is aroused through visceral sensations (hunger, thirst). Afferent vagal impulses which are of importance for hunger sensation reach the

orbital surface of the frontal lobes (59a), while changes in the water metabolism of the tissues lead to excitation of the supraoptic nuclei (1185) and, via central thalamic nuclei, to that of the cortex (615). It is of interest that bilateral lesions lateral to the ventromedial nucleus of the hypothalamus cause a cessation of eating (31) resulting in death from starvation, whereas destruction of the ventromedial nuclei results in hyperphagia and obesity (134).*

Concluding Remarks and Summary

The process of emotion results in the activation of the hypothalamus, which in turn discharges "upward" and "downward." The "downward discharge" involves not only the sympathetic system but the parasympathetic division of the autonomic system as well. The former activates the adrenal medulla, as was established through the classic investigations of Cannon and his collaborators; the latter activates the islets of Langerhans. In emotion the secretion of insulin is increased via the vagus, although its action on the blood sugar is obscured through the dominance of the sympathetico-adrenal discharge.

Although it is true that emotion may evoke mass discharges activating both branches of the autonomic nervous system, the investigations of Wolff *et al.* have shown that, depending on the type of emotional disturbance, either the parasympathetic or the sympathetic system alone may be involved. The sympathetic may be excited as a whole or in part, since emotional excitement may cause a rise in the blood pressure without alterations in the pulse rate or may increase the heart rate without evidence of vasoconstriction. This is in agreement with earlier physiological experiments in which stimulation of sympathetic centers led to a partial excitation of the sympathetic system (477). The intensity and quality of the central excitatory processes determine the type, intensity, and duration of the autonomic discharge. Fractionation of the autonomic discharge is possible within both divisions of the visceral nervous system, although more common for the parasympathetic than for the sympathetic.

Further experiments have shown that the rate of secretion of the hormones of the pituitary gland and of the adrenal cortex is likewise altered in emotion. Emotional excitation causes hypothalamic-posterior pituitary discharges leading to an increased liberation of the antidiuretic hormone, whereas in certain forms of excitement related to sexual activity hypothalamic excitation seems to be correlated with an increased secretion of the gonadotrophic hormones of the anterior

* See also the experiments of Brügger (166) on the increase in the hunger drive on hypothalamic stimulation in unanesthetized animals.

pituitary and of the oxytocic fraction of the posterior hypophysis. In addition there is in emotional excitement an increased secretion of the hormones of the adrenal cortex, initiated by the secretion of adrenalin and resulting in lymphopenia and eosinopenia.

These autonomic-endocrine discharges are accompanied by either the excitation or the inhibition of striated muscles. The former is associated with rage, the latter, involving excitation of the cortical suppressor area 24, with fear or terror.*

The long postulated "upward discharge" from the hypothalamus to the cortex has been established by several procedures. First, it has been shown that stimulation of the area of the mammillary bodies in the anesthetized cat leads to bilateral cortical excitation characterized by the disappearance of "Dial" potentials and the appearance of faster potentials of lower amplitude (lessened synchrony of cortical discharge). Second, experiments with the strychnine method of Dusser de Barenne have indicated that this hypothalamic-cortical discharge involves the midline nuclei of the thalamus as a relay station. In addition the excitation spreads to the contralateral hypothalamus and from there via the thalamus to the cortex.

The conditions which determine this "upward discharge" have been further elucidated by the observation that the injection of strychnine into the hypothalamus leads to a generalized synchronous strychnine discharge in all parts of the cerebral cortex when as a result of asphyxia the cortical potentials are greatly reduced in amplitude or have disappeared (471). These experiments prove that normal cortical activity holds in abeyance not only the "downward discharge" from the hypothalamus, as is known from observations on animals with sham rage, but also the "upward discharge" to the cortex.

The excitation of the hypothalamus through nociceptive impulses is related to emotional states accompanying pain, while the appearance of hypothalamic spikes after strychninization of a cortical area illustrates the activation of the hypothalamus by the cortex. This appears to be the basis of emotional excitement elicited by various sensations and by associations linked with them. In primates the frontal lobe, which is probably concerned with the evaluation of sensory experience, is intercalated between the excitation of the cortical sensory projection areas and the hypothalamus.

Although the central place which the hypothalamus occupies in the physiological mechanisms underlying the emotional processes is thoroughly established, it should be borne in mind that the symptoms

* It should be mentioned that attempts to demonstrate the functioning of the suppressor areas in the unanesthetized state have failed thus far (229).

resulting from excitation and destruction of this structure are to a large extent due to the connections of the hypothalamus with other parts of the brain. These relations are gradually being explored through anatomical and physiological methods. After the fiber tracts which connect the hypothalamus with orbital cortex, hippocampus and amygdaloid nucleus, and the gyrus cinguli have been adequately investigated, the understanding of the emotional disturbances which follow cortical lesions will have a firm anatomical basis.

It is suggested that (1) the autonomic-endocrine and the somatic "downward discharge" and (2) the hypothalamic-cortical "upward discharge" represent the basic physiological pattern of the emotional process. The former is the basis of the bodily expression of emotion; the latter accounts for the "feeling tone" and for the mental changes which accompany emotion. The different types of facial expression (Duchenne), the fact that rage involves the activation and fear the inhibition of the skeletal muscles, and the specific vascular and secretory changes (Weber; Wolf and Wolff) in different forms of emotion reflect the great variability in the pattern of the somato-autonomic discharge. This discharge is probably paralleled by the similar specific hypothalamic-cortical discharges which underlie the manifold forms of subjectively experienced emotion.

The quantitative determination of the neurological (somatic, parasympathetic, and sympathetic) and endocrine components of these specific patterns will be one of the chief tasks of future research in the physiology and pathology of emotion.

We shall close this discussion by a few remarks on a theory of emotion. The data presented in this chapter seem to support the fundamentals of Cannon's "thalamic" theory. The core of the theory appears to be the idea that in emotion a subcortical structure, the hypothalamus, coordinates autonomic and somatic discharges and is responsible, by way of hypothalamic-cortical impulses, for the modification of perception and of higher mental processes such as judgment. The hypothalamus may be activated reflexly, and also from cortical sensory projection areas, or from those cortical areas which are involved in memory. However, excitation of the hypothalamus does not lead to true emotion if the cortex is functionally eliminated. Sham rage is differentiated from true emotion by its briefer duration and by a lack of the directed attack which indicates the participation of the cortex in the rage reaction of the intact organism. Certain autonomic responses of cortical origin are likewise concomitants of true emotion: (1) the galvanic response (palmar sweating), which is aroused upon the excitation of the sensorimotor cortex; (2) the

sympathetic excitation of the nictitating membrane of the cat, which appears in any emotional or attention reaction and is lost even in light anesthesia.

True as well as "sham" emotion has also been observed in man. The emotional expressions seen in sham emotion may be of very great intensity and duration but occur in the absence of felt emotion. Martin has described cases of fits of laughter ("sham mirth"); they were "not backed by any appropriate emotion and, in fact, the patient's emotion may be quite inappropriate to laughter."

It appears doubtful, however, whether a sharp division between true emotion, requiring cortical activity, and sham emotion, occurring in the absence of cortical activity, can be established. There are obviously levels of emotion just as there are levels of consciousness. The two functions are intimately related, although far from identical.* It seems to the writer that the reticulo-hypothalamic-cortical discharge provides the necessary background on which the specific emotional functions can be carried out through an integration of hypothalamic and cortical activity.

To what extent is emotion a release phenomenon? In spite of recent criticism (41) it can hardly be doubted that emotional expression is released in conditions of anatomic or functional decortication. Bard (69), on the basis of new experiments, has again stressed that the threshold for sensory, sham-rage-provoking stimuli is lower in decorticate animals than that for rage in unoperated controls. The lesser duration of sham rage – the reaction ceases with the end of the stimulus – is not incompatible with such an interpretation. The hypothalamus and the thalamus send impulses to, and receive them from the cerebral cortex. These reverberating circuits, known to contribute to the duration of excitation, no longer exist after decortication.

Emotional response in man, particularly in its highest forms, appears to be due to cortical excitation. At the same time it is true that conditions leading to diminished (but not extinguished) cortical activity, such as anoxia or alcoholic intoxication, seem to predispose to emotional excitement. Reflex activation of the hypothalamus and hypothalamic-cortical discharges must be facilitated under these conditions. If the cortex is still reactive, true emotional excitement may occur; if its activity is greatly reduced, an expression of "sham" rage or "sham" mirth will result as in decorticate animals. Between these two extremes lie numerous levels of emotional response which may be described in psychological terms but as yet cannot be analyzed in their physiological mechanisms.

* In this respect I differ with Lindsley.

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Factors Involved in Conditioning

In a book dealing with the medical aspect of neurophysiology it appears necessary to discuss at least some phases of the basic physiology of conditioning, since these processes undoubtedly furnish patterns according to which individual reactions are acquired. Any reflex elicited in the normal or anesthetized organism or in an animal in which the brain has been removed is characteristic of the species. It is not always the same since it may undergo quantitative changes as the result of antecedent stimuli. Even qualitative changes occur: stimulation of a nerve of the left leg will induce, instead of the typical extension, a flexion of the contralateral leg if the latter was extended at the time of the stimulation (884). But the reflexes, although modifiable, are predictable. The behavior, on the other hand, of the normal animal and of the human organism cannot be foreseen because it depends not only on innate characteristics of the central nervous system but also on individually acquired experience. The Pavlovian experiments on conditioned reflexes demonstrate the ability of the central nervous system to react on the basis of recently acquired experience, and they permit a quantitative study of these phenomena to be made.

General Characteristics of the Conditioned Reaction (649, 995)

The principle of the conditioned reflex of Pavlov lies in the temporal combination of a neutral stimulus (conditioned stimulus) with a strong inborn reflex such as the salivary reflex, caused by food intake, or the flexor reflex, elicited by the application of a nociceptive stimulus. The stimulus evoking the innate or unconditioned reflex is called an unconditioned stimulus. If a conditioned stimulus such as a blue

light is presented for a number of times with an unconditioned stimulus such as food, the optic stimulus by itself will call forth salivation. The conditioned stimulus has become temporarily associated with the center of salivation in the medulla oblongata so that salivation as an acquired, conditioned reflex occurs. If instead of salivation the flexion of the left foreleg is chosen as the unconditioned reflex, the blue light will, after an appropriate number of combinations, produce this defensive reflex. Obviously these reactions may be measured quantitatively and thereby give a closer insight into the factors responsible for the appearance and decay of the conditioned reflex.

The wide applicability of this principle is evident from the fact that conditioned reflexes may be established in man and animals and that the nature of the unconditioned stimulus and the conditioned stimulus may be varied within wide limits. The unconditioned reflex may involve the autonomic as well as the somatic nervous system. Reactions of the former which have been conditioned include, in addition to salivation, the pupillary reflex to light, the sympathetically induced palmar sweating to nociceptive stimuli, diuresis following an increased intake of water, and pharmacologically induced reactions such as vomiting in response to morphine. Somatic reflexes which have been conditioned include the flexor reflex, bineuronal tendon reflexes such as the knee jerk, the blink reflex to a blast of air against the eye, and changes in respiration to a painful stimulus. Stimuli arousing impulses in different sensory systems have been successfully used in conditioning not only in the form of lights of different colors, sounds of various pitches, and tactile stimuli applied to different parts of the body, but also in a variety of spatial and temporal patterns (optical figures, melodies, etc.).

Depending on the temporal relation between the conditioned and unconditioned stimulus, Pavlov distinguishes several forms of conditioned reflexes. The *simultaneous conditioned reflex* is obtained when the conditioned stimulus precedes the unconditioned stimulus by 0.5 to 5 seconds and continues during the presentation of the latter. These reactions are acquired more easily than other forms of conditioned reflexes and occur with a short latent period. If the interval between the onset of the conditioned stimulus and the unconditioned stimulus is longer than 5 seconds while the experimental setup remains the same in all other respects, a *delayed conditioned reflex* results. Its latent period is longer than that of the simultaneous conditioned reflex and increases with the length of the interval separating the onset of the two stimuli. However, the conditioned reflex begins

before the unconditioned stimulus is applied. If the conditioned stimulus precedes the unconditioned stimulus and does not overlap with the latter, a *trace conditioned reflex* is developed. It begins in the interval between the two stimuli. The three forms of conditioned reflexes, in the order presented, are acquired with increasing difficulty. It should be added that Pavlov was aware of the significance of time as a conditioning factor, since he produced conditioned reflexes by application of the unconditioned stimulus at constant intervals without the aid of any conditioned stimulus.

During the development of the conditioned reflex its intensity increases and its latent period is shortened, the intensity being, at least under optimal conditions, similar to that of the unconditioned reflex. The conditioned reflex is modified in important respects by processes of summation and inhibition. The summation of conditioned reactions is best demonstrated with conditioned stimuli which affect different sensory modalities – e.g., light and sound – instead of with two sounds of different pitch. Since Konorski (797) showed that two combined subthreshold or threshold conditioned stimuli may result in a strong conditioned reflex, facilitation apparently exists in conditioned as well as in inborn reflexes.

Pavlov distinguishes two forms of inhibition. External inhibition is the temporary loss of a conditioned reflex by extraneous stimuli. It may be observed in a dog with a well-established conditioned reflex when the animal fails to show the response in attempts of the experimenter to demonstrate the conditioned reflex in a different environment. Of greater importance is the knowledge of various forms of internal inhibition, since they may be used for the maintenance and refinement of conditioned reflexes. Well-established conditioned reflexes are gradually lost unless they are reinforced by unconditioned stimuli. The gradual decrease and the ultimate disappearance of nonreinforced conditioned reflexes is termed extinction by internal inhibition. If two conditioned stimuli of the same sense modality (e.g., two tones of different pitch) have been used to form a conditioned reaction, the reinforcement of one conditioned stimulus maintains the conditioned reflex, while the lack of reinforcement of the other conditioned stimulus abolishes the conditioned reaction to it. Consequently a differentiation between an excitatory and an inhibitory conditioned stimulus is obtained. This procedure is also useful to eliminate the tendency toward generalization (Pavlov's irradiation) during the development of a conditioned reflex. During this period not only the particular conditioned stimulus which is always used to elicit a conditioned reflex may be effective but also other stimuli

affecting the same sensory modality. However, if the latter are applied but not reinforced, a specific conditioned reflex is finally developed.*

The Pavlovian conditioned reflex has been slightly modified in several ways. Two such modifications may be briefly mentioned. In the original Pavlovian setup the relation of the conditioned stimulus to the unconditioned stimulus remains fixed throughout the experimental procedures. In the "instrumental reward training" (649) the reward (in the form of food or as avoidance of punishment) is introduced provided that the proper conditioned reflex has taken place. Thus a rat may be trained to jump from one compartment (A) to another (B) in response to a conditioned stimulus (buzzer) while a shock applied to the grid in A, on which the rat stands, provides the unconditioned stimulus. As soon as the conditioned reaction to the buzzer is established, the rat avoids the punishment by jumping to B before the application of the shock. Similarly, an animal may be given food each time after a conditioned reflex has been performed. Both procedures aid in the establishment of the conditioned reflex, and the quantity of food is directly related to the speed with which the conditioned reflex is acquired (137).

This description of the conditioned reflex is admittedly incomplete, but may serve as a basis for the discussion of the physiological and medical significance of this phenomenon. The physiological questions concern the mechanism underlying the conditioned reflex and its neuroanatomical basis. Furthermore the modifiability of the conditioned reflex by physiological and pharmacological factors is of great medical interest, since the conditioned reflex constitutes at least one important element in behavior.

The Nervous Structures Involved in the Conditioned Reflex

In the normal organism the conditioned stimulus acts in most instances on a sense organ (visual, acoustic, or cutaneous) whence the impulses thus set up are transmitted to the cortex of the brain via various afferent systems. Similarly, the unconditioned stimulus elicits a reflex through the excitation of appropriate receptors. Salivation is produced through a morsel of food or acid placed into the mouth, and the flexor reflex through stimulation of nociceptive cutaneous end-organs.

A number of investigations deal with the question of which parts of the conditioned and unconditioned reflex arcs are indispensable

* For other forms of internal inhibition see Hilgard (649). The reader should consult Klüver's book (782) for an important discussion and critique of the concepts of the generalization and differentiation of conditioned reflexes.

for the establishment of the conditioned reflex. The stimulation of posterior spinal roots through an electrode buried under the skin was successfully used as an unconditioned stimulus and, in combination with a buzzer, established a conditioned reaction of the same type as when the nociceptive stimulus had been applied to the skin (873). Obviously the sense organ in the skin and the conduction of the impulses to the posterior roots do not play a specific role in the conditioning process. Of greater interest is the finding that stimulation of the posterior columns of the spinal cord is likewise an effective stimulus. Since no signs of pain were elicited by the application of these stimuli, the unconditioned reaction was probably formed on the basis of an excitation of proprioceptive nerves. Finally, it was shown that stimulation of the motor roots (unconditioned stimulus) in conjunction with a conditioned stimulus failed to produce a conditioned reaction, although the same movement was elicited as on stimulation of nociceptive receptors. Therefore it must be concluded that the central excitation elicited by the unconditioned stimulus is a prerequisite for the formation of a conditioned reaction. This conclusion is confirmed by the failure to develop conditioned reactions when peripheral processes such as pilocarpine-salivation (355), adrenalin-hyperglycemia (412), and histamine-induced gastric secretion (759) served as unconditioned stimuli.

Experiments on the motor cortex permitted a further analysis. Loucks (871) found that even after 600 trials no conditioned reflexes were formed on the basis of faradization of the motor cortex as an unconditioned stimulus. However, Brogden and Gantt (138) succeeded in establishing a conditioned reaction by means of electrical stimulation of the neocerebellum which resulted in ipsilateral movements. In both groups of experiments an acoustic stimulus (buzzer) was employed as the conditioned stimulus.

What is the nature of the central excitation elicited by the unconditioned stimulus? In most instances in which conditioned reflexes are established with inborn somatic reflexes as unconditioned reflexes, the unconditioned stimulus excites nociceptive fibers. However, proprioceptive stimulation induced by passive movements of a limb is likewise an effective unconditioned stimulus. Such impulses probably account for the development of conditioned reflexes with stimulation of the posterior funiculi and the cerebellum as unconditioned stimuli (872). The arousal of sensation by the stimulation of the motor cortex is slight, but even in man, in whom the separation of sensory and motor functions seems to be sharper than in laboratory animals, sensory effects occur on electrical excitation of the precentral gyrus

(1002). Although proprioceptive impulses reach the motor cortex (416), proprioceptive sensations on electrical stimulation of this area are not distinct, but it should be borne in mind that electrical stimulation of any part of the cortex is not an adequate form of excitation and produces at best samples of the functions incorporated in the gray matter. Consequently it is to be expected that proprioceptive effects will be more fully developed if the afferent fibers conveying these impulses are stimulated. This is the case in the experiments involving electrical activation of the posterior columns or of the neocerebellum. It is therefore likely that a great variety of neutral (conditioned) stimuli will lead to the formation of conditioned reactions if the unconditioned stimuli arouse an excitation in the brain through nociceptive or proprioceptive impulses.

In the light of previous discussions it is interesting to note that the afferent impulses which form an unconditioned reflex suitable for conditioning are those which have a tendency to activate the hypothalamic system. The salivary reflex, which has been primarily used by Pavlov for such studies, certainly involves more than afferent impulses to the medullary center for salivation and efferent tracts from this area to the gland. The emotional effect of feeding and the relation of the "hunger drive" to emotion are generally known and have been utilized in conditioning. It has been found that reward with food intensifies and accelerates the formation of conditioned reflexes. Moreover the control of food intake through the hypothalamus has been well established through the study of experimental lesions (31).* These observations seem to indicate that the formation of conditioned reflexes involves and is probably facilitated by activation of the hypothalamic-cortical system.† Such an interpretation is supported by Lashley (822), who points out the significance of "affective reinforcement" for the conditioning process. "Corresponding to the nature of the conditioning stimulus, there is fear of electric shock, objectively demonstrable by cardiac and respiratory changes, anticipation of acid in the mouth with slight nausea, or expectation of

* See p. 357.

† One would expect that stimulation of the hypothalamus would in combination with a conditioned stimulus be suitable for the development of conditioned reflexes. Masserman (906), however, was unable to produce conditioned reflexes in this manner and considered this finding an indication of the exclusively motor character of the hypothalamus. The important hypothalamic-cortical discharges discussed elsewhere (pp. 350ff) disprove this inference. The fact that in Masserman's experiments hypothalamic stimulation produced only sham rage whereas Hess (637) saw true-rage reactions under these conditions shows that, probably owing to the type of stimulation, no "upward discharge" occurred in Masserman's experiments. It seems very likely that hypothalamic stimulation leading to signs of true emotion (see p. 341) could be conditioned.

food . . . Unless this affective element is aroused, the conditioned reflex does not occur. So-called extinction of the conditioned reflex is not a weakening of the specific association, but a waning of the affective reinforcement" (Lashley). The persistence of some conditioned reaction after decortication is not in disagreement with this principle. Pseudoaffective reactions are released by decortication, and it is very likely, although not yet established experimentally, that hypothalamic discharges may increase the excitability of subcortical relay stations of the sensory systems and thereby aid in the establishment of conditioning.*

The central excitation induced by stimuli which show a great affinity to the hypothalamic system is apparently an important if not an indispensable part of the unconditioned reflex. This raises the question whether the peripheral action (movement or secretion) is also necessary for the building up of conditioned reflexes. In spite of the fact that learning and motor performance seem to be closely related, conditioned reflexes can be formed even though the peripheral effects are prevented during the training period. Thus, conditioning of salivation occurred with acid (Finch, 355) and morphine (Crisler, 246) as the unconditioned stimulus although secretion was blocked by atropine during the formation of conditioned responses. Similar results were obtained in experiments in which during the conditioning period the muscles of the hind leg could not contract in response to a shock because the anterior roots of the lumbar spinal cord had been crushed. After their regeneration a flexion of the leg appeared in the hind leg on application of the conditioned stimulus (844). This experiment, however, is less decisive than the observations on salivation, since Kellogg (761) showed that the nociceptive stimulus elicited movements in other parts of the body which had not been denervated through the operative procedure. Nevertheless it seems nearly certain that the peripheral part of the afferent and efferent neurons of the unconditioned reflex is unnecessary for the conditioning process to take place.

Similar experiments were performed to determine the indispensable part of the reflex in which the conditioned stimulus is involved. Instead of exciting sensory projection areas of the cortex through optic or acoustic stimuli, the cortex was stimulated electrically by using the buried coil technique. With this procedure Loucks (872) established the conditioned reflexes of salivation and leg movement when stimula-

* As was noted earlier, conditioned reflexes can be formed on the basis of an unconditioned reflex such as the pupillary light reflex. In this case the hypothalamus would not seem to be involved unless the visual stimulus is strong enough to arouse an unpleasant emotion.

tion of the visual cortex was used as the conditioned stimulus, and he also reported a similar success with faradization of the motor cortex. The latter resulted in a hind-leg movement (conditioned stimulus) and was combined with an unconditioned stimulus (shock to the foreleg) which caused a flexion of the foreleg. After more than 200 trials the stimulus to the motor cortex induced a conditioned movement of the foreleg. Although conditioning has not yet been studied with the conditioned stimulus applied to a subcortical relay station of a sensory system whose cortical projection area has been removed, such an experiment is likely to be successful, since this area is not necessary for the development of conditioned reflexes, as experiments on partially decorticate animals indicate.

According to these investigations conditioning is the result of the interaction between the central excitatory processes set up by the conditioned and unconditioned stimuli. Such interaction can take place when the central excitation is set up by direct stimulation of the spinal cord or brain provided that the stimulation serving as the unconditioned stimulus arouses, as in the normal animal, not only afferent neural processes but also an emotional reaction. In spite of considerable experimentation and speculation the locus of this interaction is still uncertain. Hilgard and Marquis (649) suggest that it lies in an association center outside the reflex arcs set up by the conditioned and unconditioned stimuli. However, the subsequent discussion will show that the neurological events underlying conditioning vary widely in different forms of conditioning, if the results of studies are taken into consideration in which not only the classical conditioned reflex of Pavlov but various learning procedures were used.

The Nature of the Conditioning Process

Two conclusions may be drawn from these studies: (1) that whenever conditioning occurs, the unconditioned stimulus causes a central excitation, probably involving the hypothalamic system and its projection to other subcortical structures and, in the normal animal, to the cerebral cortex; (2) that the central nervous effects of the conditioned and unconditioned stimuli interact, possibly outside their own reflex arcs. The basic problem is, therefore, to determine the mechanism of this interaction, which, whether it involves an association center or not, leads to the temporary linkage of the effect induced by the conditioned stimulus with that brought about by the unconditioned stimulus. Or, to express it more specifically: How is it possible that a neutral stimulus such as a light will eventually induce salivary secretion, i.e., act on the salivary center in the medulla oblongata?

In order to arrive at a better understanding of these processes, let us again consider the previously mentioned experiment in which it was shown that the conditioned stimulus applied to the motor cortex elicited a movement of the hind leg whereas the unconditioned stimulus caused a flexion of the foreleg. In this experiment the conditioned reflex consisted in the flexion of the foreleg. Pavlov and other students of conditioning frequently observed that the original effect of the conditioned stimulus is abolished as soon as the conditioned reflex has been fully established. Thus, when a shock to the hind leg is used as the conditioned stimulus and salivation induced by food as the unconditioned stimulus, the original defensive reflex with its corollaries is replaced by salivation.* It is evident from this description that conditioning involves the inhibition of the action of the conditioned stimulus in addition to the establishment of a temporary linkage between the nervous effects of the conditioned stimulus and the center activating the unconditioned reflex.

In this connection it is pertinent to recall the previously mentioned fact that the effect of an electrical stimulus applied to the motor cortex depends on the posture of the limb reacting to the stimulus. Thus a certain cortical focus may activate the biceps complex when the elbow is fixated in extension, and the triceps complex when this joint is held in flexion. If the biceps happens to be in a state of tonic activity, it shows inhibition of its potentials whenever the triceps contracts. These considerations are applicable to spinal reflexes (von Uexküll-Magnus law [1177, 884]), since similar observations have been made by Uchtomsky (who expressed them in his theory of dominance) (1176) and by Beritoff (91). These observations have the fact in common that the intracentral effects are not solely determined by the stimuli applied but also by the distribution of the excitation within the central nervous system. Areas of increased excitability act as if they would attract impulses to such a degree that the original action is weakened or abolished and a new effect is substituted. It is through the reinforcement of the conditioned stimulus by the unconditioned stimulus that such functional connections are established and maintained.

This phenomenon is not the expression of a sudden plasticity of the neuronal organization but seems merely to indicate that any impulse, in addition to its major effect, determined by anatomical connections involving low synaptic resistance, exerts a minor action

* On demonstration of this interesting conditioning reaction in Pavlov's laboratory, Sherrington exclaimed: "Now I understand the psychology of the martyrs" (Drabovitch, 296).

which remains usually below the threshold. Changes in excitability incident to functional activation may lower the synaptic resistance in any particular part of the central nervous system and thus account for the influence of posture on movements induced reflexly or by stimulation of the motor area; in a similar way functional connections between the impulses set up by a neutral stimulus and the center of salivation are established.

It is likely that this "minor action" of an impulse becomes more marked as the state of excitability of the central nervous system is raised. Thus a mild acoustic stimulus whose action on the cerebral cortex of an anesthetized animal is confined to the auditory projection area may spread its activity under the influence of local strychninization (4) or of systemically induced convulsive drugs (467). A state of high cortical excitability furthers conditioning, as experiments with drugs such as caffeine and with hormones such as thyroid and adrenocortical extracts indicate. This may explain why certain experimental procedures which utilize avoidance reactions and reward with food are particularly effective in conditioning. Under these emotionally charged conditions cortical excitability is increased through impulses originating in the hypothalamus.

These seem to be the processes which at least in principle govern the establishment of conditioned reflexes and their loss by lack of reinforcement. However, it must be admitted that a great gap still exists between, on the one hand, the experiments involving stimulation of the motor cortex and similar reflex studies showing the modifiability of movements through experimentally controlled shifts in foci of highest excitability and, on the other, those experiments leading to the establishment of conditioned reactions. The essential difference lies in the time factor. Facilitation and inhibition may greatly alter spinal and cortical processes, but their action is abolished after a fraction of a second. On the other hand, a conditioned reaction once established may persist for months or even years. Obviously the combination of conditioned stimulus and unconditioned stimulus has left traces in the brain, but the nature of these "engrams" is unknown.

Shock Therapy and Conditioning

In Chapter 18 it will be shown that the various procedures involved in the shock therapy of mental diseases have one significant factor in common: they involve excitation of the centers of the autonomic nervous system. Since such excitation is accompanied by "upward discharges" from the hypothalamus to the cortex and since the shock-inducing procedures lead to long-lasting changes in the reactivity

of the autonomic centers, it appeared to us not unlikely that behavioral changes might be caused by insulin hypoglycemia and experimental convulsions. The method of choice to determine the validity of this assumption was the conditioned reflex, and the problem was narrowed down to the question whether conditioned reactions are modified as the result of hypoglycemic coma and convulsions.

In these studies the rat was used as an experimental animal. First, a simple avoidance reaction was established by conditioning. The sound of a bell (conditioned stimulus) lasting 2 seconds was followed by a slight shock to the grid of a compartment (A) on which the rat was standing. The sound continued until the shock had been applied. After a sufficient number of combinations of sound and shock the rat learned to jump from compartment A over a low partition into the adjacent compartment B in response to the conditioned stimulus and thus escaped the shock. After the conditioned reflex had been established, it was gradually abolished by the application of the nonreinforced conditioned stimulus. Control experiments showed that a significant spontaneous recovery of the conditioned reflex (to more than 20 per cent) did not occur. However, convulsions induced by electroshock or metrazol led to a recovery of the conditioned reflex which frequently lasted from 5 to 10 days. During this period there was a gradual decline in the frequency of the conditioned reflex. It is evident from Figure 82 that a single shock or injection of metrazol was in no instance effective and that often 3 to 5 convulsions were necessary to restore the previously abolished conditioned reflex to a significant degree. After the effect of the "shock treatment" had worn off, a new group of convulsions could be shown to restore the conditioned reflex to a similar degree several weeks later (771).

Our experiments on the effect of insulin hypoglycemia (505) were guided by the observations of Rose, Tainton-Pottberg, and Anderson (1062) that, in a sheep, conditioned reflexes which had been spontaneously lost could be restored by a series of insulin shocks. In experiments performed in collaboration with Minatoya a large number of rats were subjected to the same procedure as in the work dealing with the action of electroshock and metrazol convulsions on conditioning. It was found that insulin hypoglycemia likewise led to the restoration of previously abolished conditioned reactions but that the effect was far greater than in the work with experimental convulsions. Closer analysis showed that different degrees in the action of hypoglycemia could be distinguished. Whenever hypoglycemia caused only a "depression," characterized by an absence of spontaneous

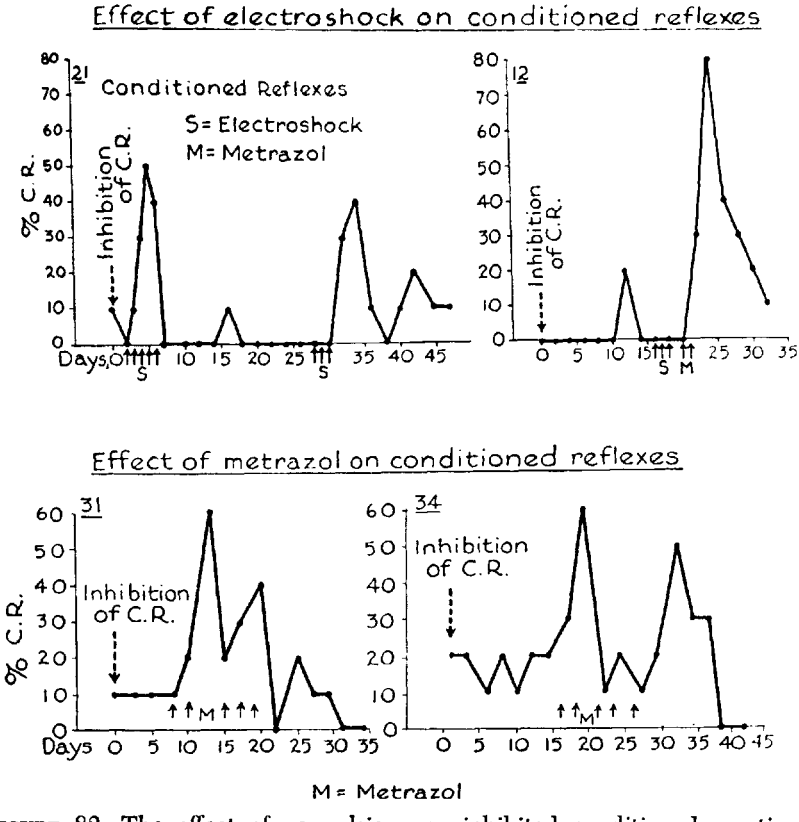

FIGURE 82. The effect of convulsions on inhibited conditioned reactions. A simple conditioned reaction was established in rats and then inhibited by lack of reinforcement. Electroshock and metrazol-induced convulsions, indicated by small arrows, restored temporarily these inhibited conditioned reflexes (C.R.). (Kessler and Gellhorn, 771.)

movements, a diminished tone of the extremities, and slow righting-reflexes, the conditioned reflexes were not restored even after the repeated application of insulin. Similarly, when convulsions were induced by insulin, the effect was negative or slight. However, insulin coma (righting reflexes and reactions to nociceptive stimuli being absent) led to a remarkable and often prolonged recovery (Fig. 83). In some cases the conditioned reaction persisted for several months without any further reinforcement.

Figure 84 gives a survey of all insulin experiments and illustrates the marked differences in effectiveness, depending on the severity of the hypoglycemic state, that exist between insulin hypoglycemias. There is a remarkable parallelism between the action of hypoglycemia

in restoring conditioned responses and the action of clinical shock therapy: insulin depression or convulsions produce in most instances very slight demonstrable action, whereas insulin coma is highly effective (Sakel, 1081).

Since it was noted that after the repeated induction of insulin comas the rats appeared excitable, the question arose whether the restitution of previously inhibited reactions was real or simply the expression

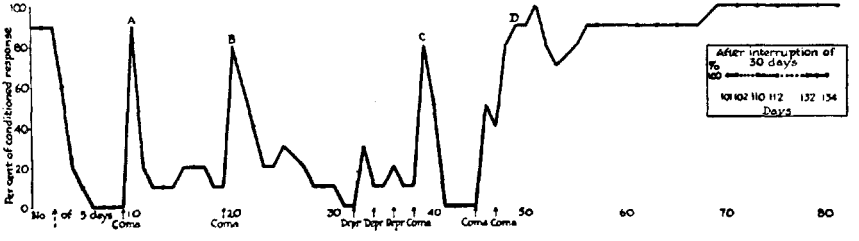

FIGURE 83. The effect of hypoglycemic "depression" (Depr.) (characterized by diminished reflexes) and of hypoglycemic coma (characterized by an absence of righting reflexes) on the restitution of inhibited conditioned reactions. The beginning of the curve shows that the conditioned response has been established in 90 per cent of the tests. Then (indicated by broken arrow) the conditioned reflex was inhibited by lack of reinforcement. In this condition coma, but not hypoglycemic "depression," led to a restitution of the conditioned reaction. The small, solid arrows indicate repeated applications of insulin. (Gellhorn and Minatoya, 505.)

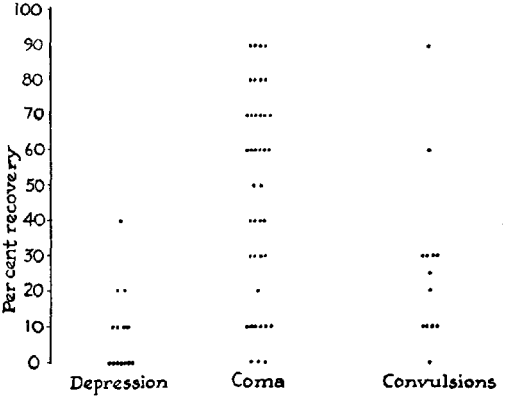

FIGURE 84. The relative efficiency of insulin "depression," coma, and convulsions on the restitution of previously inhibited conditioned reactions. The ordinate refers to the increase in the percentage of conditioned reactions following the administration of insulin. Each dot refers to an individual test. (Gellhorn and Minatoya, 505.)

of a generally increased reactivity to any environmental stimulus. It was found that rats subjected to several insulin comas without previous conditioning and inhibition of the conditioned reaction did not jump from compartment A to B in response to the bell as previously conditioned and then inhibited rats did. Apparently the "insulin treatment" can become effective only after the conditioned reaction has been previously induced and then inhibited.

A further question relates to the degree of specificity of the insulin effect. Is the restitutive effect of insulin coma confined to reactions elicited by a specific conditioned stimulus – for instance, to the sound of a bell used in conditioning the animal? The answer is yes, since after coma the bell elicited a conditioned reaction in 90 to 100 per cent of the trials whereas the effect of another sound which had not been applied before caused no significant response, the conditioned reactions varying between 0 and 10 per cent.

Further insight into the action of insulin coma is gained from experiments in which several conditioned reactions were established (449). Figure 85 illustrates an experiment in which three different conditioned reactions were formed in succession. Before a new conditioned reaction was developed, the previous conditioned reaction was always abolished by lack of reinforcement. After two insulin comas the conditioned reactions were restored temporarily but to a different degree. The conditioned reactions to acoustic stimuli re-

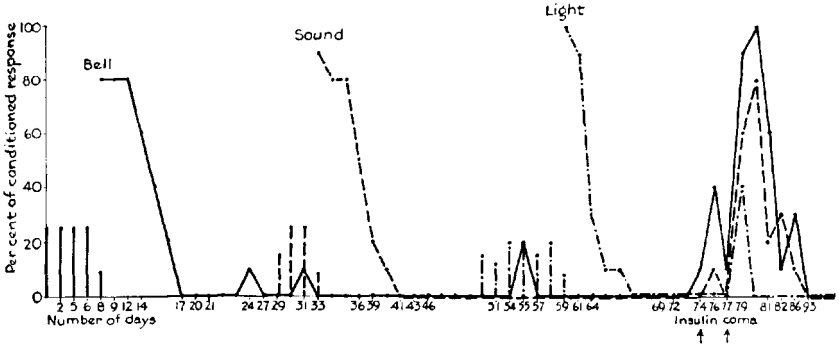

FIGURE 85. The effect of insulin coma on the recovery of three inhibited conditioned reactions. The vertical lines indicate the number of reinforced conditioned stimuli through which a conditioned reaction occurring in 80 to 100 per cent of the tests was established. Then the conditioned reaction was inhibited by lack of reinforcement. Finally insulin coma was induced in order to restore the conditioned reactions. Note that the conditioned reaction to the light recovers much less than those in response to the acoustic stimuli. (Gellhorn, 449.)

covered to a higher degree than those in which light was a conditioned stimulus, although the light-induced reaction was established last. Apparently the degree of temporary recovery of previously inhibited conditioned reactions is not related to the temporal sequence in which these reflexes have been formed. It depends rather on the stability of the conditioned reaction before its inhibition and the ease with which the conditioned reaction can be developed. The reactions to the bell were always more easily established and more slowly inhibited than the light-induced conditioned reaction (see Table 20).

TABLE 20. The Effect of Insulin Convulsions on the Restitution of Two Successively Inhibited Conditioned Reactions (Gellhorn, 449)

	Bell	Light
Number of reinforced conditioned stimuli	61	130
Degree of conditioning	100%	80%
Duration of inhibition period	49 days	9 days
Recovery of conditioned reflex through insulin convulsions	80%	40%

The unequal stability of different conditioned reactions was used as a basis for deciding whether insulin coma alters positive as well as inhibited conditioned reactions (447). If, for example, a conditioned reaction to a bell has been established and thereafter a conditioned reaction to light is produced, a lack of reinforcement may abolish the conditioned reaction to light whereas that to the bell still continues in spite of the absence of the reinforcing shock. Under such conditions it can be shown that coma restores inhibited conditioned reactions but it does not significantly alter positive established conditioned reactions (Fig. 86).

It might be thought that insulin coma would diminish both the excitatory and the inhibitory processes involved in the conditioned reaction. That the latter are weakened has already been shown by the restitution of inhibited conditioned reactions through insulin coma. The previously described experiments gave no evidence for a diminution of conditioned excitation as the result of "shock treatment," since the positive conditioned reaction seemed unaffected by it. However, the question was reinvestigated on partially conditioned animals, which might furnish a finer indicator for changes in the reactivity of positive conditioned reactions than animals in which very stable conditioned reactions had been produced. Rats which had been incompletely conditioned were injected with saline and insulin

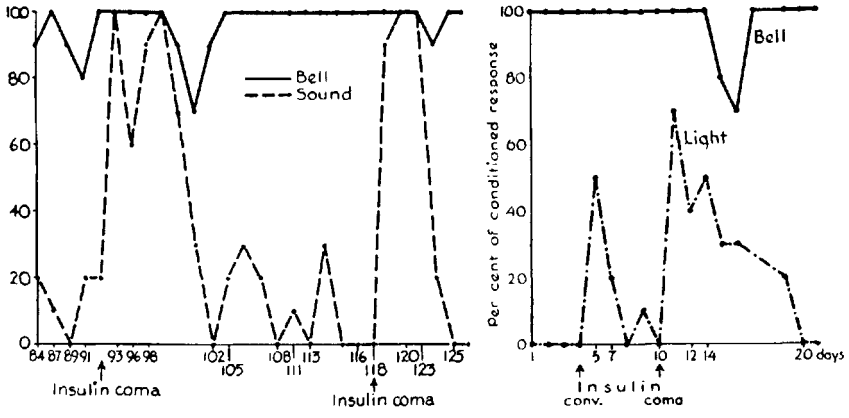

FIGURE 86. The effect of coma on the positive conditioned reaction to a bell and the inhibited conditioned reactions to a "sound" (250 vibrations per second) and to a light. (Gellhorn, 449.)

(producing coma) respectively. The saline-injected rats showed conditioned reactions in 20 per cent of the tests, and the insulin animals in 83.5 per cent (505).

If insulin coma, under the experimental conditions used, had had an inhibitory effect on the central nervous system, the percentage of positive conditioned reactions would have been smaller in the insulin than in the control group. However, the experiments led to the opposite result. The increase in the percentage of conditioned reactions induced by insulin coma in the partially conditioned animals and the restoration of previously inhibited reactions by this and other "shock" procedures show that repeated experimental convulsions and particularly insulin comas exert an excitatory effect on the central nervous system. Consequently, fully developed conditioned reactions are not altered and previously inhibited reflexes are markedly disinhibited.* This interpretation is in agreement with the classic work on conditioning according to which a disinhibition of conditioned reac-

* Rosen and Gantt (1065) studied the action of metrazol convulsions in dogs in which they had established reactions to positive and negative conditioned stimuli. After a series of convulsions the difference between excitatory and inhibitory reactions was definitely diminished. The lessened differentiation was due to partial restitution of the previously inhibited reaction in one animal while in two others this effect was combined with a weakening of the response to the positive conditioned stimulus. This loss in differentiation is commonly the result of diminished excitability and brain damage. Perhaps the convulsive treatment was too prolonged, or dogs may be more sensitive to these procedures than rats. At any rate these investigations raise the important question, To what extent does the shock treatment of mental diseases act through brain damage and to what extent through an excitatory mechanism?

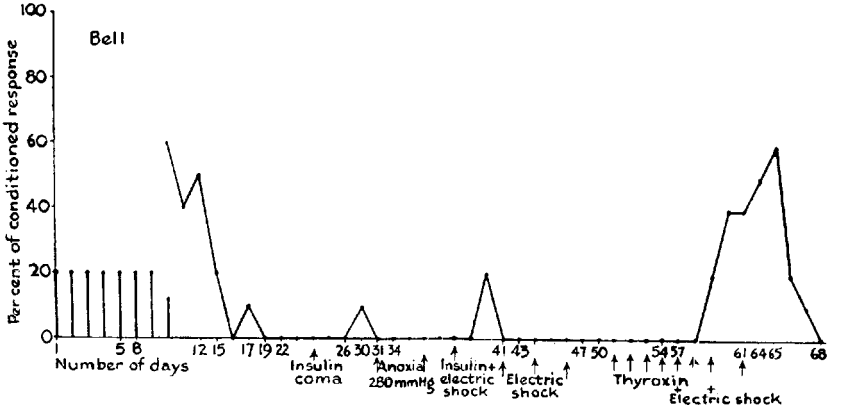

FIGURE 87. The influence of thyroxinization on the effectiveness of electroshock in restoring previously inhibited conditioned reactions. Note that in this animal neither insulin coma nor electroshock was effective, either alone or combined. However, when thyroxin was previously administered, electroshock caused the reappearance of the conditioned reaction. (Gellhorn, 463.)

tions takes place as the result of an increased excitability of the brain.*

The conclusion that insulin coma and experimental convulsions act on the central nervous system through excitation and not through depression is borne out by experiments on animals in which these procedures failed to restore previously inhibited conditioned reactions. Figure 87 illustrates an experiment in which insulin coma, electric shock, and even the combination of the two procedures were ineffective. Then thyroxin was administered. Its excitatory effect on the nervous system is well recognized, since it increases the oxygen consumption of the brain and enhances the differentiation between positive and negative conditioned stimuli. By itself it did not restore the previously inhibited conditioned reaction, but it increased the reactivity of the nervous system sufficiently so that two electroshocks were adequate to re-establish the conditioned reaction for about a week!

A final group of experiments may be briefly described in which a further attempt was made to decide whether the effect of "shock treatment" was confined to an elimination of the inhibition of conditioned responses or influenced positive conditioned responses as well. The reactions used were an inhibited and a negative conditioned reaction (450). They were similar in outward appearance and consisted in the suppression of a motor action. The inhibited reaction was the same as in our earlier work, and repeated insulin comas restored the pre-

* See Konorski (797), p. 133.

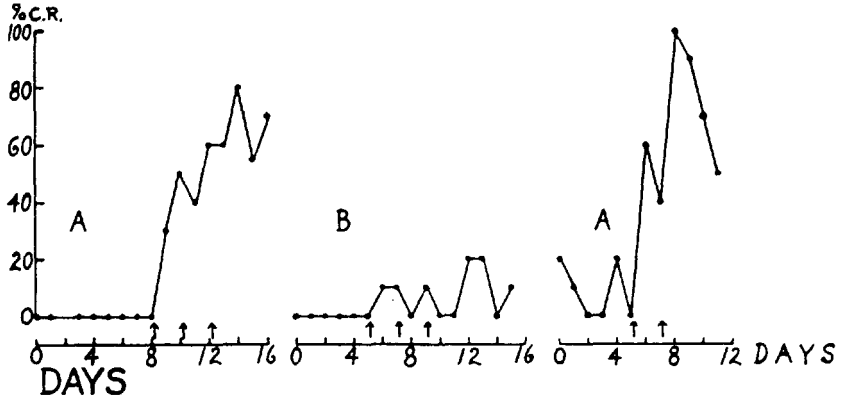

FIGURE 88. The effect of insulin coma on the recovery of the conditioned escape reaction after this reaction has been abolished by internal inhibition (A) or by application of a countershock (B). The ordinate represents the percentage of recovery of the conditioned reaction (C.R.); the abscissa, the time in days. The arrows indicate the injection of insulin, leading to coma. (Gellhorn, 450.)

viously inhibited conditioned reaction (part A of the experiment). After this effect had disappeared, the animal was again conditioned to jump from one division of the apparatus to one of the adjacent compartments in response to a bell, but thereafter this reaction was abolished not by lack of reinforcement (Pavlov's internal inhibition) but by countershock; that is, the electrical shock was applied to the grid of the two adjacent chambers when the conditioned stimulus was presented. The rat jumped, of course, into one of the adjacent compartments and was driven back through the shock into the original compartment. Repetition of this procedure for several days abolished the previous conditioned reaction and established a new negative conditioned reaction.* Thereafter insulin coma was induced in the same manner as in the first part of the experiment, and the degree of recovery of the original conditioned reaction was again determined. This section of the experiment is referred to as part B. Then the rat was retrained; that is, this conditioned reaction was again established by reinforcing the conditioned stimulus with the electric shock, and part A of the experiment was repeated.

As Figure 88 shows, insulin coma is effective in part A but not in part B of the experiment. Although the overt behavior of the animal in A and B before the "insulin treatment" is similar, since in both

* I.e., one in which the rat did not jump in response to the conditioned stimulus.

instances the rat fails to jump in response to the bell, the mechanism involved in these failures is quite different. In the conditions present in part A of the experiment the temporary association between the conditioned reaction and the conditioned stimulus still exists, although in an ineffectual form, so that, owing to the lowered excitability of the brain as a whole as a result of internal inhibition,* the conditioned stimulus is unable to elicit the positive escape (conditioned) reaction Under the influence of repeated insulin coma or similar procedures (electric shock and metrazol convulsions) these weak links between the conditioned stimulus and the unconditioned reactions are apparently intensified, and thus the original escape reaction reappears in response to the conditioned stimulus (bell).

The situation, however, in which the conditioned reaction was abolished by countershock is quite different, since a new negative conditioned reaction is substituted for the old one. The bell was the signal for an escape reaction during part A; but whereas it retained this physiologic and symbolic significance in part A, although it had lost its effectiveness owing to lack of reinforcement, it has become the signal for a new avoidance reaction in part B. Since this reaction was established under the influence of a strong unconditioned stimulus (countershock), it replaced quickly the former conditioned reaction. The new behavior was easily acquired and apparently represents a very stable conditioned reaction, in which the animal, on exposure to sound, refrains from escaping into the adjacent compartments.

If the action of insulin coma and related procedures produced an unspecific increase in the general level of excitability, it might cause an animal to react to the bell with a vigorous escape reaction in parts A *and* B of the experiment, regardless of the fundamental difference in nature between the physiologic reactions which form the basis of the behavior of the animal in the two situations. The experimental results show clearly that this is not the case. Apparently insulin coma and electrically induced convulsions have a rather specific excitatory effect on the central nervous system through (1) enhancing the development of conditioned reactions and (2) restoring conditioned reflexes which have been abolished by lack of reinforcement. The abolishment of the conditioned reaction by countershock results, in Allen's terminology, in a negative conditioned reaction. Therefore it may be said that coma and convulsions do not alter fully developed positive and negative conditioned reactions.

It will be shown in Chapter 18 that insulin coma and convulsions

* The reader is reminded of Pavlov's demonstration of the relation of internal inhibition to sleep.

act on the autonomic centers in the hypothalamus and medulla oblongata. Moreover it has previously been pointed out that increased discharges from the hypothalamus influence not only autonomically innervated peripheral structures but also the cortex of the brain. In spite of the fact that conditioned reactions can be established after decortication, the importance of the cortex for conditioning and for the complex processes of differentiation is certain. It may be concluded therefore that this increased "upward discharge" from the hypothalamus accounts for the changes in conditioned reactions that have been described in this section.

The increased sympathetic discharge is a convenient indicator of the degree and persistence of the augmented tonic activity of the hypothalamus, since "upward" and "downward" discharges frequently seem to run parallel. But it should not be assumed that the sympathetic discharge as such or the increased secretion of adrenalin which accompanies it is responsible for the altered behavior indicated by the profound changes in conditioned reactions. This is proved by the fact that the injection of adrenalin is unable to restore previously inhibited conditioned reactions in animals in which this restoration promptly occurs after repeated insulin comas (451). Furthermore it was shown that adrenodemedullation does not interfere with the restitution of inhibited conditioned reactions by hypoglycemic coma. The demedullated animals still react with increased hypothalamic-cortical discharges to insulin comas in spite of the lack of secretion of adrenalin. On the other hand, the injection of adrenalin in small doses does not elicit a hypothalamic-cortical discharge, but rather diminishes the excitability of the hypothalamus (254, 479). It is therefore not surprising that adrenalin cannot restore inhibited conditioned reactions.

The importance of increased hypothalamic discharges as the result of "shock therapy" has been stressed throughout this discussion. A depression of the central nervous system and particularly of the hypothalamus would be expected to interfere with these processes. In this connection it is of interest that barbiturates abolish the effectiveness of electroshock in restoring previously inhibited conditioned reactions. Moreover electroshock no longer elicits a pressor response as in unanesthetized animals, but calls forth a fall in the blood pressure owing to the predominance of parasympathetic (vagal) excitation (1099). The centrally induced sympathetic "downward discharge" and the hypothalamic-cortical "upward discharge" are apparently interrelated. Factors which raise central autonomic excitability (various forms of shock therapy, thyroxin) facilitate the restitution of condi-

tioned reactions and sympathetic discharges, while barbiturates abolish both processes (447). On the other hand, conditions which eliminate some of the peripheral actions of sympathetic discharges through adrenodemedullation do not interfere with the action of electroshock etc. on conditioning.*

The Cortex and Conditioning

Contrary to Pavlov's original assumptions, it has been demonstrated in his own laboratory and also by other investigators that conditioning takes place after complete decortication or after surgical removal of the sensory projection area involved in the action of the conditioned stimulus. However, it cannot be inferred from these experiments that the cortex plays only a subordinate role in conditioning, for two reasons. First, it can be shown that a change in the excitability of the cortex may influence even a subcortical conditioned reflex. Martino (904) reported that the intensity of a conditioned blink reflex is intensified by strychninization of the occipital cortex. Second, experiments involving cortical lesions demonstrate that the cortex alters both the pattern of the motor response of the conditioned reaction and the type of sensory stimuli which can be used as effective conditioned stimuli. Whereas during the development of the conditioned defensive (flexor) reflex a generalized excitation appears at first in the form of widespread movements and vocalization, it is gradually replaced by a more adapted conditioned reflex in which the movements are confined to the extremity to which the unconditioned stimulus has been applied. Such adaptive reactions do not occur after decortication (Girden *et al.*, 548).

Similar observations have been made by Allen (21), who noted that the specific flexor responses to odoriferous stimuli disappear after bilateral removal of the motor cortex. The generalized reactions seemed to this author more the expression of a state of general excitation than of a specific conditioned reaction. In lower forms such as pigeons, however, Beritoff (90) found no differences between the conditioning process before and after decortication except that the conditioned reaction did not persist as long in operated as in normal animals.

Since the extensive studies of Klüver (783) on monkeys with bilateral removal of the occipital lobes will be discussed in Chapter 17, a brief statement may suffice here. Even in the monkey conditioned responses to optical stimuli are not abolished after the elimination of the geniculo-striate system. The animals remain sensitive to stimuli of

* For further details see bibliographical entry 463.

very low intensity and retain the ability to differentiate between two luminous stimuli differing in intensity. However, conditioned responses to differences in hue or shape seem to be permanently lost and cannot be re-established in monkeys after bilateral occipital lobectomy.

Klüver's work shows clearly that certain conditioning processes remain intact after removal of the cortical projection areas on which the conditioned stimulus acts. Since conditioning to light occurs in the dog not only after removal of the occipital cortex but also when additional large portions of the adjacent regions of the gray mantle are eliminated (1150), it follows that certain visual (as well as auditory) reactions can be conditioned through subcortical structures. In the normal organism, however, the cortex seems to play an important role in influencing the motor behavior in conditioning and in extending the range and complexity of sensory stimuli which may be utilized for the development of conditioned reflexes.

Another important group of cortical ablation experiments were performed by Allen in dogs which had been trained or were retrained postoperatively to different conditioned stimuli involving auditory, cutaneous, and olfactory receptors. In agreement with previously described experiments it was found that lesions confined to the cortical projection areas or extending over large parts of the cortex in addition to the specific lesions had little effect on the ability of the animals to acquire positive conditioned reactions. However, the differentiation between a positive conditioned reflex, indicated by a flexion of the foreleg, and a negative conditioned reflex, in which the animal refrained from this specific activity on presentation of the conditioned stimulus, was greatly altered by cortical lesions. Thus the differentiation between two different odors the first of which (clove vapor) served as a conditioned stimulus for a positive response and the second of which (asafetida) was used as the conditioned stimulus for a negative conditioned response was lost after bilateral extirpation of the pyriform and amygdaloid areas. These operations did not interfere with the acquisition of positive conditioned reflexes. Such dogs had no difficulties in locating paper bags filled with meat among others of similar size and texture when sight was excluded. On the other hand, large cortical lesions not involving the above-mentioned areas did not interfere with olfactory differentiation. Apparently, specific parts of the temporary lobe are involved in olfactory differentiation (22, 23).

Allen made further important contributions to the localization of association areas specifically connected with certain sensory impulses.

Dogs in which the primary (A) and secondary (B) auditory projection areas were removed bilaterally could be reconditioned to respond positively or negatively to acoustic stimuli, but it took many more tests than in control animals or in dogs in which only a part of the auditory projection area had been removed. If in addition a small, more anteriorly located area (C), which has been identified as a third auditory projection area (1174) and which seems to include at least part of a second cortical tactile field (1247), was eliminated, the differentiation between positive and negative acoustic stimuli was lost (24).

Cutaneous stimuli were not affected in their role as conditioned stimuli for positive and negative conditioned reflexes by removal of areas A and B, although such lesions considerably delayed differential auditory reactions. On the other hand, lesions confined to C delayed cutaneous but not auditory conditioned reflexes. Finally, lesions affecting B and C abolished cutaneous but not acoustic differentiation (25).

Three important conclusions can be drawn from this work: (1) Negative conditioned reflexes cannot be established after certain specific cortical lesions which do not interfere with the retention or establishment of positive conditioned reflexes. (2) The cortical association areas represent only a fraction of the specific sensory projection areas. (3) There is an overlap between association and projection areas.

There is, however, a large mass of data which do not fit into this general scheme. As is well known, the conditioned reflex in the form of the conditioned salivary or defensive reaction represents only one of many procedures which may be employed for gaining further insight into the learning process. Psychologists have used avoidance reactions, mazes of many different kinds and degrees of complexity, latch boxes, etc., for assessing the learning abilities of experimental animals. In such studies the reward is either food or escape from pain.

In a fascinating paper (822) Lashley discusses the results of thirty years' work "in search of the engram" and considers the various attempts made to delimit the nervous structures which are involved in the development and retention of conditioned reactions. In experiments on rats the animals were trained to react to complex visual stimuli by jumping toward one stimulus but not toward another. Surgical procedures which interrupted conduction paths from the occipital cortex to the motor area did not interfere with these learned reactions. Even in the monkey no evidence could be obtained that cortical association areas are necessary in order to perform difficult conditioned reactions. First, it was found that extensive bilateral

destruction of the motor cortex did not abolish permanently the manipulative skills which are required to open a latch box. Second, it was observed that visually induced conditioning which led to the opening of the latch box in response to specific visual stimuli was retained after cortical lesions surrounding both primary visual projection areas. Apparently in rats and monkeys conditioning may be established without specific cortical association centers. In the experiments of Lashley a temporary linkage is developed between the sensory projection area in the cortex and a specific willed movement, and he assumes that only the specific projection area and subcortical structures regulating complex movements are involved.*

How is the work of Allen to be reconciled with that of Lashley? Are cortical association areas involved in conditioning? These questions are as important as they are difficult, and the answer is by no means certain, but some suggestions which may have at least a heuristic value may be advanced.

The conditioned reaction in Allen's work consists in flexion of the foreleg, whereas in Lashley's it involves a series of complex movements leading to the opening of a latch box by the monkey or, with the rat, resulting in maze running or jumping. Since the sensory phase of the reaction is similar in the experiments of both investigators and is based on sensory discrimination, it is not improbable that the different motor tasks play an essential part in the discrepancy of the results.

When the flexor reaction is compared with the movements used in the opening of a latch box, the former appears to be simpler; but is this not a rather superficial way of looking at these experiments? The classical conditioned reflex, whether salivation or flexion of a leg is taken as the indicator, is a highly complex experiment, performed under very artificial conditions. This is true not only because the dog is restrained but also because even a simple conditioned reflex requires the development of complex inhibitory processes in addition to the establishment of a functional connection between the central nervous processes initiated by the application of the unconditioned and conditioned stimuli. At the beginning of the training period the unconditioned stimulus evokes generalized movements, vocalization, and changes in the respiration and pulse rate, but as the conditioning

* Since no experiments seem to have been performed with extirpation of the motor cortex *and* lesions surrounding the visual projection area, the participation of the former in the conditioned reaction is not excluded in those monkeys which were solely subjected to the second operation. However, this argument does not invalidate Lashley's main thesis against the role of cortical association areas in conditioning.

progresses, these unspecific effects disappear and the response becomes confined to the leg to which the unconditioned stimulus has been applied. It is suggested that this suppression of unspecific reactions is of cortical origin. This interpretation makes it understandable that completely decorticate animals should react to conditioned stimuli only with a generalized orientation reaction, although elimination of the sensory projection area of the conditioned stimulus does not interfere with the formation of conditioned reactions to light, sound, smell, etc.

The building of positive *and* negative conditioned reactions within the same sensory modality requires even more specific cortical inhibitory processes. According to Allen's experiments these association areas are adjacent to the sensory projection areas but apparently not identical with them. The development of conditioned reactions in maze learning, manipulating latch boxes, and pulling in food boxes on the basis of certain sensory cues, on the other hand, takes place without external restraint. The movements of the animal are performed in a natural way even when the opening of a box requires a complex sequence of actions. Such movements can be conditioned after bilateral extirpation of the motor cortex in the monkey, but, curiously, the apparently simple flexion of the foreleg to different sensory stimuli disappears after this operation, even in the dog, an animal in which the cortical control of movements is of much lesser importance.

It seems to follow from this discussion that sensory discriminations of varying degrees of complexity can be conditioned through the activation of primary projection areas and subcortical motor mechanisms (Lashley). However, the conditioned flexor reflex requires, particularly for the maintenance of positive and negative conditioned reactions, at least one cortical motor area. It is further suggested by Allen's work (21) that specific "association areas" are activated in the differentiation of conditioned reflexes in which the flexion of the leg is used as an indicator.

Obviously this discussion has by no means clarified the numerous problems raised by Lashley; it has, however, brought out the importance of the cortex in *delaying* action, for this is the outstanding symptom of negative conditioned reflexes. It makes one wonder whether the classical conditioned reflex experiment illustrates under simplified but somewhat unphysiological circumstances the fact that delaying action – a prerequisite of intelligent behavior – requires cortical activity, particularly under such trying conditions as in Allen's conditioned reflex experiments, in which lack of differentiation is severely penalized.

Hormones and Conditioning

It is well established by clinical experience that the activity of the central nervous system is altered in conditions of dysfunction of the endocrine glands. Such circumstances seem to affect also the cortical level, as indicated by changes in the EEG. Several authors have shown that the alpha frequency increases upon the administration of thyroxin. The metabolic rate and the alpha frequency appear to be correlated in myxedema and hyperthyroidism (623). Patients with Addison's disease show slow cortical rhythms, which may be alleviated by the injection of glucose and adrenocortical extracts. Parathyroidectomy has likewise been found to affect the frequency of the EEG. These examples may serve as an introduction to a brief discussion of the influence of the endocrines on conditioned reactions.

In spite of the publication of a fairly large number of papers* dealing with the action of endocrine extracts and removal of the glands of internal secretion on conditioned reactions it is difficult to draw valid conclusions. This in part is due to the fact that the number of conditioned animals used in the individual investigation has often been not more than two and the completeness of certain operations (hypophysectomy) has not always been checked. Also different species and widely different techniques have been used, with the result that direct comparisons become rather hazardous.

In the recent literature the work of Anderson (35) seems more complete than that of earlier workers. It was found that removal of the hypophysis practically abolishes conditioned salivary and flexor responses in dogs. The administration of anterior and posterior pituitary extracts has only a slight and temporary effect. Thyroid extracts restore these reflexes to a considerable degree, so that at least an essential part of the effect of hypophysectomy seems to be due to the diminished function of the thyroid gland. Since adrenalectomy likewise causes a great reduction in the percentage of conditioned reflexes which can be established, it is likely that the diminished function of the adrenal cortex and thyroid accounts primarily for the profound influence of hypophysectomy on conditioning.† Whether ACTH restores the lost conditioned reactions remains to be seen. That the effect of hypophysectomy is primarily or exclusively due to the absence

* See Hilgard (649) and Anderson (35) for further references.

† These results are somewhat contradicted by the earlier work of Kriaschew (804), who reports conditioned reactions to sounds after hypophysectomy. The records show, however, that the conditioning consisted only in a generalized reaction to the stimulus and not in a specific flexor reflex. This author claims that differentiation is established with the first nonreinforced sound (of a different frequency)! But even in this work the generalized conditioned reactions were weak, since they were abolished by two or three nonreinforced stimuli.

of the anterior lobe is suggested by the observation that removal of the posterior pituitary does not influence conditioned reflexes.

It was mentioned that removal of the thyroid greatly reduces conditioned reflexes (35, 1257, 1258). A similar effect is seen after partial thyroidectomy, but in contradistinction to the effect of complete removal of the gland, this reduction is only temporary and disappears in the course of several months (35). In most instances the administration of thyroid extracts to normal animals increases the magnitude of the positive conditioned reactions and shortens the latent period, although it intensifies the unconditioned reaction only slightly.

In contrast to the effect of thyroidectomy or hypophysectomy, the effect of removal of the gonads is relatively slight and consists largely in a retardation of the conditioned reaction. It is interesting that these reactions are greatly augmented during estrus. Observations (on one dog only) have shown that bilateral adrenalectomy markedly reduces conditioned reactions and that they can be restored to a considerable degree by the administration of cortical extracts.* It may be added that adrenocortical hormones greatly benefit animals with experimental neuroses (36), whereas thyroxin or thyroid extracts, which increase conditioned reactions in normals, have no effect on conditioned reactions in neurotic animals.

Andreyev and Pugsley (39) have clearly shown that the injection of parathyroid hormone reduces the intensity of a positive conditioned reaction and strengthens the effect of a negative one. The strengthening may be inferred from the fact that the application of the inhibitory conditioned stimulus has a tendency to induce drowsiness and to weaken or abolish the action of conditioned stimuli to which the animal previously reacted with a vigorous salivary secretion. Moreover the extinction of conditioned reactions by lack of reinforcement proceeds much faster after the chronic administration of parathormone than under control conditions. The work provides evidence for a causal relation of these changes to the increased level of calcium in the blood. The reduction of neuronal excitability through an excess of calcium is well established for the isolated nerve, the hypothalamus, and the organism as a whole, since drowsiness and sleep have been produced by hypercalcemia resulting from the injection of calcium salts or parathormone. This lowering of excitability is apparently also characteristic of the highest level of cortical activity, where it leads to a diminution of positive conditioned reflexes and an augmentation of negative conditioned reflexes.

* It appears to be doubtful whether the effect of adrenalin in rather large doses on conditioned reactions in normal and neurotic animals is related to the physiological action of this hormone (37).

Concluding Remarks

Although our knowledge of the relation between internal secretion and conditioning is still in its infancy, it cannot be doubted that hormones modify conditioned reactions and thereby behavior. It may suffice just to mention the profound influence of the sex hormones on human and animal behavior (77) and to call attention to the significance of endocrine disturbances for neuropsychiatry (106). The dependence of endocrine secretion on the hypothalamus and on the sympathetico-adrenal system, reported earlier, seems to be a sensitive mechanism not only for providing increased amounts of specific hormones to meet the demands of the tissues but also for preventing a fall in the hormone level such as would endanger cortical reactions. This interpretation seems warranted by the fact that hormonal imbalance affects conditioned reflexes more decisively than it does unconditioned reflexes. The mobilization of hormones through nervous and non-nervous mechanisms appears to contribute to the homeostasis of cortical functions.

It has also been shown that conditioned reactions may be modified through alterations in the excitability of cortical and subcortical structures. An obvious consequence of these findings is the possibility of changing conditioned reactions through drugs. Considerable experimental material along these lines has been accumulated in recent years (357, 410, 1239).

The effects of the various procedures involving cortical lesions illustrated in Allen's and Lashley's work and the results of experiments on insulin coma have been stressed because such studies contribute to our fundamental knowledge of conditioned reactions and are of importance for neuropsychiatric research. It should not be forgotten, however, that the essential processes underlying conditioning cannot as yet be expressed in strictly neurophysiological terms. The new attempt made by Konorski (797) to explain conditioning through growth processes in the central nervous system can hardly be considered a success. But the situation is not very different in this area of research from what it is in many other sections of physiology. Few if any reactions are intimately understood. Nevertheless, data are at hand sufficient for the performance of quantitative investigations and giving enough insight into the physiology of conditioning so that correct predictions can be made.*

* Moreover both normal and abnormal behavior have become accessible to controlled experimentation through Pavlov's work. For the many interesting aspects of this field of research the reader should consult the writings of Pavlov (996), Liddell (36), Gantt (411), Masserman (906), and Anderson (37).

~ 16 ~

Homeostasis

THE concept of homeostasis is so widely used in physiology and medicine that a detailed explanation of the meaning of the term is hardly necessary. Suffice it to say that it was one of Claude Bernard's major achievements to recognize that the composition of the blood and tissue fluids is kept within narrow limits. This relative constancy of the "internal environment" is called homeostasis (Cannon, 191a, 194).

Ontogenetic and Phylogenetic Aspects

There are marked differences in the degree to which homeostasis has been developed in various organisms. One could speak of phylogenetic and ontogenetic development of homeostatic functions. In certain invertebrates which inhabit the ocean the acidity of the body fluids depends largely on that of the external environment, whereas it is fairly constant in the mammalian organism (429). This stability is due not only to the complex buffer system (425) of the blood, which resists alterations in *p*H more than the body fluids of lower forms, but also to the fact that variations in respiratory activity and in the excretion through the kidney contribute to the relative constancy of the *p*H of the blood. Thus the regulation of respiration by carbon dioxide and the lowering of the *p*H in the chemoreceptors of the sino-aortic area and in the respiratory center make it possible to dispose of the excess of carbon dioxide through the respiratory passages. Acids and alkalis may also be excreted through the kidney, the result being wide variations in the *p*H of the urine while the *p*H of the blood remains unchanged. Similarly it is seen that the osmotic pressure of the body fluids is variable, that of the blood plasma (but not of the urine) constant.

Constancy in the body temperature is an achievement of birds and

mammals, which are sharply separated from the poikilothermic group. Even in mammals, however, homoiothermia is present to a much greater degree in higher than in lower forms. Exposure to anoxia may result in a fall in the body temperature of 3 to 5 degrees centigrade in mice (493), but very little change occurs in dogs or in man. There is evidence of an ontogenetic development of homeostatic functions as well, since control of the body temperature is notoriously poor even in the human infant.

Homeostasis and the Endocrines

Constancy in the internal environment is achieved through nervous and non-nervous mechanisms. The buffer capacity of the plasma and the chloride shift between red blood corpuscles and blood plasma are examples of the non-nervous mechanisms of homeostasis. So is the removal of an excess of a physiological compound of the blood by inundation or segregation (Cannon, 191a). Thus glucose may be temporarily stored in the skin before it is retained by liver and muscle in the form of glycogen. Similarly it is found that water passes from the gastrointestinal tract into the subcutaneous connective tissue, muscle, and liver while the blood retains its freezing point with considerable accuracy. The great importance of the liver for the constancy of the blood sugar is evident from perfusion experiments which show that, depending on the glucose level of the perfusate, the liver becomes either the donor or the recipient of glucose. After hepatectomy the blood sugar falls continuously, and the injection of an excess of glucose leads to a greater hyperglycemia than in the normal animal (Mann, 893). A reduction in the concentrations of blood proteins leads to their replenishment from the liver, as indicated by the marked delay in this process in a dog with an Eck fistula or liver damage. Obviously the excretory function of the kidney, set for a certain threshold of physiological substances such as glucose, also plays a dominant role in homeostasis.

The endocrine glands are important for the maintenance of a constant internal environment. Insulin, which aids in the utilization of glucose and its conversion to glycogen, seems to be produced in greater quantities on a high carbohydrate than on a fat diet, and inanition is accompanied by a low insulin content of the pancreas (Haist, 96, 587). As experiments on the isolated pancreas show (Anderson and Long, 32), the rate of insulin secretion increases with an increasing glucose concentration of the perfusate and contributes thereby to homeostasis. The secretion of the parathyroid hormone is indirectly related to the calcium level of the blood. A diet low in

calcium or conditions such as pregnancy in which the demand for calcium is increased lead to hyperplasia of the parathyroids. The latter is the anatomical expression of an increased mobilization of calcium through compensatory hypersecretion of parathormone. The lowered level of the blood calcium acts directly on the parathyroid gland without involving the hypophysis (Carnes *et al.*, 210).

The level of several hormones in the blood is kept constant through a mechanism which appears to be as simple as it is effective. It is based on the fact that the rate of secretion of the "trophic" hormones of the anterior pituitary is chiefly determined by the blood and tissue concentration of the hormones of their target organs. If the concentration of the ovarian hormones and of androgen in the blood and tissues is lowered, an increased secretion of the gonadotrophic hormones from the anterior pituitary is elicited. Their action on the gonads restores the concentration of the sex hormones in the tissues.* Thus in parabiotic rats ovariectomy in one animal induces hypertrophy in the ovaries of the other rat owing to hypersecretion of the gonadotrophic hormones. The diminished concentration of ovarian hormones seems to be responsible for this homeostatic reaction, since the injection of estrogens prevents this effect (633). Similarly Moore and Price (943) showed that the injection of androgen causes atrophy of the testes of normal animals through inhibition of the secretion of the gonadotrophic hormones.

It was also noted that the secretion of the adrenotrophic hormone is initiated by a lowering of the concentration of the adrenocortical hormones in the tissues (Sayers, 1093). The lowest values for adrenotrophic hormone assay in the adenohypophysis was found in adrenalectomized animals; that is, the rate of secretion of ACTH was maximal when the hormone activity of the target organ was nil. On the other hand, if the level of adrenocortical hormones is raised in the tissues, the secretion of ACTH ceases even under conditions of stress.†

The same mechanism applies for the regulation of the thyroxin level of the blood, which determines the rate of secretion of the thyrotrophic hormone. Thus Astwood (45) showed that drugs such as thiourea which abolish the synthesis of thyroxin in the thyroid and thereby lower the thyroxin concentration in the blood lead to a hypertrophy of this gland provided that the anterior lobe of the hypophysis is functioning.

Since the rate of replenishment depends on the rate of hormone

* That central excitatory processes may also lead to hypothalamic-hypophysial discharges which are independent of the concentration of the hormones in the tissues is discussed in Chapter 13.

† See p. 323.

consumption, this mechanism maintains the physiological hormone level at rest as well as during activity or under conditions of alteration in the external environment (cold, etc.) which greatly increase the rate of hormone consumption by the tissues. If such conditions persist for prolonged periods, homeostasis is maintained through increased hormonal production and leads to hyperplasia of the activated organs.

It is of great interest to add that the rate of secretion of various pituitary trophic hormones may vary independently. If the thyroxin level is lowered in the blood, the secretion of the thyrotrophic hormone is increased, but that of the gonadotrophic or adrenotrophic hormone is not altered unless conditions are imposed upon the organism which influence the level of the adrenocortical or sex hormones in the blood and tissues at the same time (Dempsey and Searles, 276). Obviously the precision and specificity of these regulations contribute greatly to the hormonal constancy of the internal environment.

The Role of the Sympathetico-Adrenal System

In addition the central nervous system plays an important role in adjustment reactions designed to maintain or restore the internal milieu. The action of the sympathetico-adrenal system under these conditions has been stressed by Cannon and his school. He showed that changes in the chemical or physical characteristics of the blood induced by anoxia, hypoglycemia, hemorrhage, cold, fever, and other conditions call forth a sympathetico-adrenal discharge, and he interpreted this reaction as beneficial for the functional restoration of the organism in conditions of stress (191, 193).

A brief survey may suffice.* Hemorrhage leads to a sympathetically induced contraction of the spleen which makes available the stored erythrocytes and increases thereby the oxygen capacity of the circulating blood and consequently the oxygenation of the tissues. After the loss of blood hyperglycemia occurs as the result of a sympathetico-adrenal discharge, a reaction which may be of great restitutive value since the increased blood sugar tends to offset the effects of deficient oxygenation on the brain (498). The faster coagulation of the blood in hemorrhage is said to result chiefly from the action of secreted adrenalin on the liver, although it is present, to a small degree, after elimination of the adrenal medullae. The maintenance of the blood pressure in moderate bleeding is due to sympathetico-adrenal discharges initiated by a fall in the pressure in the sino-aortic area. The increased rate of secretion of adrenalin has been assayed directly or may be gauged by the increased rate of the denervated heart. Freeman

* For details and literature see Gellhorn, *Autonomic Regulations* (446).

showed that as the blood pressure is restored by the injection of saline or acacia solutions, the denervated heart returns to its normal rate (386a).

That hemorrhage induces a generalized sympathetic discharge in addition to the sympathetic discharges already mentioned is evident from piloerection, sweating, and vasoconstriction. The last affects the abdominal blood vessels to a greater degree than the blood flow through the extremities. The vasoconstriction extends to the large veins which return the blood to the heart and thus contributes to an adequate filling of this organ. The venomotor reflexes are of sino-aortic origin.

The homeostatic value of these reactions is shown by the fact that procedures which interfere with the sympathetico-adrenal discharges greatly increase the fall in the blood pressure and the fatality of hemorrhage. This is seen in animals which have been sympathectomized or in which the sino-aortic receptors have been eliminated.

Similar changes occur in anoxia. A sympathetico-adrenal discharge appears in anoxia no matter whether that is induced by a lowering of the barometric pressure, the inhalation of oxygen-nitrogen mixtures, or carbon monoxide poisoning. The increased blood pressure in anoxia is initiated by the chemoreceptors of the sino-aortic area (502). Impulses from these receptors enhance the reactivity of the hypothalamus. A standard stimulus applied to this area causes a greater pressure response in anoxia than under control conditions. On the contrary, a diminished hypothalamic reactivity is seen in anoxia after the sino-aortic receptors have been eliminated (475).

Asphyxia, which is characterized by deficient oxygenation of the tissues and an accumulation of carbon dioxide, is a particularly powerful stimulant of the sympathetico-adrenal apparatus. This is important from the standpoint of homeostasis, since circulatory failure results in asphyxia.

This fact has been established in cases with pneumonia and decompensated valvular lesions: in both instances severe anoxia is associated with a retention of carbon dioxide. It is interesting to note that whereas anoxia leads to increased sympathetic discharges only in animals in which the sino-aortic reflexes are intact, asphyxia also excites the sympathetic centers directly. Whereas anoxia leads to a fall in the blood pressure in the sino-aortic denervated dog, asphyxia still induces a pressor reaction in this animal. Furthermore the fall in the body temperature is greater in asphyxia than in anoxia (437), a phenomenon of importance since the oxygen consumption of the tissues is directly related to the temperature. These reactions make it

seem justified to look upon asphyxia as a final attempt toward homeostasis (438–440).*

Since hypoglycemia reduces the rate of oxidation in the brain, it is not surprising that its effect on the autonomic centers is similar to that of anoxia and asphyxia. Increased discharges of adrenalin account for the augmented rate of the denervated heart in insulin hypoglycemia. Through biological assays it is known that the adrenalin content of the blood is increased. Denervated blood vessels which are hypersensitive to adrenalin were shown to contract during hypoglycemia in man. A frequently used indicator of adrenalin secretion is the contraction of the denervated nictitating membrane of the cat. This reaction remains positive after denervation of the adrenal medullae and is interpreted as an indication of sympathin released from the endings of the discharging sympathetic system.

Since neither the pressoreceptors nor the chemoreceptors are excited in hypoglycemia, the increased sympathetico-adrenal discharge appears to be due to the direct action of hypoglycemia on the autonomic centers of the sympathetic system. This was proved by the fact that the vasomotor center shows an increased pressor response to chemical stimuli such as carbon dioxide even after the elimination of the sino-aortic nerves (500). The importance of the sympathetico-adrenal discharge in hypoglycemia is evident from the observation that adrenodemedullation or sympathectomy greatly increases the sensitivity of the organism to insulin hypoglycemia.

The Significance of Homeostasis for the Heart and Brain

The significance of the homeostatic regulations in general and those mediated by the sympathetico-adrenal system in particular lies in the fact that they tend to maintain an adequate circulation through the heart and brain in adverse conditions. The restraint of the sino-aortic depressor reflexes resulting from a fall in the blood pressure as, for example, in hemorrhage, and the activation of chemoreceptors in anoxia contribute to homeostasis through an increased respiratory activity and a rise in the blood pressure. The latter occurs at the expense of the blood supply to the abdominal organs and provides the heart and brain with indispensable oxygen. The output of the heart depends on the coronary circulation, and the latter depends on the blood pressure. Adrenalin plays an important subsidiary role by dilating the coronary vessels and increasing the minute volume of the heart.

The circulation through the brain depends primarily on the blood

* For further details see Gellhorn, *Autonomic Regulations* (446), Chapter 5.

pressure. Since a diminution of the pressure in the carotid sinus increases the blood pressure and consequently the circulation in the brain and heart, these organs may be considered to be the beneficiaries of the sino-aortic reflexes. To express the matter somewhat anthropomorphically: in times of scarcity the essential materials are distributed unequally in order to meet the demands of those organs on whose uninterrupted adequate function the continuity of life depends.

There is an important corollary of this statement: severe disturbances of brain function take place when homeostasis cannot be maintained any longer. If water is administered in excessive quantities so that excretion and storage in subcutaneous and other tissues become inadequate, the altered internal environment elicits dangerous symptoms on the part of the central nervous system. Water intoxication results in coma and convulsions, accompanied by marked changes in the EEG (465). Dehydration, on the other hand, may cause fever and mental disturbance. That these symptoms are not solely due to a change in the distribution of water in the body and that other changes in the composition of the internal milieu invariably follow (e.g., changes in the salt content) is of minor importance for the present argument.

If the blood sugar falls below a critical level, coma and convulsions occur. Since a fall in the blood sugar is easily regulated by insulin and the induction of coma is used clinically, the development of the symptoms of hypoglycemia is well known. It seems to show that the phylogenetically youngest parts of the brain (the neocortex) are first affected and that as the degree and duration of hypoglycemia increase, the brain stem becomes involved until with the advent of medullary symptoms (respiratory failure, etc.) life becomes endangered (660). At this time or even earlier convulsions ensue.

An excess of sodium induces fever; a deficiency is accompanied by weakness and finally paresis. A calcium deficiency leads to twitching and convulsions, which are only in part of peripheral origin; a calcium excess (induced by the injection of calcium salts or parathyroid extracts) results in shock. Decreased oxygenation of the blood ultimately produces coma and convulsions. They are preceded, as in hypoglycemia, by states showing a progressive involvement of cortical functions. Finally, it may be remembered that increased temperature leads to delirium, whereas hypothermia is associated with coma.

This brief enumeration of the symptoms following gross alterations in the physical or chemical composition of the blood shows an amazing uniformity in the physiological effects: coma and convulsions. In

those instances in which investigations are available on the cerebral changes (particularly in anoxia and hypoglycemia) a gradual deterioration of cortical activity is evident. With the disappearance of alpha and fast potentials in the EEG delta waves become increasingly prominent as consciousness declines, and finally convulsions occur. It is obvious that the cortical functions suffer first. As Barcroft (65) pointed out in his Terry lectures, the development of the neocortex would have been impossible without the perfection of the mechanisms underlying homeostasis.

Homeostasis as an Organismic Reaction

It follows from this discussion that homeostasis is maintained through a truly organismic reaction. The ability of certain tissues to store temporarily substances present in the organism in excessive quantities and to release them under converse conditions, the regulation of the secretion of insulin by the blood sugar level, the ability of the kidney to remove foreign substances from the blood and to regulate the excretion of water and inorganic as well as organic substances, and the maintenance of the physiological level of the hormones through regulation of the rate of secretion of the trophic hormones are some of the chief processes which contribute to homeostasis. It should be emphasized that these all-important reactions are the result of complex integrations* involving tissue reactions, the endocrines, and the autonomic and somatic nervous system as well. Thus the fact that the glucose concentration in the perfusate regulates the rate of insulin secretion in the isolated perfused pancreas is not in contradiction with findings on the influence of the vagus on the secretion of this hormone in the intact organism. It merely illustrates one of the common characteristics of physiological organization, namely, that more than one mechanism may serve the same biological purpose.

The separation of nervous and endocrine factors is not infrequently difficult. The excretory functions of the kidney are not interfered with by denervation of this organ, but the quantity and osmotic pressure of the fluid which is reabsorbed in the tubules are regulated by the antidiuretic hormone, which in turn depends on the activity of the supraoptic nuclei in the hypothalamus! The somatic nervous system is likewise involved in these regulatory processes. The contribution of shivering to the maintenance of the temperature of the body in cold and the relaxation of the muscles and the unwillingness to engage in bodily activity in heat are well known. Richter's remarkable studies

* See Barcroft's interesting discussion (64) on these problems.

(1047) have shown that rats subjected to endocrine or nutritional disturbances select instinctively the appropriate diet. This suggests that the taste sensations may contribute to homeostasis.

The role of the somatic nervous system in homeostasis is further illustrated by a study of the muscle tone in various conditions. The latter depends on somatic reflexes, since it is abolished by posterior root section. Henderson (622) stressed the importance of muscle tone for the venous return to the heart, which plays a decisive role in the determination of the cardiac output. When the blood pressure is reduced with an increasing pericardial pressure, the muscle tone rises (446). Likewise it was found that the muscle tone increases with progressing hemorrhage and returns to its control value upon the reinjection of blood (774). These somatic reactions contribute to the restitution of the cardiac output and may occur even in adrenalectomized animals. However, in the normal organism autonomically controlled homeostatic reactions such as the restitution of the blood pressure through sympathetico-adrenal discharges are aided by the increase in muscle tone. But the reverse statement seems also to be true, since adrenalin injected intravenously in small quantities raises the tone of striated muscles (82).

The fact that the sympathetic discharge is frequently combined with an increased secretion of the adrenal medulla is generally considered a mechanism of strengthening homeostatic regulations, since both processes are synergic. Thus a fall in the blood pressure is best counteracted by vasoconstriction induced by sympathetic impulses and by the secretion of adrenalin. The hormonal component reinforces the nervous discharge and prolongs its action.* In addition adrenalin may increase sympathetic discharges by its action on ganglionic transmission. Thus it was found that small amounts of adrenalin (3 to 6 gamma per minute), when added to the perfusate of the sympathetic ganglia of the abdominal chain, greatly increase the vasoconstrictor effect on the leg resulting from the stimulation of these ganglia (179), and similar effects were obtained on the superior cervical ganglion (176). Finally, it was shown that adrenalin facilitates the liberation of this hormone from the adrenal gland in response to splanchnic stimulation. Since the splanchnics are considered to be preganglionic nerves, it may be said that adrenalin in small quantities improves synaptic transmission in sympathetic ganglia.† Here

* The important question of the nature of the secretion of the adrenal medulla (nor-adrenalin or adrenalin) is discussed in Chapter 11. For the sake of simplicity "adrenomedullary secretion" and "adrenalin" are used synonymously in this chapter.

† The inhibitory action of somewhat large amounts is discussed on p. 409.

again the action of adrenalin is not confined to the sympathetic nervous system. The conduction of impulses along the sciatic nerve and their transmission through the myoneural junction (Orbeli) is likewise improved.

Somato-Autonomic Integration of Cortical and Diencephalic Origin in the Service of Homeostasis

Muscular activity, which greatly alters the metabolic requirements of the body, leads to marked changes in the composition of the blood through the accumulation of metabolic waste products and a decrease in the oxygen tension. Various mechanisms by which these changes are reduced to a minimum are chiefly due, as in the previously given examples, to reflexes and endocrine adjustment following changes in the internal milieu. However, even before these take place, central processes occur which within limits maintain homeostasis. Experiments on the motor cortex have shown that stimulation evokes somatic and autonomic effects (692): movements are accompanied by an increase in the blood pressure and heart rate. However, the cardiovascular reactions are not the result of reflexes originating in the contracting muscles but are due to the activation of autonomic structures in the cortex of the brain, since the pressor effect persists after curarization. Since rises in the blood pressure and heart rate represent the most important adjustment reactions to muscular activity, it may be said that with the initiation of reactions capable of disturbing the internal environment others which limit or prevent these changes are intimately related. This coupling of autonomic and somatic reactions at the highest level is illustrated for man by Buchanan's famous experiment (169). She observed that the duration of the first diastole of the heart following the onset of voluntary muscular work was shortened, and Weber (1213) noted that vasodilatation in the arm occurred even when a movement of the arm was intended but not carried out!

Such a coupling of autonomic and somatic processes is well established for diencephalically induced activity. Stimulation of the anterior parts of this structure leads to a fall in the blood pressure, a decrease in respiration, and lessened motor activity, while excitation of the area above and posterior to the mammillary bodies elicits, with the rise in the blood pressure and the increase in respiratory volume, signs of heightened muscular activity (Hess, 637). Since the greater degrees of muscle action as in fight and flight show emotional involvement, it may be assumed that at least in these conditions the cerebral cortex and diencephalon play an important part in homeostasis.

It was pointed out that one of the chief adjustment reactions in acute anoxia is the result of chemoreflexes originating in the sino-aortic area. If these receptors are removed, anoxia causes a fall in the blood pressure and respiratory failure in the anesthetized animal. In some unanesthetized animals, however, this is not the case (119). This observation suggests that cortical reactions which are eliminated during anesthesia may replace the chemoreceptor impulses and lead to an activation of vasomotor and respiratory centers in the medulla oblongata. It is most likely that the feeling of air hunger leads to increased impulses to the respiratory center which irradiate to the adjacent sympathetic centers.

These are only a few examples showing that cortical and also subcortical processes play an important role in homeostasis. Instinctive reactions in response to hunger and thirst contribute obviously to homeostasis; so does the specific alteration in appetite which follows endocrine and nutritional disturbances. In the higher animals and man conscious actions contribute to homeostasis. As William James put it: "Primarily and fundamentally, the mental life is for the sake of action of a preservative sort. Secondarily and incidentally it does many other things."

Subsidiary Mechanisms of Homeostasis

It was emphasized that among the adjustment reactions which re-establish homeostasis sympathetico-adrenal discharges play a prominent role. They counteract the fall in the blood pressure in hemorrhage, the decline in the blood sugar after the injection of insulin, and the fall in temperature on exposure to cold, and contribute, through changes in the heart activity and vasomotor reactions, to the increased oxygen supply to the tissues in exercise. Studies on sympathectomized cats (193, 1091, 1091a) show that these animals are more sensitive to cold, anoxia, and insulin hypoglycemia than unoperated control animals. When tested on the treadmill they run with less speed and show less endurance. On the other hand, the sympathectomized dog withstands anoxia, heat, cold, and exercise as well as the control animal, although it succumbs more easily to insulin hypoglycemia (157, 917).

These investigations suggest the importance of extrasympathetic factors in homeostasis. Further work has revealed the existence of cardioaccelerator fibers in the vagus nerve which account for the increase in the pulse rate and consequently in the cardiac output during exercise in the sympathectomized and atropinized animals (157, 744). However, cardiac acceleration through diminution in

the vagal tone is likewise of great significance. The remarkable ability of the dog to withstand environmental stress depends also on such factors as the large lung, heart, and blood volume compared to those of the cat. These are of importance in anoxia and hemorrhage, while the copious flow of saliva and the large tongue facilitate heat loss when vasodilatation is no longer possible. The well-developed muscles contribute in shivering to the maintenance of the body temperature on exposure to cold.

The vascular tone so important for the maintenance of the blood pressure is gradually restored after the elimination of sympathetic nerves. This is indicated by the decrease in the skin temperature of the denervated leg or by the decrease in the diameter of the blood vessels of the denervated rabbit's ear. About six days after denervation the tone is restored. This reaction and the vasoconstriction of the denervated vessels in struggle show parallel changes. The action can be mimicked by adrenalin and potentiated by cocaine. Le Compte's work (825) suggests that sympathin, to which the denervated vessels are sensitized, is responsible for the restitution of the vascular tone.

The Suppressor Areas and the Homeostasis of Cortical Functions

It is the essence of the concept of the organism that some of its parts are of lesser importance for the maintenance of life than others and that mechanisms exist for the protection of the latter. The study of homeostatic reactions by Cannon and his school has amply illustrated this concept. That heart and brain are the beneficiaries of circulatory adjustment reactions has already been stressed. It has also been mentioned that in Barcroft's opinion (65) the development of such regulations is the prerequisite for the formation of the highly sensitive neocortex. These observations raise the question whether Cannon's concept of homeostasis should be enlarged. Are there present in the brain physiological adjustment reactions which are operative under strictly physiological conditions – i.e., at constancy of the internal milieu – and maintain the degree of cortical excitation within fairly narrow limits?

The processes underlying the cycle of sleep and wakefulness come to mind first. Their control through the diencephalon and the importance of afferent, particularly proprioceptive impulses are discussed elsewhere,* and it may suffice here to say that wakefulness is mediated by the hypothalamic-reticulo-thalamic system. As Magoun (847) has shown, the elimination of the spinothalamic system does

* See pp. 185ff.

not interfere with the persistence of the waking state. However, this does not exclude the possibility that the system contributes to raising the level of cortical excitability.

In the deeply anesthetized preparation the effects of stimulation of various sense organs is restricted to the specific cortical projection areas. The thalamus is interposed and not only sends impulses to the cortex but receives them also. As Chang (218) showed in beautiful experiments, reverberating circuits exist between the thalamus and cortical projection areas which are initiated by afferent stimuli. They are completely independent of the hypothalamic-thalamic pathways, which utilize the midline thalamic nuclei. Consequently it may be suggested that at a given internal environment cortical excitability depends at least on these two afferent systems. Also it is not unlikely that the cerebellum, which is connected with all parts of the cerebral cortex (588) and which in addition to proprioceptive and vestibular stimuli receives tactile, visual, and auditory impulses as well, contributes likewise to cortical excitability (1124).

These considerations seem to indicate that cortical activity undergoes certain variations depending on the type and intensity of afferent impulses. But these changes have certain limits which are determined by the suppressor areas of the cortex. Dusser de Barenne and McCulloch (306) showed that excitation of the suppressor area diminishes the excitability of the motor cortex. Our own investigations suggest that the suppressor areas set definite limits to the degree of cortical excitation.

Afferent impulses set up by stimulation of the sciatic nerve, the injection of hypertonic salt solution into a striated muscle, which induces nociceptive impulses, and the stretching of a contractured muscle excite not only projection and association areas but the suppressor areas as well (453). Increasing degrees of asynchrony appear in the recorded potentials of all areas. Most important, even near-threshold stimuli excite the suppressor areas. These data suggest that with the excitation of the cortex a mechanism is called into action which reduces excessive excitation.

Such a provision would be particularly beneficial in reducing the cortical effects of emotional excitement and in protecting against convulsive discharges. Regarding the former, it is pertinent to point out that stimulation of the hypothalamus leads invariably to an excitation of the whole cortex and consequently of the suppressor areas.* Regarding the latter, Russell's observations (1076) on a large number

* However, it should be mentioned that stimulation of the suppressor area in unanesthetized animals has thus far been unsuccessful.

of cases with traumatic brain injury are of great importance. This author found that the sites of cortical injury which is not followed by convulsions showed a random distribution, whereas the sites in those patients suffering from post-traumatic epilepsy were chiefly grouped in the areas occupied by the suppressor bands. In view of these findings it would be interesting to determine the relation of suppressor activity to convulsive discharges more directly. One might assume that the functional elimination of the suppressor area by cocaine would increase the intensity and duration of experimentally induced convulsions. However, this experiment has not yet been performed.

If it is correct that the suppressor areas set definite limits to cortical excitation and if this excitability depends, to a degree at least, on afferent impulses, an influence of the suppressor bands on the effectiveness of the latter is to be expected. Experiments have shown, indeed, that the action potentials induced by optic and acoustic stimuli or resulting from electrical stimulation of the central end of the sciatic nerve or vagus are diminished or abolished following electrical stimulation of the suppressor areas (73). In such experiments spontaneous cortical potentials and those induced by sensory stimulation decline, but the two processes do not run strictly parallel. The sensory response may recover from the inhibition at a time when the spontaneous potentials are still abolished (Fig. 89).

These experiments proved conclusively that when the suppressor areas are excited by electrical stimulation, the effectiveness of afferent impulses on the cortex is reduced or abolished. They also showed that afferent stimulation alters the potentials of suppressor and non-suppressor areas in a similar manner, a result suggesting that an activation of the suppressor areas is coupled with cortical excitation as the result of spinothalamic or hypothalamic impulses. However, it remained to be demonstrated that afferent impulses lead to a degree of cortically induced suppression which is comparable to that resulting from electrical stimulation of the suppressor areas.

Two types of stimulation, stretch of a contractured muscle and very mild stimulation* of the sciatic nerve, were found to result in typical suppression (287). The suppression occurs after the long latent period (several minutes) which was noted by Dusser de Barenne and McCulloch and Barker and Gellhorn in their experiments on electrical stimulation of the suppressor areas.† The suppression could be shown in

* Strong stimuli have the opposite effect. They cause a generalized cortical excitation.

† The homeostatic function of cortically induced suppression seems valid even if the idea of fixed suppressor bands is to be abandoned (see 901, 1119, 1184).

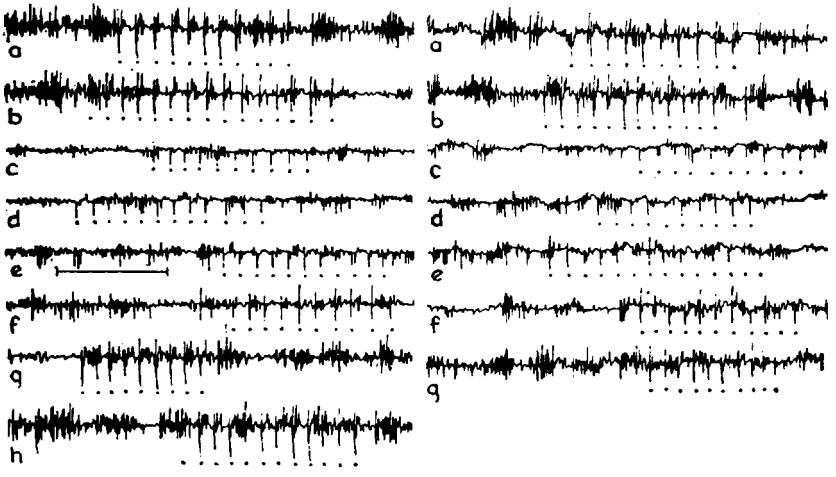

FIGURE 89. The effect of stimulation of the parietal (left half of figure) and of the anterior suppressor areas (right half) on the acoustic response recorded from the auditory area. Acoustic stimulation indicated by dots. Note that stimulation of the suppressor areas reduces the amplitude of the sensory response as well as that of the spontaneous cortical potentials. *Left half: record a,* control; *records b through h,* by number of minutes after stimulation of the suppressor area: *b,* 6; *c,* 8.25; *d,* 9.25; *e,* 10; *f,* 11.5; *g,* 18; *h,* 20.5. *Right half: record a,* control; *records b through g,* by number of minutes after stimulation of the suppressor area: *b,* 12; *c,* 15.5; *d,* 16.25; *e,* 17.5; *f,* 20.5; *g,* 21.25. (Barker and Gellhorn, 73.)

the electrocorticograms as a temporary reduction in the amplitude of the cortical potentials. This diminution of cortical activity is seen at slightly different times in different cortical areas, a fact indicating that the action on the cortex is not due to changes in the blood pressure. In addition, suppression appears under these experimental conditions in the form of a temporarily reduced responsiveness of the motor cortex to electrical stimulation.

Apparently homeostasis is not confined to those relatively gross reactions in which autonomic and somatic as well as non-nervous phenomena tend to restore cortical excitability in a variety of conditions of stress. The present experiments indicate that mechanisms exist which prevent excessive variations in cortical excitability. It is interesting to note that factors which tend to increase cortical excitation activate simultaneously suppressor areas which reduce it.

If the suppressor area 4s is stimulated with strychnine, spikes appear in the bulbo-inhibitory area. It seems to follow that activation of this inhibitory area of the reticular substance in the medulla oblongata (914), which also inhibits spinal and brain-stem reflexes (889), is

responsible for the suppression of the reactivity of the motor cortex. Recent studies show that this medullary inhibitory area has a considerable effect on the action of the hypothalamus. Somatic reflexes as well as the effects of hypothalamic stimulation on the blood pressure and respiration were enhanced by lesions in the medullary suppressor area. Contrariwise, acute destruction of the facilitatory area located in the lateral part of the reticular substance in the brain stem diminished the somatic and autonomic responsiveness of the hypothalamus (1157). Since hypothalamic activity has a profound influence on the excitability of the cerebral cortex, these findings are of great interest and suggest that the reticular substance and particularly the balance between the facilitatory and the inhibitory areas contribute to the homeostasis of brain functions.

The Brain Stem and Cortical Homeostasis

Any condition leading to a decrease in cortical function calls forth a release of the brain stem from cortical inhibition.* This holds true not only for surgical but also for functional decortication. In the former the release appears in the form of the well-known sham-rage reaction; in anoxia, asphyxia, hypoglycemia, and anesthesia, which depress cortical functions more than those of the brain stem, at a certain stage there appear signs of emotional excitation together with an increased reactivity of subcortical autonomic structures to direct stimulation.

It is shown elsewhere † that after previous strychninization of the hypothalamus, anoxia or asphyxia induces a generalized convulsive discharge which is synchronized with the hypothalamic potentials and appears in all parts of the cerebral and cerebellar cortex. Even subconvulsive activity may become manifest under these conditions. Since in the normal animal hypothalamic stimulation leads to cortical excitation via the dorsomedial nucleus of the thalamus (and possibly closely related parts of the medial thalamus) and since these discharges are apparently closely related to the maintenance of wakefulness, it may be assumed that any condition which more or less selectively depresses cortical activity releases, to a corresponding degree, hypothalamic-cortical discharges. In view of the fact that they excite all parts of the cerebral cortex, these impulses must greatly counteract the decrease in cortical excitability which initiates them. The hypothalamic-cortical discharge is paralleled by autonomic ("down-

* This topic is elaborated in its various functional aspects on pp. 276 and 352 and is discussed at this time only in its relation to homeostasis.

† See p. 152.

ward") discharges but is independent of them, since it persists after the blockage of autonomic synapses by TEA (464). That in addition the increased autonomic and particularly sympathetico-adrenal downward discharge is beneficial for the restitution of cortical function through systemic (circulatory) and local effects (on cortical synapses) has already been mentioned.

It was stated earlier that gross disturbances of the internal environment lead to coma or convulsions, the former not infrequently preceding the latter. Although coma seems to be characterized by a minimum of nervous excitability, and convulsions, on the contrary, by a maximal neuronic discharge, the fact that coma may precede convulsions just by a few minutes suggests that the two phenomena are closely related The puzzle is solved if the release of the brain stem in conditions of reduced cortical reactivity is taken into consideration.

At the early stages of coma normal cortical potentials are replaced by slow delta waves. Later, cortical potentials become minimal or disappear. Under these conditions of greatly reduced cortical function the reactivity of autonomic structures in the diencephalon and medulla oblongata is increased. Thus it is known that their excitability rises with a falling blood sugar (492, 500). The more intimate mechanism by which increased autonomic excitability is related to the increased tendency to convulsions is not well understood. It is suggested that the autonomic and somatic functions of the brain stem, which are closely interrelated both anatomically and physiologically, undergo similar functional changes in several conditions involving a disturbance of the internal environment. Cortical depression passes from coma to convulsions as soon as the release of brain-stem functions has progressed far enough, provided that no narcotics are used which depress the brain stem. This is the reason why anoxic and hypoglycemic convulsions are commonly seen in the unanesthetized but not in the anesthetized animal. In the light of the theory of homeostasis the convulsions represent an ultimate adjustment mechanism, although of a pathological form, to counteract the coma through discharges from the brain stem and particularly from the hypothalamus.

It is seen occasionally that convulsions in hypoglycemia are accompanied by a startling, though brief recovery in cortical potentials. It is worthy of note that such a recovery in cortical functions may occur even in the adrenodemedullated animal in which convulsions fail to alter the blood sugar (499). This recovery is probably in part due to improvement in the brain circulation — an explanation suggested by the fact that electrically induced convulsions increase

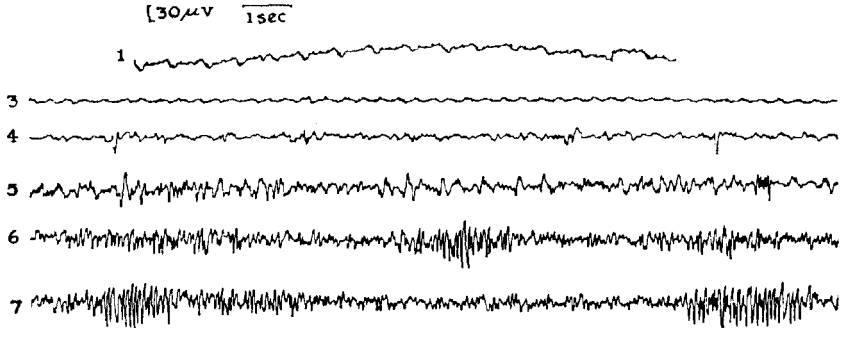

FIGURE 90. The effect of electric shock on the electroencephalogram of an adrenodemedullated rat in hypoglycemic coma (5 units of insulin injected per kilogram of body weight). In this experiment a remarkable recovery of the EEG and behavior occurred after electroshock in spite of continued coma levels of the blood sugar. *Record 1:* coma, 1 hour after injection of insulin; blood sugar, 32 mg/100 cc. *Record 3:* 2 minutes after shock. *Record 4:* 5 minutes after shock. *Record 5:* 10 minutes after shock. *Record 6:* 18 minutes after shock. *Record 7:* 26 minutes after shock; blood sugar, 30 mg/100 cc. (Gellhorn and Kessler, 499.)

the pulse rate in the hypoglycemic rat* whereas they decrease it in the rat with a normal blood sugar level. In part the restitution of cortical reactivity may be due to the excitatory effect which hypothalamic-cortical discharges occurring during the convulsive seizure exert on the cerebral cortex.

A striking recovery may be initiated by electroshock applied during the hypoglycemic state (Fig. 90). Although the blood sugar remains unchanged at the coma level, cortical potentials become normal, righting reflexes are restored, and the behavior of the animal is greatly improved. In favorable cases it may appear normal for some time. Such an improvement in cortical function seen as the result of a spontaneous or induced convulsive seizure is an impressive illustration of the homeostatic value of the seizure in hypoglycemia. In the normal organism it should be greatly enhanced by the discharge of adrenalin which accompanies the convulsions and raises the blood sugar.

This interpretation applies to convulsions induced by a release of the brain stem in conditions other than insulin hypoglycemia. One would expect that this release contributes to homeostasis in various forms of anoxia. Thus convulsions may follow a vasodepressor syncope, particularly when the patient is maintained in an erect posture, and may lead to a restoration of cortical potentials (Engel, 317).

* The experiments refer to adrenodemedullated rats exclusively.

Brain Circulation and Homeostasis

Additional circulatory reactions contribute to homeostasis. When the oxygenation of the blood decreases or carbon dioxide accumulates, the amount of blood which flows through the brain increases not only as the result of chemoreceptor reflexes which increase the systemic blood pressure but through the direct action of these gases on the cerebral vessels. Studies* on pial vessels indicate that in hypoxia and particularly in hypercapnia the blood vessels dilate. A direct determination of the blood flow showed the validity of these observations for the whole brain. Apparently this increase in the blood flow is independent of the rise in the blood pressure and the excitation of chemoreceptors, since it persists when the former is kept constant and the sino-aortic area has been denervated. However, it should be emphasized that to an important degree the rise in the blood pressure contributes to these compensatory phenomena.

The formation of lactic acid in anoxia and the increase in the carbon dioxide tension of the brain in hypercapnia appear to be responsible for the local dilatation of brain vessels in anoxia, hypercapnia, and conditions of increased cellular activity such as local convulsions. Lennox *et al.* (832) stressed the importance of these vascular reactions for the constancy of the carbon dioxide in the brain. Thus the carbon dioxide content of the blood in the internal jugular vein, which reflects the carbon dioxide tension of the brain, is little altered as the carbon dioxide content of the arterial blood is increased by the inhalation of carbon dioxide. Conversely, in hyperventilation the removal of carbon dioxide from the brain is diminished, since owing to vasoconstriction the total amount of blood circulating through this organ is reduced. Here again the local reactions are aided in their homeostatic effects by systemic changes, for the fall in the blood pressure in hypocapnia due to a diminution of chemoreceptor impulses on the vasomotor center acts toward a diminution of the cerebral blood flow and preserves the carbon dioxide tension in the brain under these conditions.

The physiological significance of these vascular reactions lies obviously in that they minimize the effects of changes in the internal milieu on the neurons in general and those of the cerebral cortex in particular. In view of this fact it is of interest that these reflexes are magnified under conditions of restricted brain circulation (510). If both carotids are ligated, the pressor reaction to anoxia and the respiratory response to carbon dioxide greatly increase. The ligation of one carotid or both vertebral arteries does not alter these reactions

* See Gellhorn, *Autonomic Regulations* (446) for further literature.

in common laboratory animals, and Rein and Schneider found that the total blood flow is not decreased under these circumstances (1041)!

It should be added that the blood supply to the brain depends not solely on systemic factors related to sino-aortic reflexes and sympathetic discharges but also on the tonic innervation of the cerebral vessels. It was pointed out earlier that a diminution of the carotid sinus reflexes, which leads to increased generalized sympathetic discharges and thereby to a rise in the blood pressure and vasoconstriction in the splanchnic area, is not accompanied by cerebral constriction in spite of the presence of sympathetic constrictor nerves to these blood vessels. On the other hand, the parasympathetic tone of the blood vessels seems to be of importance, particularly in hyperventilation.

This procedure commonly induces profound alterations in cortical activity in man, as seen in the occurrence of large, slow potentials in the EEG. An analysis of this phenomenon in animals shows that the effect is related to the parasympathetic impulses which reach the brain vessels via the facial nerves. Darrow (255) modified the intensity of these parasympathetic vasodilator discharges by surgical procedures or pharmacologic agents. Stimulation of these nerves by electrical currents or physostigmine and also nerve section or atropine were tested in their effect on brain potentials during a standard hyperventilation. It was found that the procedures which induce cerebral vasodilatation counteract the effect of hyperventilation on brain potentials, whereas atropine or sectioning of the facial nerve produces the opposite result. Apparently the parasympathetic tone which is opposed to the vasoconstriction resulting in the brain during hyperventilation is an important factor in the maintenance of the cerebral blood supply and normal activity.

The Homeostatic Action of Adrenalin on the Autonomic Nervous System

From Cannon's work it is evident that the secretion of adrenalin represents a powerful mechanism of reinforcing sympathetic discharges. If its action were to go on without restraint, it would tend not to restore homeostasis but produce various effects resulting from excessive sympathetic discharges. Therefore the question may be raised whether central regulatory mechanisms are called into action which tend to terminate the sympathetico-adrenal discharge. Or, to relate this problem more specifically to the secreted adrenalin, is there any evidence that adrenalin, if its concentration in the blood

reaches a critical level, exerts a damping effect on the centers of the sympathetic system?

This problem was first investigated with respect to vascular reflexes. It was found that the pressor effect induced by reflex or direct stimulation of the vasomotor center was diminished if adrenalin had been added to the circulation (224, 710). From these investigations it was concluded that adrenalin fulfills a homeostatic action in vasomotor reflexes. In view of the fact that the vasomotor center in the medulla oblongata is really a center regulating the activity of the whole sympathetico-adrenal system (Chen *et al.*, 221) it may be surmised that adrenalin may reduce the activity of this system through a central damping action and thereby restore normal conditions.

Specific experiments directed at determining whether adrenalin is able to reduce sympathetic reactivity in general showed that sympathetic reflexes leading to the contraction of the nictitating membrane were greatly diminished in the presence of adrenalin (254). Similarly it was found that the reactivity of the hypothalamus to electrical stimuli was reduced by adrenalin. That this effect is central and not due to the action of adrenalin on the structure serving as the indicator of sympathetic excitability is evident from the following observation (444). The effect of hypothalamic stimulation was measured by the contraction of the nictitating membrane of one side while the nictitating membrane of the other side was stimulated through the peripheral end of the cut sympathetic superior cervical trunk. The latter test indicates any change in the excitability of the peripheral structure, the former reflects the alteration in the responsiveness of sympathetic centers if no change occurs in the reactivity of the nictitating membrane itself. It was found that under the influence of adrenalin the effectiveness of the hypothalamic stimulus is reduced while that of the peripheral stimulus remains unchanged. This indicates clearly that adrenalin reduces central sympathetic excitability and may thereby contribute to the restitution of homeostasis after a sympathetico-adrenal discharge.

At the same time evidence for a reduction of sympathetic discharges by adrenalin in physiological concentrations and for its role in homeostasis was presented by Marrazzi (897), who studied the transmission of impulses through sympathetic structures such as the superior cervical ganglion. He stimulated the preganglionic nerve with submaximal stimuli and recorded postganglionic action potentials. The injection of minute quantities of adrenalin (5 micrograms) reduced the amplitude of these potentials. The physiological nature of this effect is illustrated by the observation that adrenalin liberated

by stimulation of the splanchnic nerves exerts a similar effect. Bülbring (176) confirmed this work and showed that ganglionic transmission was depressed not only in response to preganglionic stimuli but also to injected acetylcholine; in both instances the contraction of the nictitating membrane was temporarily depressed by adrenalin.* Obviously a reduction in the transmission of sympathetic impulses across synapses is a very effective mechanism through which sympathetic discharges of central origin would be diminished. The general significance of these findings lies in the fact that the inhibition of synaptic transmission through adrenalin has been confirmed for other ganglia of the sympathetic nervous system (181, 898, 1027).

Bülbring and Burn (179) further contributed to an understanding of this problem by perfusing abdominal sympathetic ganglia and the hind leg separately. The degree of vasoconstriction in the latter to a standard stimulus applied to the former depended on the transmission of impulses through the sympathetic ganglia. In such experiments perfusion of the ganglia with 10 gamma of adrenalin per minute greatly reduced the vasoconstrictor effect. Furthermore it was noted that the pressor effect resulting from the stimulation of the splanchnic nerves decreased in adrenalectomized dogs under the influence of injected adrenalin. Since the pressor effect of adrenalin remained unchanged, the diminished effectiveness of splanchnic stimulation could have been due neither to a lesser responsiveness of the blood vessels nor to a greater action of the sino-aortic reflexes, since any change in these structures and functions would equally affect any vasoconstrictor action and could not selectively alter that produced by the stimulation of sympathetic nerves. Thus the temporary diminution in the nervous vasoconstrictor effect appears to be due to a partial blocking in abdominal sympathetic ganglia.

Since the adrenal medulla is a modified sympathetic ganglion, one would expect that adrenalin might be able to reduce the reactivity of the adrenal medulla to stimuli which elicit a secretion of adrenalin. Two methods have been used: the intraarterial injection of acetylcholine in atropinized animals and the stimulation of the splanchnic nerves. In either case it has been found that adrenalin injection reduces the responsiveness of the adrenal medulla to secretory stimuli. There is, however, a considerable discrepancy in the doses required. Bülbring and Burn, who used acetylcholine as a stimulus, found it necessary to inject 30 gamma of adrenalin in order to obtain a

* The facilitatory effect on ganglionic transmission of still smaller doses of adrenalin is discussed on p. 397.

measurable reduction in adrenalin output, whereas King and Marrazzi (776) accomplished this effect with as little as 0.1 gamma.

From these experiments it may be concluded that although the secretion of adrenalin acts at first as a powerful synergist of sympathetic excitation, it may, through its depressor action on sympathetic ganglia, including the adrenal medulla, reduce discharges over the sympathetic system and thereby contribute to homeostasis. This mechanism is operative in emotional excitement. It has the tendency to restore hypothalamic reactivity to normal levels and to reduce the responsiveness of the hypothalamic-hypophysial system. Verney (1185) showed that the injection of adrenalin prevents the secretion of the antidiuretic hormone from the posterior pituitary which ordinarily follows emotional excitement and pain.* This sensitivity of sympathetic synapses to relatively small concentrations of adrenalin is surprising inasmuch as even the complete cessation of circulation for several minutes does not interfere with the transmission of impulses through a sympathetic ganglion (141).

It was mentioned earlier that the secretion of adrenalin leads to the mobilization of adrenocortical hormones in various forms of stress. This phenomenon is of great importance for the survival of an organism in extreme environmental conditions and for the restitution of the internal environment. The resistance to cold depends on the amount of circulating adrenocortical hormones to such a degree that they can be assayed through their protective action on adrenalectomized animals exposed to cold. The adrenocortical secretion in insulin hypoglycemia has a similar homeostatic value. It is well established that adrenalectomized animals are more sensitive to insulin than adrenodemedullated or normal ones. Moreover, cerebral symptoms and changes in the ECG induced by insulin are more severe at a given blood sugar level in adrenalectomized than in normal animals (40) (Table 21). Similarly it was found that coma as the result of starvation occurred in adrenalectomized rats at a relatively high blood-sugar level which caused no symptoms in unoperated control animals.

Whether the greater sensitivity of adrenalectomized animals to insulin is due to the more rapid fall in the blood sugar, as Arnett and Gellhorn assumed, or rather is the expression of the increased sensitivity of the brain to changes in the internal environment in the absence of circulating adrenosteroids cannot be said at present. How-

* Adrenalin also counteracts the effect of acetylcholine (299) on the anterior hypothalamic nuclei which leads to the liberation of the antidiuretic hormone.

TABLE 21. The Relation of the Hypoglycemic Level to Cerebral Symptoms (Arnett, Kessler, and Gellhorn, 40)

Blood Sugar Level, mg. %	Number of Rats Showing Cerebral Symptoms			
	None	Depressed Reflexes	Coma	Convulsions
Adrenodemedullated Rats				
74	6			
70	13			
66	6	1	2	
62	3	1	1	
58	1	2	2	
Adrenalectomized Rats				
77–80	6		2	
74	1	1	1	
70	2	4	1	
66			1	
62			5	2
58			1	5

ever, it may be mentioned that in some incidental observations* patients with frequent spontaneous attacks of hypoglycemia were found to show mental symptoms at much lower blood-sugar levels than normal persons. Perhaps frequent episodes of hypoglycemia lead to adrenocortical hyperreactivity as the result of repeated adrenocortical stimulation initiated by the secretion of adrenalin in hypoglycemia, and the increased concentration of adrenocortical hormones in the blood accounts for the apparent resistance of the brain to hypoglycemia.

The Homeostatic Action of Adrenalin on the Somatic Nervous System

It was pointed out earlier that on stimulation of the motor cortex and also on excitation of diencephalic structures somatic effects are accompanied by autonomic and particularly sympathetic discharges. Apparently somatic and autonomic processes are frequently intertwined. These observations suggest that the central action of adrenalin may not be confined to the sympathetic system alone, and experiments have shown indeed that parallel changes occur in the somatic nervous system. Thus the injection of small amounts of adrenalin may temporarily inhibit metrazol convulsions (Table 22). The relation to normal somatic excitability is even more obvious in observations on rabbits previously anesthetized with sodium barbital and then given just

* Unpublished.

TABLE 22. The Effect of Epinephrine on Metrazol Convulsions in the Rabbit (Gellhorn, Darrow, and Yesinick, 479) *

Time	Injection	Observations
10:47 A.M.	....Metrazol, 60 mg/Kg, intravenously	Immediate severe clonic-tonic convulsions
10:48 A.M.	....Epinephrine hydrochloride, 0.023 mg. intravenously (0.0079 mg/Kg)	Immediate flaccidity; occasional twitches of head and forelegs
10:52 A.M.	....	Clonic movements begin to recur. Extensor tonus increases also until, at 10:57 A.M., typical clonic-tonic convulsions are present.
10:57½ A.M.	....Epinephrine hydrochloride, 0.03 mg. intravenously (0.01 mg/Kg)	
10:58 A.M.	....	Tonus normal; no convulsions; pupils maximally dilated
11:00 A.M.	....	Animal still relaxed; occasional twitches; no convulsions
11:02 A.M.	....	Clonic movements; tonus of extremities increased
11:19 A.M.	....	Clonic convulsions, 10 to 12 per minute
11:23 A.M.	....Epinephrine hydrochloride, 0.03 mg. intravenously (0.01 mg/Kg)	
11:24 A.M.	....	Extremities completely relaxed; no convulsions. Animal remained normal.

* A rabbit weighing 2.92 Kg. was injected subcutaneously with ethyl carbamate, 1 Gm/Kg. The animal was not fully narcotized, and its head was held up during the observations.

enough metrazol to wake them so that they sit or move about without showing any convulsive activity. The injection of adrenalin induces sleep under these conditions (479).

It is interesting to mention that the same amount of adrenalin which reduces excitability in the normal animal increases it after sino-aortic denervation. However, it should be borne in mind that the removal of the "buffer" nerves greatly augments the pressor effect of adrenalin, and in view of the great influence which changes in the blood pressure and oxygenation have on normal and particularly on convulsive brain potentials (490) the reversal in the action of

adrenalin may well be related to the change in its pressor effect. At any rate, the role of the sino-aortic reflexes in the regulation of cerebral excitability deserves further study.

There is another line of evidence which links adrenomedullary secretion with the reduction in excitability of the somatic nervous system. Certain depressant substances such as morphine induce a sympathetico-adrenal discharge, a result indicated by the hyperglycemia which is seen after the injection of this drug in normal but not in adrenodemedullated animals (110). Friend and Harris (394) observed that the analgesic effect of morphine is reduced by inactivation of the adrenal medullae. This experiment suggests that the secreted adrenalin exerts a sedative effect of its own (as in the earlier work of Gellhorn *et al.*, 254, 479) which increases the effectiveness of morphine. Such a summation in the total effect is quite conceivable even if the mechanism by which morphine and adrenalin reduce the responsiveness to environmental stimuli is different for each drug. In this connection it should be mentioned that intracisternal and intrathecal injections of adrenalin produce sleep and surgical anesthesia (830). However, the concentrations used are outside the physiological range.

This work shows that adrenalin within the limits of adrenomedullary secretion may diminish the excitability of central autonomic and somatic structures. Reduction in synaptic transmission may be involved in both instances. Recent experiments seem to show, on the basis of studies on postsynaptic action potentials recorded from the cortex after stimulation of afferent nerves, that adrenalin depresses somatic synaptic conduction (899). However, this finding does not exclude the possibility that the reactivity of the cortex is lessened when, through the action of adrenalin on the hypothalamus, the excitability of this structure and consequently the hypothalamic-cortical discharge are diminished.*

Shock and the Secretion of Adrenalin

The ease with which physiological adjustment reactions pass over into definitely pathological conditions is illustrated by a study of the sympathetico-adrenal discharge in the development of shock. Although hemorrhage is better tolerated by normal animals than by sympathectomized animals, it is found that bleeding leads more easily to circulatory shock in the former. Sympathetic excitation following hemorrhage, although very important for homeostasis, may lead to shock when persisting for long periods of time. A prolonged secretion

* This aspect of the problem of sleep is discussed on p. 193.

or injection of adrenalin causes a reduction in the blood volume unless sympathetic effects are prevented by ergotoxin, which blocks sympathetic nerve endings, or by sympathectomy (386, 387). Apparently, marked constriction of the blood vessels for prolonged periods causes anoxia of the tissues and makes the capillaries more permeable so that plasma passes through their walls. Thus a reduction in the circulating blood volume develops which tends to aggravate the already existing fall in the blood pressure by impairing the venous return to the heart. The further reduction in the blood pressure calls forth increased sympathetico-adrenal discharges via sino-aortic receptors with consequent further vasoconstriction and capillary damage. Thus a vicious cycle is established. It may be prevented in the case of hemorrhage, for instance, by the transfusion of blood, provided that the changes in the capillaries have not gone too far.

There is, however, one other possible cause of shock as the result of the increased secretion of adrenalin. It has been mentioned that adrenalin causes a temporary depression of conduction through sympathetic ganglia. With increasing amounts of adrenalin, although still within the physiological range, this depression may become irreversible. Thus it has been shown that the transmission of impulses through the celiac ganglion is permanently inhibited after the injection of 0.3 mg. of adrenalin (181). It is quite probable that the amounts of adrenalin secreted under conditions of emergency approximate this figure and induce shock through the blocking of central synapses. Since the depression of synaptic conduction is not confined to the celiac ganglion but has been observed in other sympathetic ganglia as well, it may be assumed that this mechanism accounts for progressively diminished discharges from the vasomotor center, a result that contributes to the condition of shock.

Physiology and pathology are only quantitatively different. The secretion of adrenalin contributes, as Cannon showed, to homeostasis and reinforces the peripheral action of the sympathetic nervous system. In addition adrenalin in minute quantities facilitates ganglionic transmission and may therefore by its central action increase the effectiveness of the sympathetico-adrenal discharge. However, if the secretion of adrenalin becomes greater, it depresses sympathetic conduction, lowers the excitability of autonomic and somatic central structures, and paves the way to a return of the central nervous system to its original condition. Finally, prolonged severe secretion of adrenalin may contribute to pathology by permanently interfering with synaptic transmission in the sympathetic nervous system and by its unfavorable action on the capillaries.

Concluding Remarks on the Homeostasis of the Internal Environment

It may be unnecessary to emphasize that the concept of homeostasis involves an ideal state toward which the various adjustment reactions are directed without ever attaining it. Obviously a severe hemorrhage leads to a greater fall in the blood pressure and a greater reduction in the hemoglobin content of the blood than can be compensated for, as far as the oxygenation of the tissues is concerned, by vasoconstriction, an increased minute volume of the heart, constriction of the spleen, and an augmented respiratory volume. And insulin hypoglycemia is only partially offset by the increased secretion of adrenalin and the adrenocortical hormones. In addition it should be noted that the adjustment reactions alter the internal environment in certain respects. Thus the sympathetico-adrenal discharge occurring in cold, fever, anoxia, etc., raises the blood sugar far above the physiological level. Furthermore these conditions may, through activation of the hypophysial adrenotrophic hormone, greatly alter the cellular count of the blood (lymphocytes, eosinophils).

It would seem, therefore, that the reactions called forth by alterations of the external and internal environment lead less to a restoration of the original condition (homeostasis) than to the establishment of a new balance. This is particularly evident in chronic experimental conditions. Exposure to anoxia (high altitude) produces an increase in the number of red blood corpuscles for the duration of the experiment. What is important to emphasize is the fact that the new equilibrium represents an organically balanced reaction which tends to weaken the harmful effects of an altered internal or external environment on the organism. Such an interpretation is in harmony with the fact that the increased blood sugar seen in anoxia diminishes the effect of reduced oxygen tension on the brain. Moreover the loss of carbon dioxide which accompanies the increased respiratory activity seen in anoxia is less damaging to the cortex of the brain when the blood sugar is high.

Another example may be cited. In starvation the lymphocytes and eosinophils are reduced because of the increased rate of destruction of these cells which results from the augmented secretion of ACTH. However, this disturbance in homeostasis is more than offset by the fact that thereby the rich protein resources of the lymphatic tissue are made available to the organism. White and Dougherty (1232) have also shown that the same reaction leads to the liberation of antibody globulin. Here the change in the internal environment may save life. It is probably initiated by the fever which was shown to

induce the secretion of ACTH, with consequent lymphopenia and eosinopenia.

One more illustration may be given. As Cannon emphasized, the sympathetico-adrenal discharge is of great importance for fight and flight. The circulatory and respiratory changes are directed toward meeting the higher oxygen requirements of the body in a state of heightened activity. The action of adrenalin on the muscle in delaying fatigue is particularly appropriate in this condition, as is the reduced clotting time if a wound is suffered in the fight. The increased blood-sugar level is as important during heightened activity as it is for the resting organism during anoxia, since in both conditions the relative oxygen supply tends to be deficient. As pointed out earlier, the simultaneously increased secretion of insulin improves the utilization of glucose.

Since the sympathetico-adrenal discharge plays such a prominent role in homeostasis, it is of great interest to know what factors contribute to the reactivity of the centers of the sympathetic system. Experiments on rats, as Figure 52 has already shown,* suggest that age exerts a decisive influence (1078). If the rise in the blood sugar in anoxia is used as an indicator of central sympathetic responsiveness, the experiments reveal a decreased reactivity with increasing age. A similar result would be obtained if the reactivity of the sympathetico-adrenal system remained unchanged while the vago-insulin system increased in excitability. However, such an interpretation is not warranted because the blood sugar response to anoxia does not vary significantly with age in adrenodemedullated rats.† It may therefore be concluded that, at least in the rat, age alters the responsiveness of the sympathetic system.

A deficiency of magnesium in the diet also leads to an increase in the central response of the sympathetico-adrenal system (482). The vago-insulin system remains unchanged. However, this alteration in sympathetic responsiveness is not restricted to the autonomic system. An increased irritability and a greater susceptibility to convulsions indicate definite changes in the somatic nervous system as well (571). No other investigations seem to have been performed on the important question of diet and autonomic reactivity.

Studies on the relation of the endocrines to sympathetic centers are few. It was found that thyroidectomy diminishes central sympathetic excitability without altering the responsiveness of the vago-insulin

* See p. 176.

† It was shown on p. 293 that the blood sugar falls in anoxia in such animals as the result of vago-insulin discharges.

system, and conversely, thyroxin in moderate doses increases central sympathetic responsiveness without affecting the peripheral action of adrenalin (483).*

Cannon has called attention to the diminishing of homeostatic reactions during senescence (194). Although the temperature of the body remains constant under ordinary conditions, sensitivity to cold seems to increase with age. He relates this phenomenon to the decreased heat production in the body, which appears to be due to involutionary processes in the thyroid. He further mentions that the adaptability to increased environmental temperature is likewise impaired with increasing age. Changes in the reactivity of the capillaries and in the glandular structure of the skin may well play a part in the homeostatic defects of old age, as Cannon surmises, but it may not be superfluous to point out that the reactivity of diencephalic autonomic centers may likewise be diminished. This is suggested by the animal experiments just mentioned and is also supported by the common observation that the emotional reactivity and expression of emotion which depend on these structures are markedly diminished with age. The increasingly diabetic character of the glucose tolerance curve with advancing age is in agreement with our interpretation. Since this reaction depends on central vagal impulses (476), with a consequent increased liberation of insulin, it is not unlikely that the reactivity of parasympathetic and sympathetic centers is reduced in old age.

* In higher doses thyroxin and adrenalin act synergistically on the blood sugar.

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The Constancy of the External Environment

IN THE preceding pages the evidence for the existence of homeostasis and the mechanisms contributing to it have been reviewed, and their value for the survival of the organism and for the development of the brain has been emphasized. But it may be said that the survival of an organism in general and of the most complex species, man, in particular, depends not only on relative constancy in the internal milieu but also on a similar constancy in the external environment, since the latter is the basis of orientation and purposeful action. No attempt will be made to discuss this field of research adequately, but a few examples may be cited sufficient to characterize the general problem and to indicate its neurological foundation.

Visual Orientation Reactions

Orientation in the external environment is based on sensory impressions. Since for the human being the visual sense is of primary importance,* some mechanisms through which orientation in the visual world is made possible will be mentioned.

It is obvious that the visual environment remains unchanged if during volitional movements of the eyeballs the retinal image of an object passes over different parts of the retina. On the other hand, the displacement of the retinal image of an object through passive eye movements – the simplest example being those resulting from a lateral pressure exerted on the eyeball with the finger – leads to an "apparent" movement of the object. The directional change is due to the fact that the previously fixated object no longer produces an image on the fovea centralis but on a peripheral part of the retina.

* The marked discrepancy between visual and tactile perceptions (422, 423) of space is easily demonstrated, but it does not cause any difficulties in perception because visual perceptions predominate.

From these elementary observations it must be inferred that only the displacement of an image on the retina which accompanies voluntary movements of the eye is compensated by central nervous processes; that resulting from involuntary movements is not. The compensation is nearly perfect for most movements* provided that the innervation of the eye muscles is normal. With paresis of an eye muscle – that is, under conditions in which the executed movement is much less than the intended one – the visual objects appear displaced in the direction of the action of the paretic muscle.

Thus with paresis of the right abducens the attempt to turn the eye to the right is accompanied by an apparent movement of the visual field to the right. Hering (624) pointed out that with the intention to move the eye to the right the attention is directed toward the new object, and this shift is accompanied by a revaluation of the spatial characteristics of the retina. On the basis of experience and with the cooperation of proprioceptive impulses these movements, guided by optical perceptions, are carried out with great precision, and no shift in the visual environment results. In paresis or paralysis of an eye muscle the interplay between the change in the focus of attention and the eye movements which normally bring the image of the new object to the retinal fovea is interfered with, and a gross disturbance of the optical environment results. This failure in adjustment is apparently not related to associated movements of the normal eye, since it occurs when both eyes are paralyzed. Moreover mechanical displacement of the covered normal eye during attempted movements with the paralyzed eye does not have any effect upon these optical perceptions of space.

A more physiological explanation of these phenomena is suggested by von Holst (699). He calls attention to the fact that in persons in whom the eye muscles have been paralyzed experimentally the visual environment likewise moves to the right with the intended movement to this side. The results are similar to those seen in patients with ocular paralysis. On the other hand, as has been mentioned, passive movements of the eyes also induce such apparent movements, but in opposite directions. Consequently, during a voluntary movement of the eyes the relation of the subject to visual objects is influenced by motor and by sensory (retinal) impulses. Since the directions of the apparent movements of the environment which are induced by these two groups of impulses are opposed to each other, it is understandable that through an intracentral fusion their action is canceled

* For exceptions and details as well as the extensive literature see Hofmann (696).

out. This accounts for the stability of the visual objects during voluntary eye movements.

The laws governing the movements of the eye contribute likewise to the constancy of the visual environment. Since the bulbus can perform movements not only upward and downward and laterally but also of a rotatory kind (around the sagittal axis), it is conceivable that the degree of rotation for a given line of regard is variable. Under such conditions a vertical line would no longer form an image on the vertical meridian of the retina, and the optical perception of verticality would be seriously disturbed. However, Donders found that as we move the eyes from the primary into the secondary position,* no rotation takes place, and the rotations occurring in tertiary positions are fixed for a given line of regard. Or, as Boring (114) expresses it, "The retinal image of any object fixed in the field of vision will, for any given position of the head and fixation of the eye, always fall upon the same retinal points."

The disturbances due to the rotation in tertiary positions are well established. Thus when we follow a vertical line with the eyes directed toward the right, it is noted that the upper and lower ends are turned toward the median plane. These discrepancies between objective reality and subjective perception are not serious, however, because under ordinary conditions we move the head to the side and follow the line from the primary position and thereby avoid the consequences of rotation of the eyeballs.

Phenomena of Constancy

The laws of the movements of the eye and the revaluation of the spatial properties of the retina in conjunction with volitional eye movements are insufficient to provide the psychophysiological mechanism for the recognition of objects involving under natural conditions changes in distance and illumination. Consequently the data underlying the constancy of visual objects as to size, color, and brightness have to be considered.

Without furnishing documentary evidence of the following statements, it may be said that our sensory perceptions, particularly those utilizing distance receptors, are objectivated and form in our minds an intimate relation with the objects and not with the sense organs. Thus the red color of an apple is to the observer part of this object and cannot be separated from it in the physiological, i.e., sensory,

* Primary position: looking forward and horizontally into the distance; secondary position: moving laterally or vertically; tertiary position: moving laterally *and* vertically.

perception. The analysis of the characteristics of a visual object into color, shape, size, etc. involves logical operations. They are certainly quite unrelated to the functioning of the retinal projection system, which is primarily concerned with optical perception. But this objectivation would be insufficient to permit the recognition of objects under various conditions, and compensatory central nervous reactions are necessary.

If we look at a book or a person at close range or at a distance of twelve feet, the size of the object does not seem to vary appreciably. The biological significance of this phenomenon is obvious for a freely moving organism. It indicates that in the judgment of size the size of the retinal image as well as the distance is taken into account. This is apparent from Emmert's law according to which the size of an optical after-image increases in direct proportion to the distance from the observer at which it is projected. As Boring (114) points out, this means that the "apparent size remains constant when the retinal size diminishes in direct proportion to the distance of the object from the observer." This law, although not mathematically correct, explains the practical constancy of the size of visual objects. Thus, as Martius (905) showed, rods of equal length seen at a distance of 575 cm. and 50 cm. appear only very slightly different, whereas their apparent size would increase 11 times if it were determined by the size of the retinal image independent of the distance of the object. Although factors of experience play a role in this experiment, as the constancy of size seems to be less for children than for adults, it should be emphasized that experimental animals with such primitive brains as those of chickens react correctly when trained to pick up the larger grains, even when, as a result of the increased distance, these grains are seen under a much smaller visual angle than the objectively smaller (and closer) particles.

Objects appear constant in size in spite of variations in distance from the observer provided that natural conditions prevail during the experimental test. If, however, the observations are made with one eye through a long, dark tunnel, and with the use of an artificial pupil, the object seems to vary in size with variations in the distance, since under these conditions empirical factors as well as physiological cues from the eye muscles are minimized or eliminated (Holway and Boring, 704).

However, there are good reasons to assume that these phenomena of constancy are not chiefly based on experience but that physiological principles are involved. Since the distance between an object and the observer is judged by the degree of convergence and not by

changes in accommodation (360), it seems reasonable to explain the constancy of the size of an object as the result of efferent impulses involved in the convergence reaction and afferent impulses originating in the retinae. The following observations are in agreement with this thesis: (1) A change in convergence during the observation of an after-image by projecting it first to a close and then to a more distant plane is associated with an alteration in size. In this case the afferent impulses from the retina remain constant, but the efferent impulses change. (2) Two objects of different sizes seen at the same distance appear different. In this case the retinal impulses (size of area) are altered, but the efferent impulses are unchanged (same degree of convergence). (3) If the same object is seen at two different distances, the object does not seem to vary in size. In this case the afferent and efferent impulses are altered at the same time. Apparently their interaction contributes to constancy.

At least one other physiological factor should be mentioned which contributes to the constancy of size of three-dimensional objects. This is the binocular parallax, which in the absence of empirical factors is mainly responsible for the perception of depth. The binocular parallax through which the perception of depth occurs contributes likewise to the constancy of size and shape. If an illuminated rod is observed in the dark room during rotation around the transverse axis, it appears little shortened in spite of the perspective shortening as long as it is seen with both eyes. Viewed with one eye only, its length seems to equal that of the mathematical projection (424).

As to the constancy of color and brightness, Hering (625) points out that we do not see the spectral wave lengths but see objects of different colors. The constant changes in the illumination and consequently in the reflected light would lead to marked changes in the appearance and therefore in the recognition of objects if compensatory processes were not present. Without them a piece of chalk and one of coal of similar shape would hardly be distinguishable if the former were seen on a dark day and the latter in bright sunlight. A white flower under a green tree would appear green, and colors would cease to be attributes of objects and would appear to be rather indicators of the conditions of illumination. Hering explained the constancy of color as a result of retinal adaptation processes. The sensitivity of a given retinal area seemed to depend on the state of excitation of the remainder of the retina.

The correctness of this interpretation is shown by Katz's experiments (758a, b). If a gray paper placed in a dark corner is equalized in brightness with a color wheel consisting of variable white and

black sectors and placed near a window, it is found that the gray paper appears brighter than corresponds to the amount of light which it sends into the eye of the observer. This follows from the fact that when these two areas of apparently similar brightness are looked at through a "reduction screen" which blocks out the environment, the equation no longer holds, and the gray paper in the corner appears darker. Similarly Katz, Gelb, and others have shown the relative constancy of colored objects in chromatic illumination, which greatly alters the nature of the reflected light.

The relative constancy of size and color is stressed because it is best established experimentally and of greatest importance for optic orientation. But other phenomena can be added which support the thesis that compensatory processes contribute to the relative constancy of our environment. Katz (758, 758b) mentions that if an object moves at a certain speed and is seen at different distances, the speed seems to be independent of the distance from the observer, although the retinal images move slower with increasing distance. Similarly, the same sound heard from various distances remains, within limits, nearly constant in spite of the variations in the physical intensity of stimulation of the auditory apparatus. Finally, the perceptions initiated by cutaneous and proprioceptive receptors, which in the active contact with an object furnish material for its recognition, contribute to the constancy of the environment. As the hand moves over the edge of a chair, the object seems to remain in its place, as do visual objects whose retinal images are displaced as the result of volitional eye movements. Moreover, in spite of the fact that the sensitivity of the skin to pressure and temperature and the perception of space (422, 423) vary considerably in the different parts used in such observations, the object appears to have constant characteristics of shape, hardness, and temperature.

The Role of the Cortex in the Apparent Constancy of the External Environment

The fundamental studies of Klüver (783) on monkeys in which both occipital lobes had been removed throw a light on the physiological mechanisms underlying these phenomena of "constancy." Such animals are unable to recognize color and shape, but they react to light, and their threshold seems not to be essentially different from that of unoperated controls. Their behavior to stimuli of varying brightness, however, is fundamentally different from that of normal monkeys.

On the basis of conditioned reactions it can be shown that the

operated monkey can be trained to respond to the brighter (or dimmer) of two areas of equal size presented at equal distance. But no distinction is possible if at the same distance the product of light intensity and area is constant although the apparent brightness is widely different. Similarly it is found that the monkey trained to react to the brighter of two equidistant areas of similar size will respond positively to the dimmer area if, owing to increased size, the amount of light entering the retina is greater than from the brighter area of smaller size. If distances are varied, corresponding results are obtained. The monkey trained to the brighter light reacts positively to the dimmer light if the latter is brought so close that again the total amount of light affecting the retina is greater. For the normal monkey (and for man) the brightness of an object is relatively constant and remains uninfluenced by alterations in size and distance within fairly wide limits. For the monkey deprived of the geniculo-striated system this constancy is lost, and the reactions are solely determined by the density of the luminous flow. These important studies suggest that the constancy of the external environment is a cortical function.

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PART VI

Applications

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Schizophrenia, the Autonomic Nervous System, and Shock Therapy

BASING his conclusions on a study of the clinico-experimental literature and on experiments concerning the physiological mechanisms involved in various forms of shock therapy, the writer emphasized in 1938 (441, 442) the autonomic disturbances in schizophrenes and the compensatory action of shock therapy. Analyses of the blood of excited psychotics for insulin gave further evidence for an imbalance of autonomic centers. The studies on alterations in conditioned reactions reported earlier have explained, at least in principle, how insulin coma and convulsions induced for therapeutic purposes may alter behavior. The thesis presented in this chapter is not different from that presented in 1938 or 1949 (456a), but its basis has been broadened by the inclusion of the most recent literature.

Autonomic Reactions in Schizophrenia

Numerous clinical investigators have asserted that disturbances of autonomic centers play a central role in the causation of schizophrenia (339, 549, 731, 972, 1115). Perhaps the anatomical changes in hypothalamic nuclei (944) in the early stages of the disease are not impressive, but functional studies seem to point definitely to the hypothalamus* and the inadequate responsiveness of its sympathetic division. Two fundamental mistakes should be avoided which will hinder further advancement: first, omitting to distinguish between higher and lower sympathetic centers; second, assuming that the peripheral action of sympathetic neurohumors is identical with that resulting from excitation of the hypothalamus.

* Hoskins (708) cites a personal letter of Ranson "expressing the belief that the best place to seek a solution of the schizophrenia problem is in the hypothalamus."

Since the work of Jung and Carmichael (742) it has been known that local autonomic responses are not absent in catatonia; such reactions are also present in the experimental animal after transection of the spinal cord (1079) and are based on the action of spinal autonomic centers. Apparently, spinal autonomic reflexes are not essentially altered in schizophrenia. The opinion of the present writer (442, 456a) that diminished central sympathetico-adrenal reactivity is at the core of the schizophrenic disturbance was "refuted" by the failure of adrenalin to improve this clinical condition (189, 659). Obviously the refutation involves a mistake in the understanding of some basic physiology. That the stimulation of autonomic centers such as the hypothalamus is accompanied by the secretion of adrenalin is undoubtedly true; however, the assumption that the secretion of adrenalin represents the sole important effect is logically and physiologically erroneous. The complex action of central autonomic excitation cannot be arbitrarily identified with only one of the factors involved.

Functional tests have revealed numerous autonomic defects in schizophrenes, particularly under conditions of stress. Finkelman and Stephens (356) found that after exposure to cold, heat production as measured by the consumption of oxygen increased less in schizophrenic patients than in normals. They also observed that the temperature fell more in the former group. This suggests that the temperature-regulating centers in the hypothalamus are less responsive in schizophrenes than in normal persons.*

Autonomic vascular responses are likewise deficient. Postural changes from the reclining to the vertical position cause a fall in the blood pressure and no change in the pulse rate in schizophrenes, whereas in normal persons the blood pressure remains unaltered and the pulse rate rises (1008). Obviously this result indicates a diminished reactivity of the sympathetic centers, which is confirmed by the relatively low systolic and diastolic blood pressure of schizophrenes as compared with that of controls (385). Experiments involving cardiovascular (Schneider) tests lead to similar conclusions (849). On the basis of these and similar investigations Hoskins (709) characterizes the schizophrene as a person with "sluggish sympathetic reactivity." In our interpretation this applies particularly to the diencephalic centers and not to the peripheral structures. Bumke's finding

* Whether the lessened diurnal temperature variations (172) can be explained on a similar basis seems to be doubtful in view of certain animal experiments described on p. 442.

(185) that excitement does not cause a rise in the blood pressure in schizophrenes is another illustration of this fact.

Comparative studies on normals and schizophrenes in situations leading to lymphopenia, to which reference has been made previously, have shown that procedures such as electroshock which stimulate the brain stem, including the medulla oblongata, are equally effective in both groups (929);* but more subtle conditions of stress, apparently operating directly or indirectly (through the cortex) on the hypothalamus, do not evoke lymphopenia in schizophrenes (383, 991) whereas they do so in normals.† The occasional association of schizophrenia with changes in the activity of the anterior hypophysis (106), which is controlled by the hypothalamus, supports the argument that the hypothalamus is involved in schizophrenia. Disturbances in the sexual sphere and in food intake occur in schizophrenia and in other functional psychoses and are to be expected if hypothalamic-hypophysial functions are altered in these pathological conditions.‡

The study of the blood sugar in excited schizophrenic patients gives further evidence for a deficient reactivity of higher sympathetic centers. Man and animals react to severe emotional excitement with a rise in the blood sugar. In the human being this has been shown clearly by the study of athletes during a football game and by the observation of blood sugar reactions in patients who were informed of an impending dangerous operation. Psychotic patients, however, show no decisive hyperglycemia in spite of a very conspicuous emotional display (120, 545, 1234). Since no hyperglycemia occurs in adrenodemedullated animals under conditions of emotional excitement, the rise in the blood sugar is due to a sympathetico-adrenal discharge (476). The absence of this reaction in psychotics appears to be due to the lack of responsiveness of autonomic centers to emotional stimuli.

* It should be mentioned, however, that emotionally deteriorated schizophrenes may fail to show signs of sympathetic excitation under conditions of electroshock (665).

† It was pointed out on p. 328 that the absence of lymphopenia in certain forms of stress appears to be due to a lessened excitability of hypothalamic-sympathetic centers, which normally initiate the secretion of adrenalin, which in turn activates the hypophysial-adrenocortical system. It is of interest to note that the weight of the adrenal cortex greatly diminishes with domestication (Richter, 1048) and that of the thymus increases. This indicates a lower level of activity of the hypophysial-adrenocortical system which is probably related to the more tranquil life of domesticated animals and the lesser excitability and tendency to fight. It is not unlikely that under conditions of domestication, and still more of civilization, the initiation of hypophysial-adrenocortical discharges from sympathetic centers is progressively diminished.

‡ For further literature see Delay (270, 271).

In view of the fact that emotional excitement induces a discharge over both branches of the visceral nervous system (vago-insulin and sympathetico-adrenal systems), the failure of the hyperglycemic reaction to occur in schizophrenes could be due either to a loss of reactivity of both autonomic divisions or to a shift in their balance. In order to decide this question a method was needed through which minute quantities of insulin could be discovered in the blood. It was found that the hypophysectomized-adrenodemedullated rat (484) reacts to very small amounts of insulin. Such animals respond to the injection of adrenalin like unoperated controls, with hyperglycemia. If blood containing both insulin and adrenalin is injected and the effect on the blood sugar of the test animal is determined, the relative balance between insulin and adrenalin in that blood can be ascertained.

In such studies (485) it was found that the blood obtained from excited mental patients produces a hypoglycemic reaction in the test animal, accompanied by typical hypoglycemic symptoms, such as a lack of righting reflexes, and occasionally by hypoglycemic convulsions (Fig. 91). The analyses of the blood sugars of the test animals showed very low values (29–40 mg. per cent). In no case were such values noted when blood from nonexcited normal persons or psychotic patients was injected into the test animal. It is concluded from these observations that in the blood of the excited psychotic patients the insulin/adrenalin ratio is greater than normal. Since in emotional excitement the blood of the patients does not show any increased blood sugar, it is inferred that the shift in the insulin/adrenalin ratio is largely due to a diminished reactivity of the sympathetico-adrenal system, with a consequent lessened adrenalin content of the blood in emotion. On the other hand, normal persons subjected to mild excitement do not show any measurable amounts of insulin in the blood and their blood sugar rises.

Two conclusions may be drawn from these experiments: (1) Emotion is accompanied by a discharge of the vago-insulin and sympathetico-adrenalin systems. (2) The sympathetico-adrenalin system predominates over the vago-insulin system in physiological conditions, but in psychotic patients, under emotional excitement a marked quantitative alteration occurs which, owing to a deficient reactivity of sympathetic centers, leads to a relative predominance of the vago-insulin system.*

* Walther (1205) reports that in 25 per cent of his schizophrenic patients the blood sugar *falls* after the administration of electroshock.

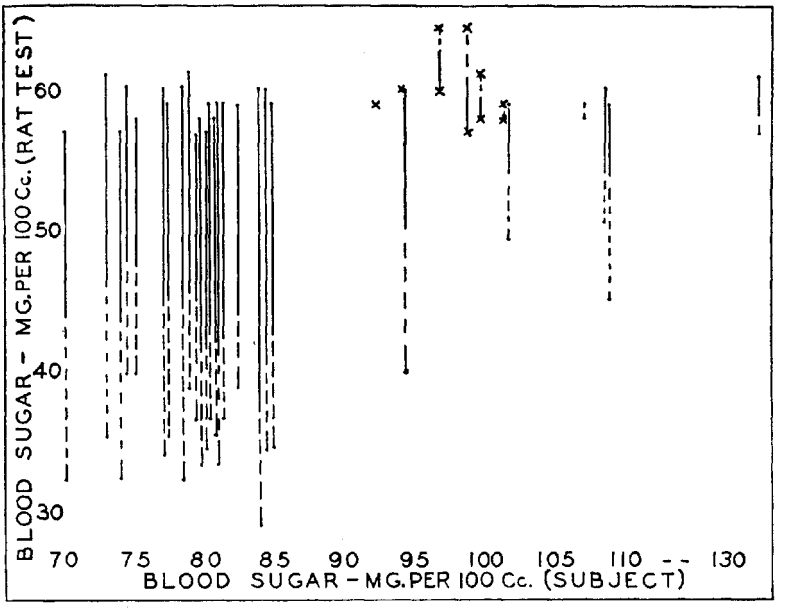

FIGURE 91. The effect of emotional excitement on the insulin content of the blood in normal subjects and in psychotic patients. The blood sugar values of the subjects are indicated on the abscissa. The effect on the blood sugar of hypophysectomized-adrenodemedullated rats of injecting 1 cc. of the blood of excited normal and psychotic persons per 100 Gm. of the rat's body weight is indicated on the ordinate. The initial and the final blood sugar values of the test animal are connected by a line which near the initial value is continuous and near the final value is interrupted. The tests made with the blood of excited normal controls are indicated by lines with crosses to distinguish them from those made with the blood of excited psychotic patients. (Gellhorn, Feldman, and Allen, 485.)

The Endocrines and the Autonomic System in Schizophrenia

Systematic studies performed under the guidance of Hoskins (708) have revealed in schizophrenes some defects in endocrine activity, although in general the changes are slight. Some degree of hypothyroidism, characterized by a low oxygen consumption, secondary anemia, and a reduction in the urinary excretion of water and nitrogen, was seen not infrequently.* The poor responsiveness of the adrenal cortex under conditions of stress has been described earlier,† although no signs of adrenocortical deficiency were found to be present in schizophrenic patients. Recent work (620) seems to indi-

* The recent work of Bowman *et al.* (121) suggests that the changes in thyroid function are more complex.

† See p. 328.

cate that gonadal atrophy not explainable on nutritional grounds likewise occurs in this condition. The various forms of endocrine therapy were in general little effective. This is perhaps not surprising if the endocrine dysfunction is the effect but not the cause of the schizophrenic disturbance.

The work on hypothalamic-hypophysial relations shows that extensive diencephalic lesions diminish the activity of the thyroid, the gonads, and the adrenal cortex. Obviously, mere functional disturbances in this area will result in lesser changes. Moreover our previous discussion has shown that hypothalamic centers have primarily the function of regulating hormonal secretion under conditions of great stress.* Under strictly physiological conditions the endocrine activity of these and other glands may not be grossly altered. If this is the case, it is not surprising that the hormonal changes in schizophrenia are not conspicuous and appear particularly when factors induced by stress operate on hypothalamic centers.

There is, however, one other aspect of endocrine physiology which should be considered in the problem of schizophrenia. Hormones are of importance to the central nervous functions because they alter the excitability of the brain. The profound influence of thyroid and adrenocortical secretions is evident from the study on conditioned reflexes. The effect of thyroid medication on the mental state and on nitrogen excretion was shown by Gjessing (549) in periodic catatonia. Stupor or excitement occurred when the nitrogen balance was positive; then a counterreaction set in during which the nitrogen balance became negative, and in this phase the mental condition of the patient improved. Upon the administration of thyroxin both the mood changes and the cycles in nitrogen excretion ceased.

The suggestion of this work that thyroid secretion may influence autonomic centers is borne out by experiments in which the sympathetic reactivity of animals to metrazol as measured by the changes in the blood sugar was studied in relation to the thyroid gland. It was found that the hyperglycemic reaction was diminished after thyroidectomy and increased on the administration of thyroxin (483). The latter effect is due to the action on sympathetic *centers*, since it occurs with subtoxic doses of thyroxin which fail to sensitize the effector organs to adrenalin.

Cortico-Hypothalamic Relations in Schizophrenia

The interdependence of cortical and hypothalamic activities and the significance of this function for various physiological and patho-

* See Chapter 13.

logical processes have been discussed previously. On this basis a deficient central sympathetic responsiveness in schizophrenia may be expected to affect the hypothalamic-cortical relationship. Although this is still a somewhat virgin territory, some pertinent observations may be cited.

Cortical stimuli are known to alter autonomic activity (398, 446, 743), and in some instances even the anatomic paths connecting various parts of the frontal cortex with the hypothalamus have been traced. Stimuli acting on the cortex must have a relatively small autonomic effect if the reactivity of the hypothalamus is reduced. This may account for the lessened palmar sweating reaction (galvanic reflex) to ideational stimuli in schizophrenes (256).

The responsiveness of the hypothalamus is diminished in schizophrenia not only to excitatory stimuli acting on this structure via the cortex but also to conditions which cause a release of the hypothalamus when cortical activity is reduced. This seems to follow from the important contribution of Hill *et al.* (650), who studied in normals and schizophrenes the effect of insulin hypoglycemia on somatic and autonomic reactions and established the following significant differences. Slow cortical rhythms of 5 to 6 per second appear in the schizophrenic group later (measured from the time of insulin injection) and at lower blood-sugar levels than in the control group. In normal persons the appearance of these slow rhythms in the frontal and central parts of the skull was promptly followed (within 1 to 2 minutes) by a rise in the heart rate and a fall in the skin resistance. Both reactions are expressions of a sympathetic discharge which is also apparent from a slight rise in the blood sugar concentration. The close temporal relation suggests that hypoglycemia diminishes cortical activity, as indicated by the increased synchrony in the EEG (theta potentials), and that it leads to a release of diencephalic and medullary sympathetic centers. Their increased discharge accounts for the changes in the heart rate and palmar sweat secretion and, through secretion from the adrenal medulla, for the rise in the blood sugar curve.

In the majority of schizophrenes theta potentials precede, as in normal persons, the appearance of the described augmented sympathetic discharges, but the time interval is greater. Here again sympathetic reactivity appears to be sluggish when compared with that of normal persons subjected to a similar strain. Moreover in a considerable number of observations the rise in the blood sugar occurs before the EEG or the palmar sweat secretion are altered. This is in agreement with the fact that the secretion of adrenalin is regulated not

only by the hypothalamus but also by lower sympathetic centers. Apparently the function of the lower (medullary and spinal) autonomic centers is not affected in schizophrenia.*

It is noteworthy that in the most severe cases (catatonic stupor) the changes in the EEG as well as the autonomic adjustment reactions are absent. A greatly diminished reactivity of the cerebral cortex is apparently associated with a lack of sympathetic excitability in these cases. Whether the former is a consequence of the latter cannot be said with certainty at present, but the profound influence which the hypothalamus exerts on the cortex makes such an interpretation not unlikely. It is important to note that with clinical improvement typical EEG changes appear in hypoglycemia and with them the above described autonomic effects on the heart and palmar skin resistance and the arrest of the fall in the blood sugar.

The fact that the reactivity of the cortex to changes in the internal environment is diminished may explain another set of data known from studies of the Worcester group. The metabolic rate of schizophrenes is significantly depressed. McFarland reported a reduction in the oxygen content (708) of the arterial blood in schizophrenes, a finding which was confirmed through continuous oximetric studies by Doust (295). Since hypoglycemia and hypoxia act similarly on the cortex of the brain – in both instances the oxygen uptake is reduced (657) – it appears likely that the failure of schizophrenes to react to a decreased oxygen saturation involves the same mechanism as in Hill's experiments. In either case cortical activity is diminished and the hypothalamus is released correspondingly, but this reaction is lessened or absent in schizophrenes, although medullary sympathetic centers continue to react to somewhat stronger stimuli and maintain homeostasis to a slightly lesser degree.†

The diminished reactivity of the cortex to hypoglycemia is perhaps the clearest example of electroencephalographic changes in schizophrenia under conditions of "functional electroencephalography." Although routine examinations have not revealed consistent differ-

* See the earlier discussed work on lymphopenia and eosinopenia.

† This interpretation is supported by the experiments of Decharneux (267) and Heymans (119), who found that denervation of the sino-aortic receptors leads to respiratory failure only in the anesthetized animal. Apparently in the waking state the diminished activity of the cortex releases the hypothalamus and initiates discharges to the vasomotor and respiratory centers in the medulla. Sino-aortic impulses originating in the chemoreceptors probably summate with those arriving from the released hypothalamus and determine thereby the degree of excitation of medullary centers in anoxia. The interrelation of sympathetic and respiratory activity in the posterior hypothalamus was emphasized by Hess (637).

ences between the EEG's of normal and psychotic persons, there is some indication in the literature that the latter group show defects in cortical reactions to stimulation. Thus a persistence of alpha potentials with open eyes and lesser changes in the EEG's of schizophrenes under the influence of hyperventilation have been reported (651). In the chapters on consciousness it was shown that the state of awareness depends on the activity of the hypothalamic system. The disappearance of alpha potentials due to fixation of an object is a reaction of attention; that is, it is linked to an increased degree of awareness. A diminution of this reaction is conceivably related to the lessened "upward discharge" from the hypothalamus in schizophrenes. Their decreased sensitivity to hyperventilation may also depend on their relative insensitivity to changes in the blood sugar, since its level is one of the determinant factors for the appearance of slow potentials in the EEG during hyperventilation (651).

A functional defect affecting primarily the sympathetic division of the hypothalamus is bound to have additional effects, particularly on nociceptive reactions, whose affinity to the hypothalamic cortical system has been discussed earlier. Indeed, Malmo (892) finds that patients in the early stage of schizophrenia do not show increased responses to increased intensities of nociceptive stimulation.

It is not unlikely that the disturbed hypothalamic-cortical relation in schizophrenia has secondary effects on the cortex, which in turn aggravate the hypothalamic defect. Such an interpretation is suggested by the observation that the diurnal variations in body temperature become more regular and approach the normal pattern after frontal lobotomy (173). However, more evidence is needed to justify this assumption.

The changes which occur in the hypothalamic-cortical system during schizophrenia probably account to a considerable extent for the clinical course of the disease. The restitution of normal hypothalamic-cortical discharges is thought to influence behavior, as indicated by the changes in conditioned reflexes following shock treatment.* Whatever its cause, it is not unlikely that a deficiency in hypothalamic function occurs after a period of excessive activity, at least in some cases. The study of schizophrenic geniuses indeed shows that a period of increased creativeness precedes the relatively slow process of decline, as evidenced from Jaspers' analysis (737) of Hölderlin and Van Gogh. During the former period even the physical strength seems to be increased. This illustrates the ergotropic effects of the sympathetic division of the diencephalon (Hess, 637) and its

* See pp. 370ff.

association with a corresponding excitation of the hypothalamic-cortical system.

We come, therefore, to the conclusion that schizophrenia is physiologically characterized by a deficient reaction of the sympathetic division of the autonomic nervous system at the hypothalamic level,* possibly initiated by overactivity and favored by constitutional factors. The weakened sympathetic and somatic "downward discharge" is expressed in a decreased blood pressure and lessened circulatory adjustment reactions, and also a diminished muscle tone, whereas the failure of the hypothalamus adequately to regulate hypophysial secretions leads to endocrine disturbances. The reduced reactivity of the hypothalamus to cortical stimuli further contributes to defects in homeostasis. The mental changes attending schizophrenia are primarily related to a defective hypothalamic-cortical discharge.

If this theory is correct, at least in its core, it is to be expected that procedures which attempt to remedy the disturbed equilibrium by supplementing the deficient "downward discharge" by the injection of adrenalin or applications of various hormones are bound to fail. What is needed is procedures which increase hypothalamic reactivity and maintain this effect for an adequate period of time so that hypothalamic-cortical relations approach normality. The following discussion will show that various shock treatments belong in this category. It is hardly necessary to emphasize that the suitability of a therapeutic agent, particularly in mental disease, has to be determined by clinical observation. Physiological research can provide only blueprints for therapy. But progress in psychiatry, as in any other branch of medicine, will be delayed unless a knowledge of the basic physiology underlying the clinical disturbances is utilized.

Electroshock and Related Procedures

The introduction of shock therapy was founded entirely on empirical grounds which need not be reviewed here. Since convulsions, hypoglycemic coma, and barbiturate sleep act quite differently on the cortex, these effects can hardly be assumed to reveal the physiological principle upon which shock therapy rests. However, in view of the importance of the hypothalamus for normal emotion as well as for disturbances of mood and behavior the effect of these procedures on the autonomic system must be considered if a common basis for their action is to be found.

* The recent work reported in the last chapter indicates that deficient sympathetic reactivity is characteristic of only a part of the entire number of schizophrenic patients.

Electroshock as well as metrazol induces a sympathetico-adrenal discharge indicated by hyperglycemia, which is prevented by splanchnicotomy or adrenodemedullation. After elimination of the adrenal medullae convulsive procedures lower the blood sugar, but this effect is absent when the vagi are cut below the diaphragm. The experiments prove that convulsions excite the centers of the autonomic system and cause a sympathetico-adrenal and a parasympathetic (vago-insulin) discharge, with the former predominating in normal animals (351, 497). The changes in the blood pressure following electroshock support this interpretation. The initial fall is of vagal origin and followed by a prolonged rise due to increased sympathetic discharges (1011). The depression of sympathetic centers with barbiturates reveals the parasympathetic action which is absent in curarized unanesthetized animals (1099). The shortening of the blood-clotting time after electroshock (1205) suggests in the light of Cannon's studies (191) the secretion of adrenalin, and chemical analysis of the blood has indeed shown that the adrenalin content of the blood is increased (777).

The excitation of the autonomic system after the injection of metrazol has been studied in the anesthetized animal through its action on the pupil, nictitating membrane, and blood pressure (478). The pupils dilate (the normal to a greater degree than the sympathetically denervated one), the nictitating membrane contracts, and the blood pressure shows after an initial fall (parasympathetic excitation) * a prolonged rise (Fig. 92). These autonomic effects are independent of convulsions, since they occur after metrazol in curarized animals.

The change in the responsiveness of sympathetic centers under the influence of metrazol or other convulsants can be demonstrated through somato-visceral reflexes (478). If the stimulation of the brachial plexus has no effect on the nictitating membrane and causes either no change or a slight fall in the blood pressure, this action will be greatly changed after metrazol. A contraction of the nictitating membrane and a pressor response indicate increased sympathetic reactivity (Fig. 93). That the hypothalamus undergoes similar changes follows from stimulation experiments with the nictitating membrane as indicator (208). Other convulsants act in like manner. Moreover subconvulsive doses of metrazol cause a severe emotional response (1074). The action of subconvulsive electroshock studied in the barbiturized patient gives evidence for hypothalamic excitation

* Parasympathetic excitation can also be demonstrated in the sympathectomized pupil (1180).

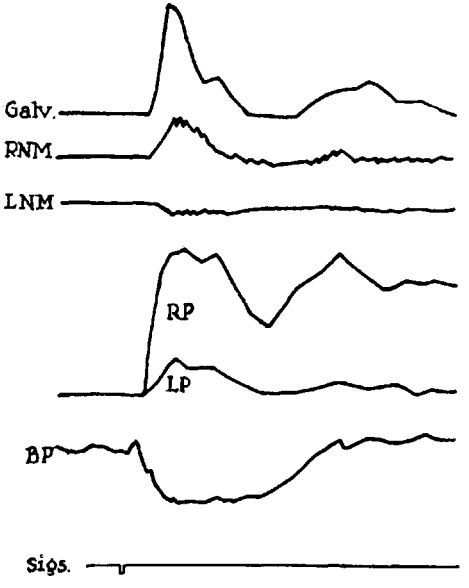

FIGURE 92. A diagram of the autonomic effects induced by the intravenous injection of metrazol (signal). Galv., galvanic reflex; RNM, right normal nictitating membrane; LNM, left denervated nictitating membrane; RP, normal pupil; LP, sympathectomized pupil; BP, blood pressure. The galvanic reflex (sweat secretion), the contraction of the nictitating membrane, and the difference in dilatation between the normal and sympathectomized pupil indicate sympathetic excitation. (Gellhorn and Darrow, 478.)

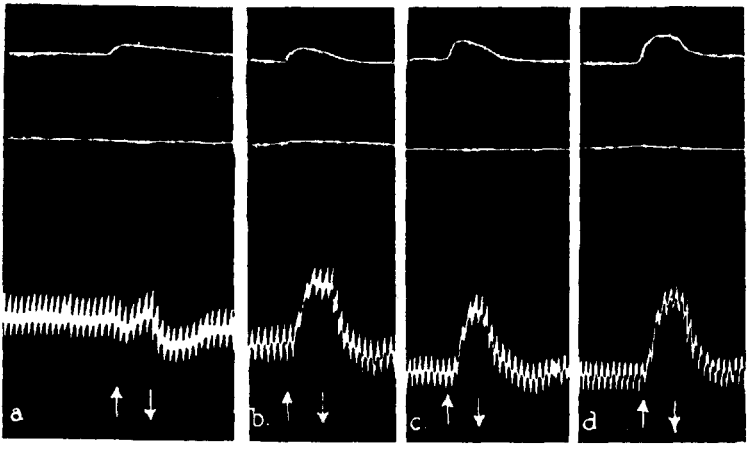

FIGURE 93. The action of metrazol on the reflex stimulation of the blood pressure and nictitating membrane (n.m.) of the cat (top record, innervated n.m.; middle record, denervated n.m.; bottom record, blood pressure). Stimulation of the brachial plexus between arrows. *Records a:* before the injection of metrazol. *Records b, c, and d:* after the injection of 0.2 cc. of 10-per-cent metrazol. Note the increase in sympathetic responsiveness. (Gellhorn and Darrow, 478.)

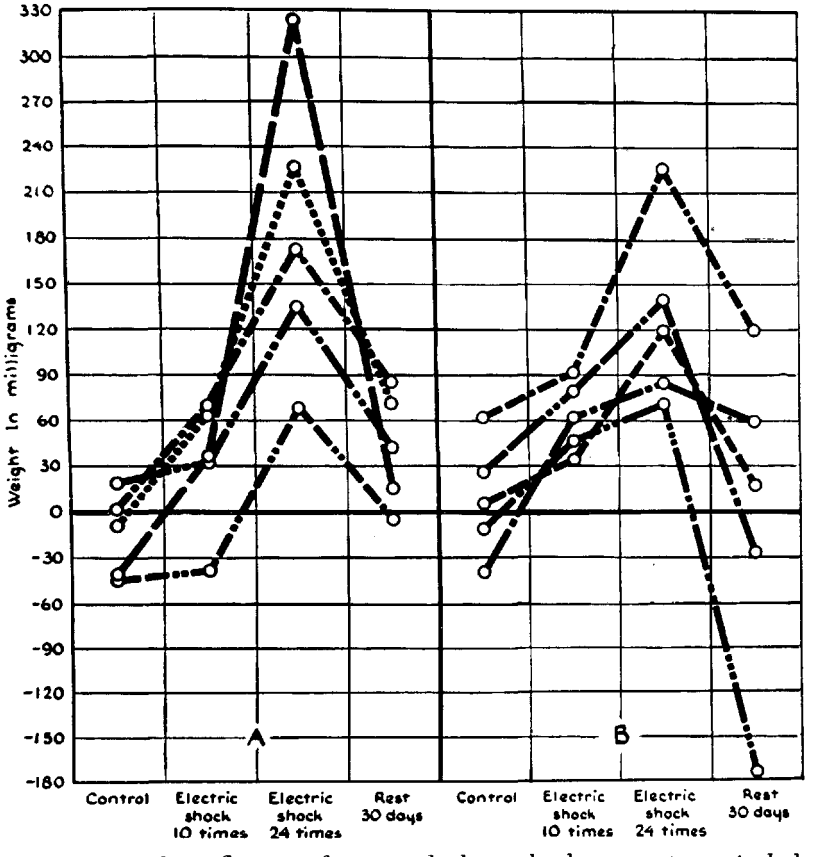

FIGURE 94. The influence of repeated electroshocks on autonomic balance. The blood sugar curve to a standard anoxia was graphed for each animal, and the weight of the area of hypoglycemia was deducted from that of the area of hyperglycemia. Positive numbers indicate sympathetico-adrenal predominance; negative numbers, vago-insulin predominance. The figures are divided into A and B in order to avoid superimposition of the curves. They show increased sympathetico-adrenal predominance after a series of electroshocks. (Gellhorn and Safford, 513.)

(crying and rage reactions). With convulsive shocks signs of sympathetic excitation increase and a profound perspiration as in insulin coma is observed (665). That metrazol and picrotoxin induce ovulation in rabbits provided that the hypophysial stalk is intact (153) likewise proves hypothalamic excitation in convulsions.

The sympathetico-adrenal discharges and the augmented excitability of autonomic centers appear to be the basis of increased hypothalamic-cortical discharges. In order to link these phenomena to changes

in behavior, it is necessary to show that alterations in the autonomic centers outlast the period of excitation for a considerable time.

This is the case after repeated electroshocks,* as indicated by the blood sugar reactions to a standard anoxia. An increased hyperglycemic response persists for several weeks (513) (Fig. 94). Moreover a period of ten daily electric shocks was shown to alter the temperature control of the rat. The daily temperature variation was less and the level of the temperature of the body was higher than that of control animals in spite of lessened activity (712). These observations strongly suggest that as the result of repeated electroshocks the activity of the sympathetic division of the hypothalamus is increased. Consequently the heat loss is reduced and possibly the production of heat is raised. The activity of the parasympathetic hypothalamic centers controlling the loss of heat is not altered to a similar degree; otherwise the temperature of the body would not be elevated.

The studies on the action of repeated electroshocks on the blood sugar and temperature control indicate that the autonomic balance is shifted toward the sympathetic side. That repeated insulin comas have a similar effect seems to follow from Hill's work (650) which was discussed earlier.

Insulin Hypoglycemia, Sleep Treatment, and the Autonomic System

The action of insulin coma and induced-sleep treatment (*Dauerschlaf*) on the cerebral cortex is quite different from that of electroshock or metrazol. Instead of producing convulsive discharges (frequent spike potentials of high amplitude) hypoglycemic coma and barbiturates depress cortical activity, as indicated by the slowing of potentials in the EEG and the appearance of grouped sleeplike potentials in the ECG. Nevertheless the functional changes in the autonomic nervous system are similar in both groups.

The occurrence of a sympathetico-adrenal discharge in hypoglycemia has been well established by numerous investigations. More adrenalin appears in the blood during hypoglycemia than under control conditions, and the adrenalin content of the adrenal medulla is diminished (609). The greater sensitivity of sympathectomized

* Experiments on the effect of repeated insulin comas on the blood sugar response to a standard anoxia test were not successful because such rats fail to react with a glycogenolysis even to injected adrenalin. This work should be repeated with a method not involving the blood sugar as an indicator. Perhaps the changes in temperature regulation after a series of hypoglycemic comas will be found to be similar to those after electroshocks.

animals to insulin is accounted for by the absence of the compensatory sympathetico-adrenal discharge. That the excitation of the sympathetic system is not confined to the release of adrenalin is shown by the fact that insulin hypoglycemia causes constriction of the denervated nictitating membrane in animals in which the adrenals have been functionally eliminated. Therefore the contraction of the denervated nictitating membrane appears to be due to the release of sympathin from postganglionic sympathetic nerve endings. It has also been shown that hypoglycemia leads to a fall in lymphocytes which is partially initiated by a sympathetico-adrenal discharge (487).

As to the action of barbiturates on the autonomic nervous system, it may be said that they raise the blood sugar temporarily. This effect is due to a sympathetico-adrenal discharge, since it is absent after adrenodemedullation (446). This interpretation is supported by the observation that barbiturates lead to a temporary dilatation of the chronically denervated pupil, suggesting again a release of adrenalin (511). However, with higher degrees of barbiturate narcosis the pupils constrict, since the reactivity of the hypothalamus declines under these conditions.

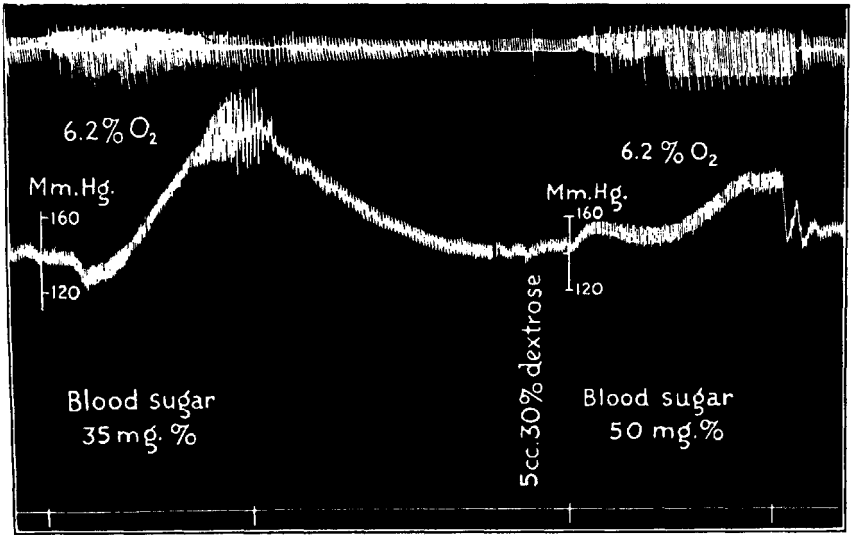

FIGURE 95. The influence of the blood sugar level on the reaction of the blood pressure to the inhalation of 6.2-per-cent oxygen, in a dog under sodium barbital anesthesia. Records are shown for the respiration (top) and for the blood pressure. Between the marks on the bottom line 6.2-per-cent oxygen was inhaled for 3 minutes. Note that the (sympathetic) pressor response increased with the fall in the blood sugar. (Gellhorn, Ingraham, and Moldavsky, 492.)

An increased reactivity of autonomic centers in hypoglycemia is inferred from a study of the pressor effects induced by the inhalation of oxygen-nitrogen mixtures at various blood-sugar levels (492). It was found in experiments on anesthetized animals (Fig. 95) as well as in man (800) (Fig. 96) that the vasopressor action of anoxia increases with a decreasing blood-sugar level and that a similar effect can be demonstrated when carbon dioxide is used as a stimulus (500).

Since carbon dioxide continues to have an increased vasopressor action in hypoglycemia after denervation of the sino-aortic receptors, it may be said that there is an increased reactivity of autonomic centers to reflex stimulation (action of anoxia on the chemoreceptors of the sino-aortic area) and to the direct stimulation of sympathetic centers (carbon dioxide pressor effect in the sino-aortic denervated animal). Similarly it was found that the rise in the blood pressure

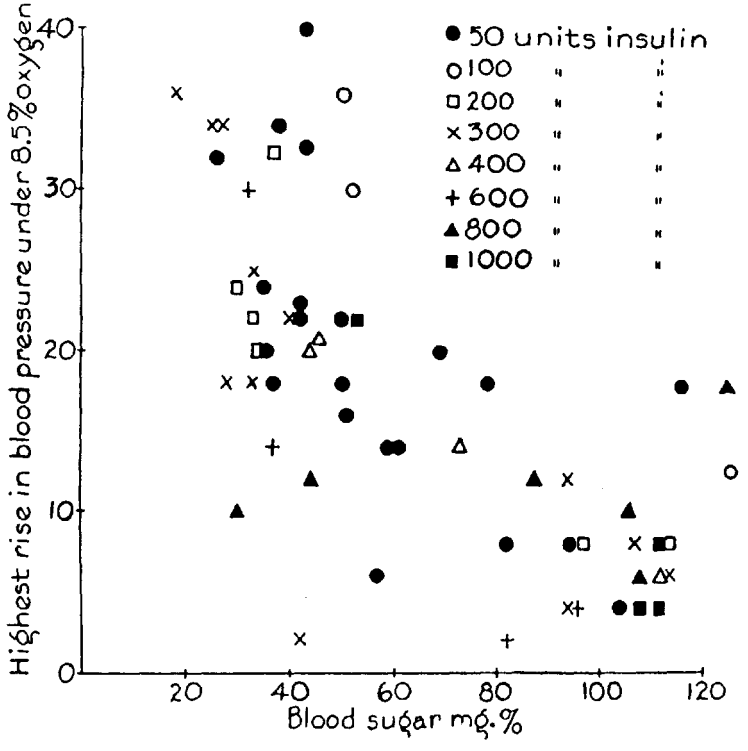

FIGURE 96. The effect of a lowered blood sugar (injection of insulin) on the reaction of the blood pressure in man to the inhalation of 8.5-per-cent oxygen. Note that the blood pressure response to hypoxia increases with a falling blood sugar. (Kraines and Gellhorn, 800.)

subsequent to increased intracranial pressure increases with a falling blood sugar and that this result persists after sino-aortic denervation (1253). Although it may be stated with confidence on the basis of these experiments that the reactivity of the sympathetic centers to afferent impulses originating in the chemoreceptors of the sino-aortic region and to direct stimulation is increased in hypoglycemia, it remains to be shown that these changes affect medullary *and* hypothalamic centers.

It should be added that as in other shock procedures the excitation is not confined to the sympathetic division. Increased gastric secretion and motility appear as the blood sugar falls (378), a fact suggesting that parasympathetic discharges are also augmented as the inhibitory action of the cortex on the diencephalon diminishes. Whereas the pulse rate rises in the normal animal as the blood sugar falls, a slowing of the heart rate occurs under these conditions if the sympathetico-adrenal system has been surgically eliminated (308). Apparently moderate hypoglycemia induces vagal and accelerator discharges with predominance of the latter. Only in the final stages of hypoglycemia is this balance between the parasympathetic and sympathetic division reversed (657).

Some Modifications of Shock Therapy

A few comments may be made on the physiological action of some modified shock procedures. Electronarcosis shows initially signs of parasympathetic discharge, followed by tachycardia, a marked rise in the blood pressure, and hyperglycemia (122, 1040). In the guinea pig it is regularly accompanied by ejaculation. As in electroshock, lymphopenia occurs, probably owing to direct action of the electric current on the hypothalamic-hypophysial system. In animal experiments it could be shown that electronarcosis after repeated applications leads to the hypertrophy of endocrine glands (thyroid, adrenals, and gonads) and that the amount of thyrotropic hormone circulating in the blood is increased (314). It is of importance that the excitatory effect on the sympathetico-adrenal system of electronarcosis has been found to be based at least in part on the accompanying respiratory arrest (1159).

While electronarcosis resembles electroshock in that in both procedures the hypothalamus is directly excited (741) and induces hypophysial and autonomic discharges, the action of anoxia is closely related to that of hypoglycemia. The treatment of schizophrenia by the inhalation of nitrogen has been in vogue only temporarily. Anoxia excites the centers of the autonomic system. The effect is again more

marked on the sympathetic than on the parasympathetic division (446), except for the final stages in anoxia (1083). Sympathetic excitation is primarily a reflex effect from the sino-aortic chemoreceptors (502), but the release of autonomic centers in the hypothalamus and medulla oblongata likewise plays an important role (475).

Fever therapy has also been employed in schizophrenia. Although its action on the cortex of the brain is fundamentally different from that induced by convulsions, insulin coma, or anoxia, the effect on the visceral system is similar to that produced by other shock procedures. Studies on the blood sugar show an excitation of the sympathetico-adrenal and vago-insulin systems, with a predominance of the former (353). The blood pressure, heart rate (132), and secretion of adrenalin also increase (201).

Finally, it should be mentioned that the basic shock procedures are applied in certain combinations or in conjunction with other drugs. Sargant (1084) uses electroshock at the beginning of the insulin coma with favorable results. Sympathetic reactivity is greatly increased under these conditions, as seen by the changes in the pulse rate. Whereas electroshock temporarily slows the heart beat in normal animals, the rate is augmented when the shock is applied during hypoglycemic coma, and this effect persists for a long time (499). The action on the circulatory system is so great that normal cortical electrical potentials appear even in adrenodemedullated animals in which, owing to the elimination of increased adrenalin secretion, the blood sugar remains at coma levels!

As far as the autonomic nervous system is concerned, the combined insulin-histamine treatment (652) acts in a similar manner. The fall in the blood pressure induced by histamine must call forth a sympathetico-adrenal discharge which may be expected to be greater in hypoglycemia than at a normal blood-sugar level, since in the former condition the centers of this system are in a state of heightened excitability.*

In the two combinations discussed so far hypoglycemia was used as a means of increasing autonomic reactivity through a release from cortical inhibition. A similar effect may be produced if such a release from cortical control is induced by barbiturate sleep and the autonomic centers are excited through sympathomimetic drugs, for instance, amphetamine (259).

* Acetylcholine injected intravenously in doses to cause temporary circulatory and respiratory failure is bound to induce prolonged sympathetico-adrenal discharges (354). This procedure has been used therapeutically.

Concluding Remarks

It may be inferred from this analysis that the various procedures used in the "shock treatment" of schizophrenia act on the centers of the autonomic system, produce intensive and prolonged sympathetico-adrenal discharges, and alter, through augmented hypothalamic-cortical activity, mental processes and behavior. Each of the procedures used, however, exerts a multiple action on the organism, and the question remains whether the emphasis on the autonomic system and its cortical projection is justified or whether other mechanisms play an equally important role.

The main argument showing the relation of schizophrenia to the hypothalamus and the changes in sympathetic reactivity as improvement takes place* need not be repeated. The suggestion that cortical damage, which undoubtedly accompanies repeated insulin comas (359, 870), is responsible for the therapeutic effect is unlikely because: (1) marked changes in behavior, as indicated by the reappearance of previously inhibited conditioned reactions, appear after very few comas; (2) repeated electroshocks which act similarly on conditioning do not alter the cortex structurally in experimental animals (1112); and (3) anoxia, which produces severe cortical changes (241), has relatively little influence on conditioned reactions (463) and is apparently ineffective in schizophrenia (380). It is not denied, however, that the shock procedures produce cortical damage which may be responsible for the slight defect in learning processes seen in experimental animals (1023).

That anoxia is commonly involved in shock treatment is undoubtedly true. In the state of hypoglycemia the reduction in the oxygen uptake of the brain (657) and the increased sensitivity of the cerebral cortex to mild degrees of anoxia (498) are well established. However, if anoxia were the determining factor (Himwich, 659), one would expect nitrogen therapy to be the most effective, and this is not the case. The decrease in the oxygen saturation of the arterial blood during metrazol seizure is only slight and very brief (858).

Although the available data do not support the assumption that anoxia is the therapeutic agent, studies on the action of anoxia on the reactivity of autonomic centers are of some interest in an attempt to evaluate further the conditions which are operative in shock therapy. It was found that repeated periods of hypoxia lead to a prolonged increased reactivity and a change in the balance of autonomic centers, with predominance of the sympathetic. Nevertheless the effect of anoxia on conditioned reactions was slight, contrary to

* See pp. 436 and 479.

that of repeated electroshocks, although the influence of both procedures on the autonomic centers was similar.

These data allow one to define more precisely the changes involved in effective shock therapy. First, they depend, as has been emphasized throughout this chapter and in earlier work (456a), on the prolonged increased reactivity of sympathetic hypothalamic centers, leading to an intensified discharge to the thalamus and cerebral cortex. Second, they presuppose a state of the cortex which is responsive to quantitative alterations in the hypothalamic-cortical discharge. Anoxia and particularly asphyxia are powerful stimulants of the sympathetic system, but their profound effect on the cortex counteracts the beneficial activation originating in the hypothalamus. This may explain why electronarcosis is not more effective than electroshock in the treatment of schizophrenia in spite of greater sympathetico-adrenal excitation (1114).

Some of the major points presented in this chapter may be summarized as follows:

1. Reactions to stress, particularly in its more subtle forms, which elicit sympathetic responses in normal persons are weak in schizophrenes. This suggests that the higher sympathetic centers in the diencephalon are less reactive in this psychosis. Studies on the insulin and adrenalin content of the blood under conditions of emotion confirm this conclusion. Moreover it is known that sympathetic reactivity increases with clinical improvement.*

2. Procedures used in the shock therapy of mental disease invariably involve in the experimental animal an excitation of the sympathetico-adrenal system, as indicated by hyperglycemia, contractions of the nictitating membrane, a rise in the blood pressure, sweat secretion, lymphopenia, etc. Hypothalamic and/or medullary autonomic centers are in a state of heightened excitability, as seen in experiments involving direct or reflex stimulation. Chronic experiments indicate that this state of increased sympathetic reactivity may persist for relatively long periods of time.

3. It is suggested that this state of heightened hypothalamic and medullary discharges is caused by two fundamentally different mechanisms. In insulin hypoglycemia and barbiturate medication (*Dauerschlaf*) it is the result of disinhibition from cortical control; in convulsions induced by metrazol or electroshock the direct excitation of these centers appears to be primarily involved, although the cortical silence following generalized convulsions may also contribute to hypothalamic excitation through disinhibition.

* See p. 466.

4. Activation of the hypothalamus, directly or reflexly, is accompanied by excitation of the ipsilateral and contralateral cortex. This "upward discharge" also occurs in conditions in which cortical excitability is reduced or abolished, and it is due to hypothalamic excitation through cortical disinhibition. These hypothalamic-cortical changes are believed to be responsible for the alteration in behavior patterns seen after successful treatment in clinical cases as well as in conditioned reactions of experimental animals. Procedures which increase hypothalamic-cortical discharges but cause considerable damage to the cortex at the same time are unsuited for shock therapy. This appears to be the reason why anoxia is little effective in schizophrenia and in the restitution of previously inhibited conditioned reactions.

5. That changes in conditioned reactions which occur in normal as well as in adrenodemedullated animals as the result of shock therapy cannot be induced by the injection of adrenalin is not in contradiction with the theory. Its core is not that insulin coma and electrically or chemically induced convulsions act through the secretion of adrenalin but that these procedures greatly increase the reactivity of autonomic centers which in turn may influence the brain in such a manner as to restore normal behavior.* The peripheral manifestation of the convulsions is likewise of no consequence, since the therapeutic effect of electroshock is not reduced if convulsive responsiveness is greatly diminished through blocking agents which like C_{10} (bis-trimethylammonium decane diiodide) act on the neuromuscular junction (583).

* Frontal lobotomy might be expected to influence hypothalamic reactivity and hypothalamic-cortical functions, since close relations exist between the frontal lobe, and particularly its orbital part, and autonomic reactions (743). However, the observations of Rinkel *et al.* (1055) on the influence of lobotomy on autonomic reactions (blood pressure rise induced by the injection of adrenalin, and effect on the EEG of stimulation of the carotid sinus) do not seem to lend themselves to a physiological interpretation. Perhaps studies with the mecholyl test will be more successful. (See p. 485.)

~ 19 ~

The Physiological Foundation of Carbon Dioxide Therapy

IT WAS shown in the preceding chapter that through a study of the physiological mechanisms involved in the shock therapy of mental diseases some light is thrown on the nature of the disease process and a new approach to therapeutic problems appears to be possible based not on empirical data but on physiological principles. In 1929 Loevenhart and his associates (853) made some interesting observations on establishing contact with catatonics under the influence of high concentrations of carbon dioxide. This study has been resumed by Meduna (923), who reports favorable effects from carbon dioxide therapy in psychoneurotics. These clinical observations pose the question of the basic mechanism in the action of carbon dioxide on the central nervous system. No attempt will be made to review the extensive literature on this subject, but a brief discussion of some of the fundamental aspects of the problem is deemed necessary before the influence of very high concentrations of carbon dioxide on the nervous system is discussed.

The Action of Non-Narcotic Doses of Carbon Dioxide on the Somatic Nervous System

In view of the fact that the role of carbon dioxide in the regulation of respiration and the blood pressure has long been recognized, it is not surprising that its action on the central nervous system has been studied extensively. It will be apparent from the discussion that the effect of carbon dioxide depends somewhat on the site of action.

Thus it was found that the knee jerk is influenced differently in the intact animal and after a spinal transection (775). In the former

condition it may be abolished by the inhalation of 10-per-cent carbon dioxide, and even a lesser concentration (4.5 per cent) may reduce it considerably; in the latter 10-per-cent carbon dioxide does not alter this reflex and a decline of this response requires concentrations up to 42 per cent! That spinal shock is not the basis of this differential behavior is shown by the fact that the knee jerk behaves similarly with respect to carbon dioxide in chronically and acutely operated animals with spinal transections. The observation that decerebrate animals are as resistant to carbon dioxide as spinal animals suggests that carbon dioxide acts on a supracollicular area of the brain and thereby inhibits the spinal knee jerk. In a recent study 8.9-per-cent carbon dioxide induced a greater depression of monosynaptic than of polysynaptic spinal reflexes (778).

The linguo-maxillary reflex, which is elicited by the stimulation of nociceptive receptors in the tongue and causes a contraction of the digastric muscle, is definitely inhibited by 7-per-cent carbon dioxide (572). This phenomenon is the more striking as the reflex center is located in the medulla oblongata, which under the influence of carbon dioxide increases the blood pressure and respiratory activity. The action of carbon dioxide on the linguo-maxillary reflex persists after bilateral vagotomy and denervation of the carotid sinus area and is consequently independent of the chemoreceptors and due to a direct influence on somatic medullary reflex centers. Apparently carbon dioxide alters somatic multineuronal reflexes in the same manner at the medullary as at other levels of the nervous system. Only respiratory activity, although involving striated muscles, behaves differently. Respiratory activity is increased in hypercapnia even after denervation of the sino-aortic area. This phenomenon is a homeostatic reaction of greatest importance, since the increased respiration eliminates the excess of carbon dioxide and thereby its deleterious action on the somatic nervous system.

Vestibular reflexes with their reflex centers in the brain stem, including the medulla oblongata, have likewise been shown to be sensitive to carbon dioxide. In man the inhalation of 6-per-cent carbon dioxide leads to a reversible reduction in the number of nystagmic movements following caloric stimulation (516). In animals, particularly in light urethane anesthesia, the nystagmus resulting from galvanic stimulation of the internal ear is diminished during the administration of 10-per-cent carbon dioxide (518). The threshold of the corneal reflex rises in these circumstances (1028).

The action of carbon dioxide on the cortex of the brain has been studied in man through the use of sensory tests. Thus it was found

that visual functions decline reversibly in hypercapnia. This is indicated by the increase in the threshold for the discrimination of brightness (435) and by the lengthening of the latent period of negative after-images (515). The effect occurs a few minutes after the inhalation of carbon dioxide in concentrations of 5 to 7 per cent. Similarly the threshold for hearing rises under these conditions (514). Studies on action potentials in unanesthetized rabbits indicate that 8-per-cent carbon dioxide reduces the responsiveness of the cortical visual projection area to optical stimuli (799). Finally, it should be mentioned that association tests and the performance of simple mental operations show qualitative and quantitative deterioration in hypercapnia (496, 501).

The motor cortex has likewise been found to respond rapidly to the inhalation of 10-per-cent carbon dioxide. The effect of cortical stimulation is abolished in a few minutes; it returns upon the readmission of air (464).

The Excitatory Effects of Carbon Dioxide

One might be inclined to conclude from these data that carbon dioxide in moderate concentrations decreases somatic functions at all levels of the central nervous system and that, in analogy with the action of anoxia, the cerebral cortex is more sensitive than the medulla or the spinal cord. There are, however, some important indications that the action of carbon dioxide is far more complex.

It is well known that carbon dioxide increases the frequency and decreases the amplitude of cortical potentials as noted in the human EEG and direct recordings from the cortex of animals (544). This phenomenon is similar to the changes in the EEG seen during mental activity or sensory stimulation and appears primarily to be due to an excitation which results in a decreased synchrony of cortical potentials. A further sign that cortical activity is greater during hypercapnia than under control conditions is the increased frequency of convulsive discharges (after strychnine spikes have been produced by the application of this drug to the cortex). It may be seen in the same animal that the sensory response to acoustic or optic stimulation is decreased, while strychnine spikes become more frequent and cortical potentials undergo changes in the direction of less synchrony ("Dial" potentials disappear, background activity is augmented) (488).

In the discussion of the problem of consciousness it was pointed out that cortical excitability depends on at least two systems, the long afferent tracts, which send impulses to the specific projection areas, and the hypothalamus, which through its "upward discharge"

influences the cerebral cortex as a whole. The experiments already discussed and the following observations show that these two systems are influenced by carbon dioxide in opposite ways.

Upon the inhalation of 10-per-cent carbon dioxide signs of decreasing synchrony appear in the ECG which in degree depend on the state of anesthesia. If the animal is relatively "light," the grouped "sleep" potentials may become less frequent or disappear and are replaced by small and more frequent "background" potentials. If the animal is in a state of relatively deep anesthesia, the cortical changes may be insignificant, but even under these conditions the action of carbon dioxide on the hypothalamic-cortical system can be demonstrated through the application of proprioceptive or nociceptive stimuli. It will be remembered that these stimuli act on the hypothalamus and cortex and that the degree of generalized cortical excitation is paralleled by that of the hypothalamus. If a mild stimulus is applied, its effect on the hypothalamus and cortex is greatly intensified during the inhalation of 10-per-cent carbon dioxide, and subthreshold stimuli become effective. At the same time the potentials evoked in the specific projection areas by acoustic or optic stimuli which do not alter hypothalamic activity are slightly diminished (462).

Figure 97 shows that a mild nociceptive stimulus has a moderate excitatory effect on the sensorimotor area, indicated by an increase in background activity. If, however, the same stimulus is reapplied while the animal inhales 10-per-cent carbon dioxide, a very dramatic effect occurs in all areas. In the cortex and hypothalamus both frequency and amplitude increase, and this effect persists for a considerable time after cessation of the stimulus. The generalization of the cortical effect and its intensification are due to the summation of the excitatory action of carbon dioxide and of nociceptive impulses on the hypothalamic-cortical system.

There is some further evidence for the dual mechanism which determines the action of carbon dioxide on the cerebral cortex. It was mentioned earlier that cortically induced strychnine spikes increase in frequency during hypercapnia. If this effect were due to increased hypothalamic-cortical discharges, one would expect that their elimination would reveal a direct cortical action of carbon dioxide on strychnine spikes. For this purpose a large section of one cortex was surgically isolated, and the behavior of topically induced cortical strychnine spikes was studied on this and the intact contralateral cortex under the influence of carbon dioxide. It was found that whereas the frequency of the spikes increased under these condi-

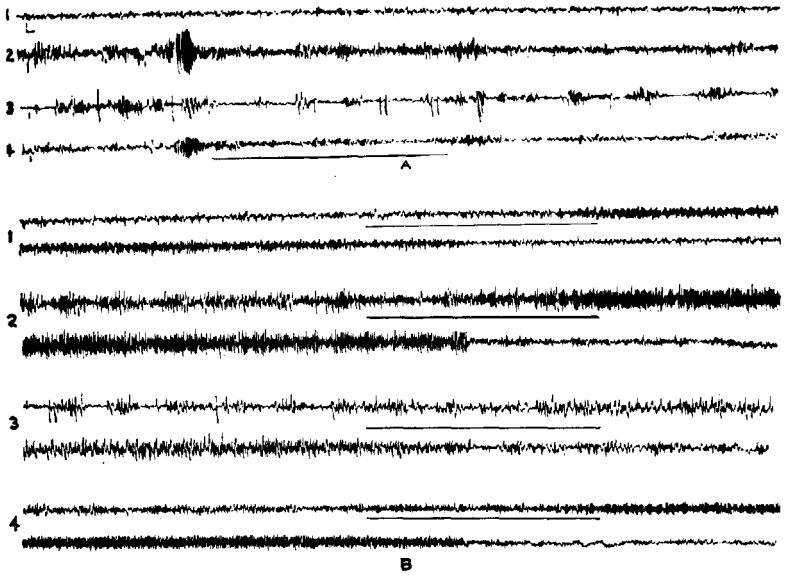

FIGURE 97. The intensification of the action of nociceptive stimuli on the hypothalamic-cortical system by the inhalation of 10-per-cent carbon dioxide. Between the points indicated by the horizontal lines, the hind leg of a cat was immersed in water of 60° C. for 25 seconds. Records 1 are from the right hypothalamus; 2, from the left motor cortex; 3, from the left gyrus suprasylvius; and 4, from the right motor cortex. *Records A:* before the inhalation of carbon dioxide. *Records B:* during the inhalation of 10-per-cent carbon dioxide. The four records of *B* are continuous. (Gellhorn, 462.)

tions in the normal cortex, it declined in the isolated cerebral gray matter (488). The conclusion from this experiment is obvious:

1. The increase in frequency of cortical strychnine spikes occurring during the inhalation of 10-per-cent carbon dioxide is due to subcortical discharges.

2. If subcortical discharges are eliminated, the effect of carbon dioxide on the cortex results solely in a decrease in excitability.

3. Subcortical discharges account for the increased responsiveness in hypercapnia of the cerebral mantle to nociceptive and proprioceptive excitation.

The subcortical discharge responsible for these phenomena originates in the posterior hypothalamus, since lesions in this area abolish increased spike frequency to carbon dioxide and reduce or eliminate the generalized excitation of the cortex following nociceptive stimulation (790). It is particularly interesting to note that through a

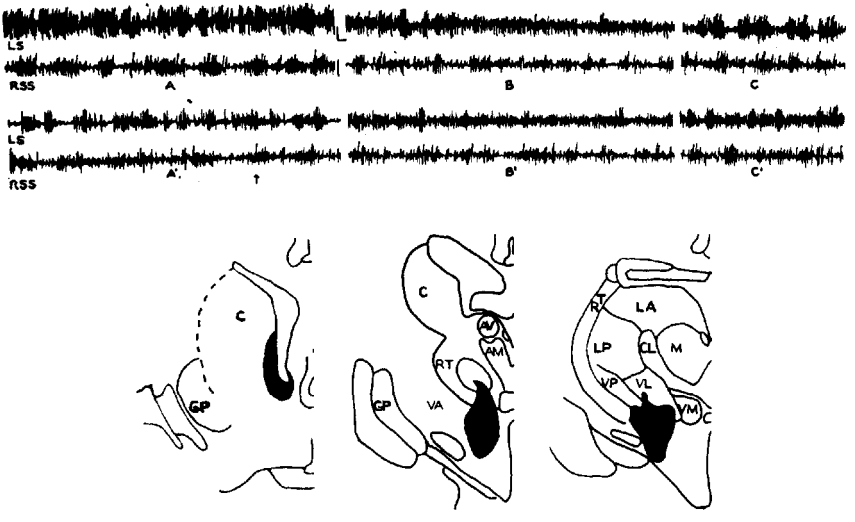

FIGURE 98. The effect of the inhalation of 15-per-cent carbon dioxide on cortical potentials before (records A, B, and C) and after (records A′, B′, and C′) coagulation of the right posterior hypothalamus extending into the anterior hypothalamus and caudate nucleus. LS, left sigmoid gyrus; RSS, right suprasylvian gyrus. *Records A and A′:* control. *Records B and B′:* during the inhalation of carbon dioxide. *Records C and C′:* after the readmission of air. Before coagulation the excitatory effect of carbon dioxide is bilateral; after coagulation it is confined to the left cortex contralateral to the lesion. (Koella and Gellhorn, 791.)

unilateral lesion in the hypothalamus these effects may be abolished ipsilaterally but persist in the contralateral cortex (Fig. 98). The effect of carbon dioxide on potentials of the auditory projection area induced by acoustic stimuli persists under these conditions.

That the hypothalamus is excited when 10-per-cent carbon dioxide is inhaled is evident not only from the changes in the potentials recorded from this structure but also from its increased reactivity. The greater effect of proprioceptive and nociceptive stimulation on the cortex paralleling its action on the hypothalamus has already been mentioned. Electrical stimulation of the hypothalamus elicits a greater autonomic response in hypercapnia than under control conditions, indicated by the increased rise in the blood pressure* and augmentation of the contraction of the nictitating membrane (446) (Fig. 99). Here again is an example of parallel changes in the autonomic "downward" and the somatic "upward discharge" from the hypothalamus.

* This increased response occurs in spite of the fact that the sino-aortic reflexes are intensified in hypercapnia (446).

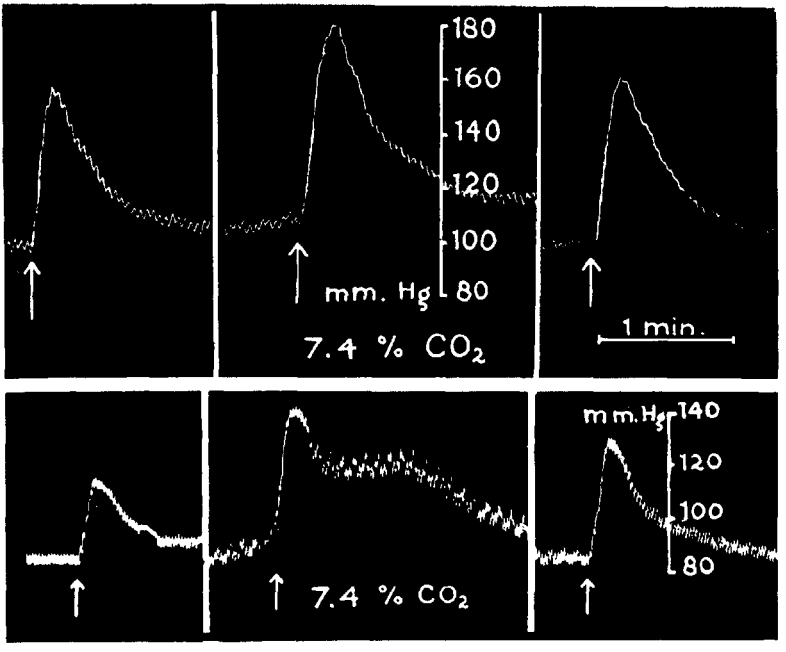

FIGURE 99. The effect of the inhalation of carbon dioxide on the responsiveness to electrical stimulation (arrow) of the hypothalamus in the cat. *Upper half:* carotid sinuses denervated, vagi intact. *Lower half:* carotid sinuses denervated, vagi cut. The increased response of the blood pressure in both cases indicates that the raised excitability of the center is independent of the buffer nerves. (Gellhorn, 446.)

The Effect of High Concentrations of Carbon Dioxide

As Meduna has pointed out, the anesthetic properties of high concentrations of carbon dioxide have been known for more than a hundred years. A gradual development of anesthesia is seen upon inhalation of 30-per-cent carbon dioxide (Friedländer, 392; Hill and Flack, 653) and the blood pressure rises; only in higher concentrations does a depression of the blood pressure and respiration occur which finally leads to death. Corneal reflexes and nociceptive reactions to stimulation of the central end of the sciatic nerve are absent, and the nerve and muscle retain their excitability: the chief effect of carbon dioxide is clearly of central origin. The anesthetic action of 30- to 40-per-cent carbon dioxide was confirmed by Leake (824), who found that it was not infrequently followed by convulsions if the period of inhalation was continued for 10 to 15 minutes. The effects of high concentrations of carbon dioxide are not due to anoxia, since

similar concentrations of carbon dioxide in oxygen likewise produce anesthetic effects.

Brown (159, 160), noted in man that the inhalation of 5- to 6-per-cent carbon dioxide for many hours results in dyspnea, dizziness, and nausea; in higher concentrations up to 12.4 per cent "drowsiness tending to actual stupor" occurs in a few minutes and the facial expression is "dazed." The systematic application of 30-per-cent carbon dioxide in oxygen by Meduna showed that brain activity is gradually depressed and anesthesia ensues. It is accompanied by states of reliving past experience and by vivid dreams not unlike those observed in mescaline poisoning.

On the motor side several stages can be distinguished. A phase of psychomotor excitement may be followed by rhythmic movements of the extremities imitating locomotion and known to physiologists as narcosis movements. These may be accompanied or followed by adversive movements ("conjugate deviation of the eyes and torsion of the body in the same direction, usually with flexion of the leg and extension of the arm on the side towards which the eyes have turned"). At later stages signs of decerebrate rigidity with areflexia or tonic-clonic convulsions develop, the light reflex remaining present. Meduna mentions that, according to Gibbs, during the carbon dioxide sleep high-voltage discharges of 3 to 4 per second appear in the EEG which persist for 20 to 25 seconds after the end of the treatment. As consciousness is lost, the slow activity is reduced to 1 to 2 per second. The EEG is different from that of sleep inasmuch as the 14-per-second spindles are absent. It is also unlike the EEG of barbiturate anesthesia, since the fast potentials of the induction phase are missing.*

Studies on the influence of high carbon-dioxide concentrations on cortical and hypothalamic potentials have given further insight into the basic physiological mechanisms involved in this treatment. In lightly anesthetized cats it is found that both cortical and hypothalamic activity gradually decline. The effect is particularly marked on the background activity, which may be reduced or disappear, while the grouped ("Dial") potentials are relatively little affected (462).

Figure 100 shows that after 3 minutes' inhalation of 35-per-cent carbon dioxide the "Dial" potentials of the motor cortex are somewhat reduced in frequency and duration but their amplitude is changed little, whereas the nongrouped potentials are minimal. Under conditions of a more prolonged administration of carbon dioxide cortical potentials may disappear temporarily, but not infrequently they return

* Personal communication of F. A. Gibbs.

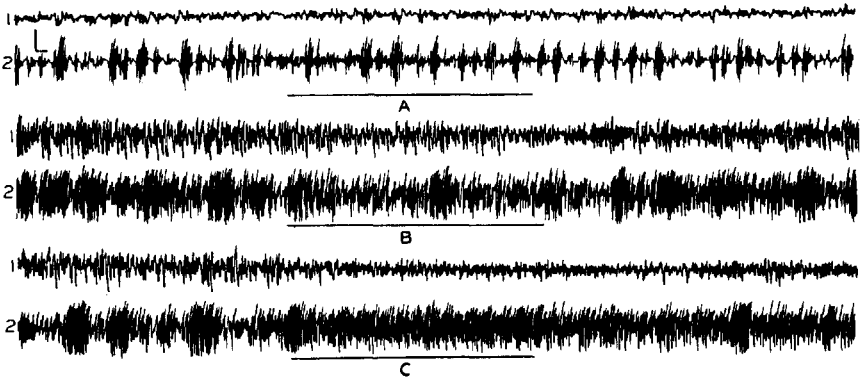

FIGURE 100. The effect of proprioceptive stimulation (indicated by the horizontal lines) on hypothalamic and cortical potentials, as this is influenced by high carbon-dioxide concentrations. The first of each pair of records represents the hypothalamus; the second, the motor cortex. *Records A:* after 3 minutes' inhalation of 35-per-cent carbon dioxide. *Records B:* 3 minutes after the readmission of air. *Records C:* 5½ minutes after the readmission of air. Note the absence of a response to proprioceptive stimulation, the reduction in background potentials, and the preservation of grouped ("Dial") potentials after 35-per-cent carbon dioxide. (Gellhorn, 464.)

and show pure grouped potentials, which occur now at shorter intervals than under control conditions, but without any background activity. The potentials of the hypothalamus are likewise reduced in amplitude and frequency. Since lower concentrations of carbon dioxide increase the background activity of the cortex and hypothalamus and have a tendency to reduce the frequency of occurrence of "Dial" discharges, it may be said that these effects are diametrically opposed to those induced by high concentrations of carbon dioxide. The latter appear to depress hypothalamic activity, whereas the former increase it. It seems to follow that the background potentials depend primarily on hypothalamic discharges, since both undergo parallel changes on exposure to carbon dioxide.*

It has been shown previously that proprioceptive and nociceptive stimuli act upon the hypothalamus and cortex and that under the influence of low (10-per-cent) concentrations of carbon dioxide the action on both structures is greatly increased. Consequently it was to be expected that, if the changes occurring in cerebral potentials have been correctly interpreted, these stimuli would become less effective under high carbon-dioxide concentrations. Figure 100A illustrates that proprioceptive impulses exert only a minimal influence on the motor cortex: the background activity is slightly increased during

* See bibliographical entry 464a and also p. 481.

the first half of the stimulation period, and no distinct effect is present in other cortical areas and in the hypothalamus. After the readmission of air the background potentials return and proprioception exerts now a distinct effect on the cortex and hypothalamus (Fig. 100B). A few minutes later the reactivity to proprioceptive impulses has returned to the control level, as shown in part C of the experiment, which demonstrates the prolonged action of these afferent stimuli on the motor cortex and hypothalamus. It may be added that under these conditions other cortical areas likewise show signs of excitation (asynchrony plus recruitment).

Similar effects were obtained with nociceptive stimulation. Therefore it may be said that nociceptive and proprioceptive impulses which under normal conditions induce a generalized cortical excitation associated with that of the hypothalamus either fail to induce these changes during the administration of 30- to 40-per-cent carbon dioxide or this influence is slight and restricted to the sensorimotor area. It is interesting to mention, since hypothalamic reactivity and muscle tone have been linked in the theory of sleep, that high carbon-dioxide concentrations induce complete muscle relaxation and that the return of the reactivity of the hypothalamus and cortex to proprioceptive stimulation appears to be correlated with the recovery of the muscle tone.

It was mentioned earlier* that the hypothalamic-cortical system which activates the cortex as a whole is sharply separated from the long afferent tracts which transmit impulses from the various sense organs and affect primarily specific cortical projection areas. A functional separation of the two systems can be accomplished by high concentrations of carbon dioxide. In this condition the reactivity of the hypothalamic-cortical system is abolished but that of the specific projection systems is preserved. Figure 101 shows that after the inhalation of 35-per-cent carbon dioxide for 8 minutes the potentials in various cortical areas are greatly reduced or eliminated. Nevertheless the acoustic reaction of the auditory cortex is nearly unchanged and the responsiveness of the visual cortex to optic stimuli is distinct, although somewhat diminished. Apparently the functional elimination of the hypothalamic-cortical system, as indicated by the progressive diminution and even cessation of spontaneous potentials in both areas and by the marked reduction in hypothalamic potentials, produces effects similar to those resulting from large lesions in the hypothalamus or reticular substance, as in the work of Obrador (979), Kennard (768), and others. The result is narcosis or coma. In this

* See Chapter 9.

condition, however, just as in barbiturate anesthesia, the cerebral cortex remains responsive to specific afferent stimuli.

Two facts stand out from these investigations. First, carbon dioxide has at least two points of attack in its action on the brain: it diminishes (in concentrations of 10 to 15 per cent) cortical excitability, as indicated by the reduced responsiveness of sensory projection areas

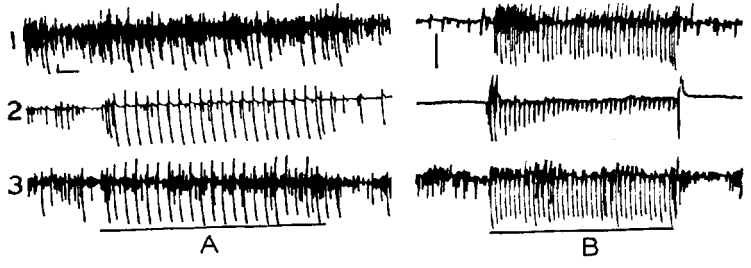

FIGURE 101. The effect on the acoustic and visual reactivity of the cortex of a "Dial" cat of inhaling 35-per-cent carbon dioxide. *A:* auditory cortex; *B:* visual cortex. *Records 1:* control. *Records 2:* after 8 minutes' inhalation of 35-per-cent carbon dioxide. *Records 3:* 5 minutes after the readmission of air. (Gellhorn, 464.)

to specific afferent impulses and of the motor cortex to electrical stimulation, and it increases the discharges and reactivity of the hypothalamic-cortical system. This differential action of carbon dioxide is retained in anesthetic concentrations which eliminate spontaneous hypothalamic and cortical potentials whereas the responsiveness of specific projection areas persists in a somewhat reduced degree.

Second, this work confirms, on the basis of different experimental procedures, the conclusions arrived at earlier:* (1) that awareness is abolished when the hypothalamic-cortical system is anatomically or functionally eliminated; (2) that perception, which is absent in high carbon-dioxide as well as in barbiturate anesthesia, is only possible if afferent discharges to the cortex persist from peripheral receptors *and* from the hypothalamus. It is believed that these investigations and not Lorente de Nó's important observations (869) on the effect of carbon dioxide on the membrane potential of the isolated nerve, which Meduna stresses in his book (923), can serve as a basis for a physiological explanation of the action of carbon dioxide in certain neurological disturbances.

* See p. 202.

The Physiological Basis of Carbon Dioxide Therapy

This is perhaps the place where some remarks on the principles relating physiology to neuropsychiatry are in order. The success of modern physiological research has made imperative its application to various branches of medicine, including psychiatry. Some of the possible means of attacking pertinent problems are illustrated in Chapters 18 and 20 through the study of autonomic reactions in psychotics before and after treatment or following spontaneous remissions and through the physiological analysis of the action of shock therapy on the nervous system.

Numerous questions involved in the study of psychoneuroses are likewise amenable to physiological analysis. Liddell's work (36) has uncovered the resemblance between experimental neurosis in lower experimental animals and human neurosis. On this basis a study of the factors contributing to the development of nervous disorders as well as an investigation into curative agents promises rich rewards (see Anderson, 37; Maier, 890a; and others).

To what extent brain lesions interfere with the development of experimental neuroses has not yet been studied, although fundamental changes in behavior patterns have been produced by cortical and subcortical lesions. It is to be expected that the different forms of lobotomy will furnish valuable material for the establishment of the neurological foundation of behavior, although the results of physiological analysis have been somewhat disappointing up to the present time.

In spite of valuable results, investigations of this type have been unable to bridge the gap which exists between physiological functions of the central nervous system expressible in terms of motor function, changes in sensory threshold, conduction of impulses, and the like, and the simplest type of behavior, let alone the complex deviations seen in neuroses and psychoses. This situation makes understandable the reasons why investigators of these disorders have attempted to discover the elements of human behavior.

These elements should play, at a much higher level of nervous organization, the role which the motor unit, the synapse, the central excitatory state, and other fundamental structural and functional concepts have played in the analysis of the integrated reflex action by the Sherringtonian school.

Whether the psychological or psychoanalytical study of behavior has contributed to the unraveling of these important problems is not for the writer of this book to decide. He feels, however, that a mild

protest should be made against the misuse of the term "physiological" in Meduna's theory of the action of carbon dioxide in psychoneuroses. The only physiological elements in Meduna's interpretation lie in the recognition of the depressing action of carbon dioxide on neuronal excitability and of the increased excitability of the central nervous system in psychoneuroses. The importance of the latter is evident from the fact that agents producing experimental neurosis are little effective under the influence of alcohol, which diminishes nervous excitability (907).

The increased reactivity of the central nervous system in psychoneurosis and the depressing action of carbon dioxide on peripheral and central nervous structures appear to be a correct but rather inadequate basis for an understanding of the physiology of the carbon dioxide therapy of neurosis. But it is hardly permissible within the framework of a "physiological" theory to link psychological tension with the breakdown of homeostatic brain mechanisms. Nor can the assumption be accepted that carbon dioxide through its threshold-increasing effect achieves homeostasis "by turning positive feed-back circuits into negative feed-back circuits," since no experimental evidence is available on these points.

The time when it will be possible to understand complex psychological concepts in terms of anatomical structure and well-defined physiological function seems to lie in the distant future. For the present it seems to the writer preferable to confess our ignorance rather than to consider "suffering," "procreation," and "conation" as the basic principles of behavior, and psychoneurosis as a disturbance of their balance.

Experimental physiology and clinical medicine show clearly that diencephalic mechanisms play a predominant role in emotion. Impulses impinging on this system produce somatic as well as autonomic responses. The type of environmental stimuli and constitutional factors (including endocrine balance) may account for the variability in the emotional responses of normal persons and explain the multiformity of symptoms in psychoneurotics. As pointed out previously, excitation of the hypothalamus results not only in these "downward discharges" but affects the cortex of the brain. These discharges initiate the various "psychic" experiences which accompany emotion under normal and pathological conditions.

To understand the action of carbon dioxide therapy consisting of repeated sessions during which 30-per-cent carbon dioxide is applied until consciousness is lost, it is not sufficient to stress the threshold-raising action of carbon dioxide on the peripheral nerve; its effect,

rather, on hypothalamic-cortical mechanisms must be studied. From this work it is obvious that carbon dioxide in high concentrations reduces or abolishes hypothalamic activity and the persistent discharges to the cortex which originate in this subcortical structure and form the basis of consciousness. In addition carbon dioxide reduces the reactivity of the hypothalamus to afferent impulses which, like those arising in proprioceptors and nociceptors, act on this system. It appears to be justified to emphasize the effect of carbon dioxide on the hypothalamic-cortical system as basic to the carbon dioxide therapy of psychoneuroses for the following reasons:

1. Thirty-per-cent carbon dioxide acts differentially on the hypothalamic-cortical system and the specific-projection systems, the former being functionally eliminated whereas the latter continue to respond to adequate stimuli.

2. The psychoneurotic seems to be emotionally hyperreactive. Translated into physiological terms, this statement implies a hyperexcitability of the hypothalamic-cortical system which could be counteracted by carbon dioxide in high concentrations.

Two supplementary assumptions are necessary before this interpretation of the action of carbon dioxide in psychoneurosis can be accepted: (1) it must be shown that repeated carbon dioxide "treatment" reduces hypothalamic responsiveness for long periods of time; (2) "ideational" stimuli should act on the hypothalamic-cortical system in a manner similar to that described for nociception and proprioception. The first supposition has not yet been proved but can be tested experimentally. Since procedures which exert excitatory effects on the hypothalamus increase its responsiveness for a long time when applied repeatedly, the basic property of the hypothalamus, that it can undergo long-lasting changes, is well established.* That ideational stimuli act on the hypothalamus is made probable by their influence on potentials in the vicinity of this structure in man (579, 669) and by the appearance of typical "downward discharges" involving the parasympathetic and sympathetic system (1126, 1238).

Meduna has applied carbon dioxide therapy to a large group of psychoneurotics. Obviously such a group is bound to be heterogeneous and may comprise cases where the classification psychoneurosis versus psychosis is uncertain. It would be of great importance if the functional reactivity of the hypothalamus could be tested before treatment was commenced.† The experiments described in this chapter suggest that this form of therapy could yield favorable results only

* See Chapter 18.

† See Chapter 20.

in conditions characterized by a hyperreactivity of the hypothalamus.

For the sake of completeness the excitatory effects of high concentrations of carbon dioxide, first described by Loevenhart, Lorenz, and Waters (853) and recently restudied by D'Elseaux and Solomon (272), should be discussed. It was observed that during the inhalation of 25-per-cent carbon dioxide patients became more alert but fell back into their previous condition on removal of the mask. In view of the low excitability of the hypothalamus in schizophrenia (and particularly in catatonic patients) and the relation of the hypothalamic-cortical system to the state of awareness, it seems to follow that 25-per-cent carbon dioxide may temporarily increase diencephalic reactivity, as was described for lower concentrations of carbon dioxide. Such an excitatory effect with relatively high doses of carbon dioxide was frequently seen in our experiments either at the beginning of the administration of the gas or in conditions in which the excitability of the brain was low. Apparently the activation by carbon dioxide of the hypothalamic-cortical system, as indicated by asynchrony of cortical potentials and the increased frequency of strychnine spikes in the cerebral gray matter, requires relatively high concentrations in catatonic conditions or in animals in which, owing to deep barbiturate anesthesia, the hypothalamus is rather unexcitable.

On the other hand, it was observed in catatonic patients that somewhat longer periods of alertness appeared on the readmission of air after carbon dioxide administration had been continued to the coma level. This temporary effect was also seen after the inhalation of low oxygen, but it was less prompt. The explanation seems to be the same in both cases. Severe anoxia or high carbon dioxide which has led to a marked depression of cortical and hypothalamic potentials is followed, on the readmission of air, by brief periods of excitation. Such "rebound" phenomena are well established in man and animals at all levels of the central nervous system. D'Elseaux and Solomon (272) argue that because different procedures produce similar results, the effect is not due to clear-cut physiological factors. This reasoning is obviously erroneous. Neurons change in response to gross alterations of the internal environment only in two directions: increased or decreased excitability. The diversity of the causes is in no way reflected in the type of the neuronal change. The final physiological effect may be the same but may have been accomplished by a multiformity of stimuli and widely different disturbances of the neuronal metabolism.

The conclusion drawn from these investigations seems to be that

high concentrations of carbon dioxide greatly reduce the excitability of the hypothalamic system and that this action accounts for the anesthetic effect in the normal person and for the reduction in emotional responsiveness in the psychoneurotic. The value of carbon dioxide therapy will be the greater the more the hypothalamic-cortical system is hyperreactive and the more prolonged the action of carbon dioxide is on this system.

The excitatory effect of 30- to 40-per-cent carbon dioxide is too short to be of therapeutic usefulness. The "rebound" after the administration of this gas, which Loevenhart used in his experiments on catatonics, is often weak or absent in animal experiments in which a rebound after anoxia or asphyxia is very marked (490). To achieve prolonged excitation of the hypothalamus the procedures of shock therapy appear to be more suitable than either carbon dioxide or anoxia, and apparently clinical studies are in agreement with this statement.

The action of carbon dioxide on the brain and particularly on the hypothalamic-cortical system has been stressed in this chapter because this system is chiefly responsible for the physiology and pathology of emotion. It is not assumed that this action of carbon dioxide is the only important one on the brain. The striking improvement in cerebral circulation effected by carbon dioxide is generally recognized and may play a part in carbon dioxide therapy. Augmentation of the cerebral circulation, however, would hardly require 30-per-cent carbon dioxide, since cerebral vasodilatation could be accomplished by concentrations which would not abolish consciousness.

~ 20 ~

Physiological Principles for the Therapy of Psychoneuroses and Functional Psychoses

"Warum willst dich von uns allen
und unsrer Meinung entfernen?"
ich schreibe nicht euch zu gefallen,
ihr sollt was lernen!
Goethe, *Zahme Xenien**

IN THE last two chapters an attempt has been made to relate mental disease to a dysfunction of the autonomic nervous system. The reactivity of the sympathetic centers has been found to be subnormal in schizophrenes, and the therapeutic effect of so-called shock therapy has been interpreted as being due to the prolonged excitatory action of these procedures on central sympathetic structures, particularly on the hypothalamus. This interpretation is supported by observations showing increased sympathetic responsiveness with clinical improvement. Such observations were made not only by Hill (650) in an important study which has been discussed earlier but also in older investigations. Solomon and Darrow (1126) noted an increased responsiveness of the sympathetic system with a progressive improvement of the schizophrenic patient. They observed that ideational stimuli which before the treatment produced only a slight sweat reaction on the palm of the hand (galvanic reflex) in addition to a rise in the blood pressure caused in improved patients an intense sweat reaction associated with the blood pressure rise.† Jahn (731) states that schizophrenes who recover from the disease following treatment with insulin show signs of increased sympathetico-adrenal

* "'Why do you wish to withdraw from us all and from our opinions?' I do not write to please you but that you may learn something."

† However, a responsiveness to ideational stimuli which had been absent before the treatment could account for these findings.

reactivity in response to hypoglycemia, whereas such a change in reactivity does not occur in patients not benefited by the insulin treatment.

The effectiveness of carbon dioxide therapy in psychoneurosis seems to involve a similar principle. Observations on these patients suggest an increased emotional reactivity, probably based on an augmented responsiveness of the posterior sympathetic hypothalamus, which is known to be involved in the expression of emotion. Consequently it is to be expected that carbon dioxide therapy will have a tendency to restore hypothalamic reactivity to a normal level because high concentrations of carbon dioxide diminish the spontaneous potentials of the hypothalamus and also hypothalamic-cortical discharges in response to nociceptive stimuli and presumably to other stimuli (emotional excitement) which act on the hypothalamus.

Autonomic Tests in Mental Disorders

It must be admitted that this presentation of the problem of functional mental disorders is confined to the physiological point of view and also that it is a simplified one. Several important questions, however, are raised by it:

1. Granted that a hypothalamic imbalance is associated with psychological disorders, is it justifiable to assume that the hypothalamic dysfunction plays an *essential* role in psychoneuroses and functional psychoses?

2. To what extent is the clinical classification of mental disorders into schizophrenia, psychoneurosis, manic-depressive psychosis, etc., with their various subdivisions, satisfactory from the physiological point of view?

3. Is it possible to measure central autonomic reactivity in the human being and thereby to obtain objective evidence of an interdependence between mental behavior and the reactivity of autonomic centers?

These are questions of great significance; fortunately, recent work seems to provide at least a partial answer. The studies of Funkenstein, Greenblatt, and Solomon (400–402) form the basis of the following discussion and of the experimental work which has been undertaken in the writer's laboratory in collaboration with E. S. Redgate. Against this background an attempt will be made to determine the nature and significance of the central autonomic disturbance associated with and probably underlying the psychic dysfunction and to propose forms of therapy which correct the autonomic imbalance.

Funkenstein and his collaborators applied in psychotic patients and

some normal controls adrenalin and mecholyl and recorded at ½ to 1-minute intervals the effect of these drugs on the systolic blood pressure. Depending on the degree and duration of the hypertensive and hypotensive effects of these drugs, they divided the patients into several groups, the chief of which are illustrated in Figure 102, and also established a relation between these autonomic tests and the effectiveness of electroshock therapy.

In Groups II and III, to which 80 per cent of their nonpsychotic controls belonged, the hypertensive reaction to adrenalin was either

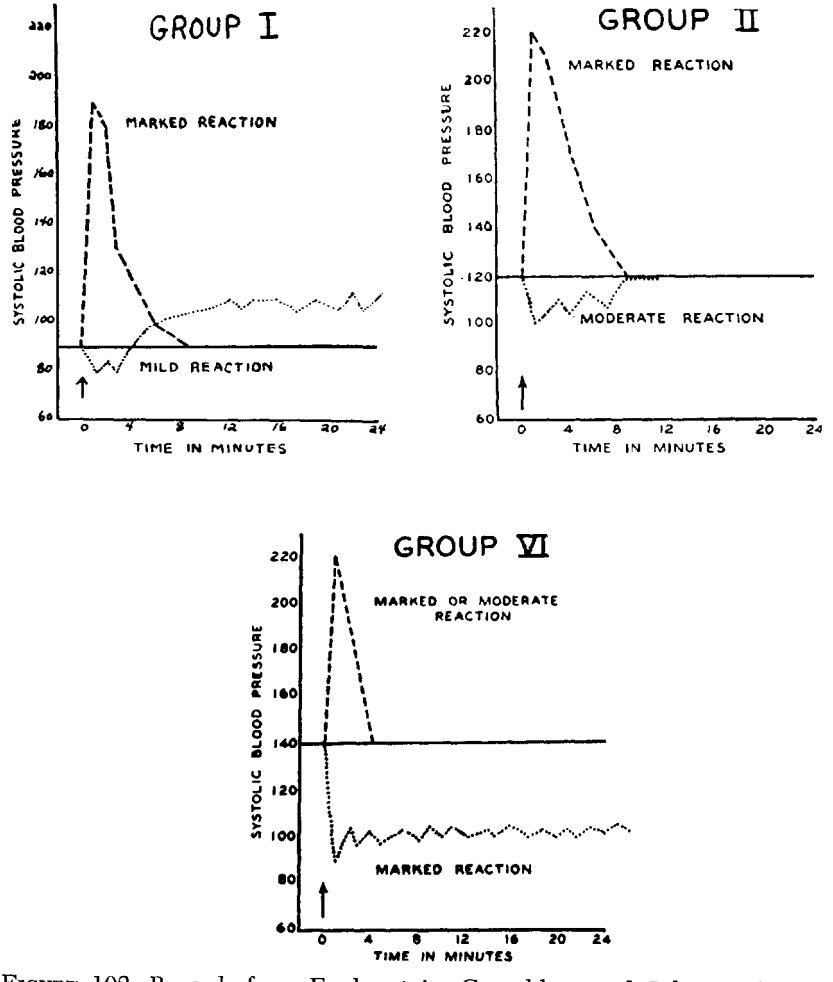

FIGURE 102. Records from Funkenstein, Greenblatt, and Solomon (400) on the action of adrenalin and mecholyl on the blood pressure of psychotic patients.

marked or moderate while the hypotensive effect of mecholyl was only slight and brief, so that the original blood pressure level was restored within 10 minutes. Groups I and IV deviated from this scheme not in their response to adrenalin, which was marked in Group I and moderate in Group IV, but in their reaction to mecholyl. In both groups the fall in the blood pressure was similar to that in the control groups (II and III), but after the initial fall the blood pressure rose above the control level. This rise occurred early in Group I and relatively late in Group IV (4 and 10 minutes respectively following the injection of mecholyl). The last three groups (V–VII) were characterized by the fact that the hypotensive action of mecholyl was greater and more prolonged than in the control group and that it ended in a marked chill in Group VII. The adrenalin effect in Groups VI and VII was within normal limits – i.e., "moderate" or "marked." Group V, however, was the only group which showed an unusually mild hypertensive effect. The present discussion is concerned with Groups I–IV and VI and VII.*

The most important finding of Funkenstein *et al.* is the fact that "when the psychological picture changes, the physiological picture changes and vice versa"; that is, improvement or impairment of the clinical condition of the patient is associated with an alteration in the blood pressure reactions that are induced by mecholyl and adrenalin. If these reactions do not change, the clinical picture is unaltered Moreover certain changes in these autonomic reactions are associated with clinical improvement regardless of the means through which the clinical (psychological) changes in the patient's condition are brought about.

Experimental Analysis of Autonomic Tests

These clinical observations are a challenge to the neurophysiologist who is concerned with psychophysiological relations in general and with an understanding of mental disorders in terms of central nervous functions in particular. The studies of Funkenstein *et al.* pose the question whether the type of blood pressure reaction induced by the aforementioned drugs is related to or possibly a measure of the

* The very slight hypertensive effect of adrenalin on Group V suggests that the central parasympathetic reactivity is intensified in these patients. The injection of adrenalin raises the pressure in the sino-aortic area and causes an increase in the vagal tone (in addition to a decrease in the sympathetico-adrenal discharge). The greater the excitability of the parasympathetic centers, the less must be the pressor effect of injected adrenalin if other factors are kept the same. It is not unlikely that variations in central parasympathetic centers play an important role in functional mental disorders. However, these problems require further investigation.

reactivity of specific parts of the brain which play a fundamental role in mental disorder.

Obviously a physiological interpretation of the relation of the adrenalin and mecholyl reactions to the mental state of the patient must begin with the changes in the central nervous system induced by the injection of the two drugs. That autonomic changes are involved is recognized by Funkenstein *et al.*, who speak of "autonomic changes paralleling psychologic changes in mentally ill patients." What is the nature of these autonomic changes? Here the observations on Groups VI and VII are particularly relevant, since autonomic changes are associated with improvement or cure. The alterations in these reactions through electroshock consist in an increase in the pressor action of adrenalin and a lessening of the hypotensive effect of mecholyl. From these data the authors conclude that this procedure caused an "increase [in] the reactivity of the sympathetic central nervous system to stimulation. Decreased reaction of the parasympathetic system is often a corollary." Apparently in the opinion of Funkenstein *et al.* sympathetic reactivity is increased and parasympathetic responsiveness is decreased as a result of electroshock. The reactions obtained after electroshock are indeed as if the authors had injected more adrenalin and less mecholyl than before the treatment. This result could be caused by a change in the reactivity of peripheral structures or it could be due to a fundamental change in the responsiveness of autonomic centers, which are activated reflexly whenever vascular pressor or depressor effects are induced.

Assuming that the experimental results are correct and that psychological changes parallel these autonomic changes to such a degree that the beneficial results of electroshock can be predicted in a significant number of cases, it is quite certain that if the reactivity of the blood vessels were altered in peripheral organs, the change in reactivity would not modify behavior, nor would it be a measure of the changed mental condition of the patient. There is no evidence that the essential changes which occur in schizophrenia and other functional psychoses are of peripheral origin. On the contrary, a large number of experimental tests discussed earlier show that the central and not the peripheral autonomic reactivity is altered. One can even go a step further and state that the reactions which are based on spinal and medullary discharges do not deviate from the norm in psychotic patients (742, 991). Thus we reach per exclusionem the hypothalamus as the structure in which functional reactivity seems to be altered in these psychoses. The importance of the hypothalamic-cortical system for emotion has been discussed, and the significance of

emotional disturbances in functional psychoses is generally recognized. This fact and other signs of diencephalic involvement (106, 271) have induced numerous authors to assign to the hypothalamus a key role in the causation of functional psychoses.

In the light of this discussion we must raise this simple question: To what extent do central autonomic structures determine the blood pressure effects induced by the injection of peripherally acting drugs such as adrenalin and mecholyl? Confining the discussion to mecholyl, which will presently be shown to be the more important test substance, it may be said that any procedure leading to a fall in the blood pressure of sufficient magnitude induces a sympathetico-adrenal discharge which tends to counteract the hypotension (Gellhorn, 446). That this interpretation is valid for the special case of mecholyl

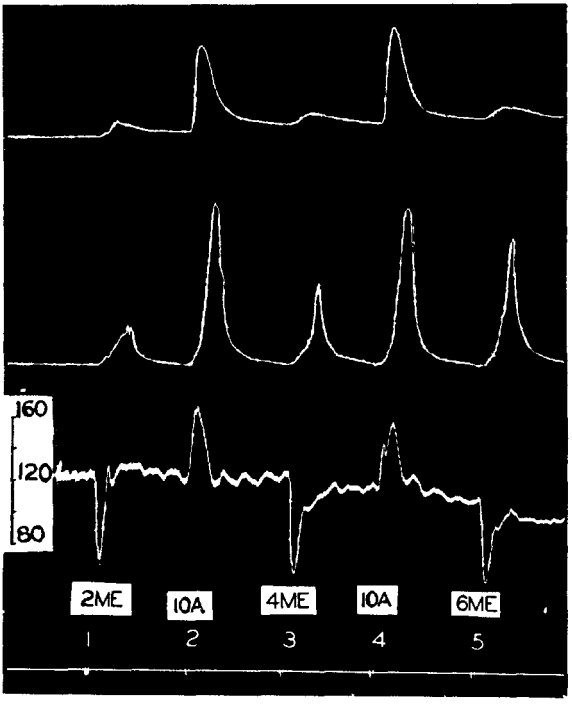

FIGURE 103. The effect of increasing concentrations of mecholyl, injected intravenously, on the blood pressure, normal nictitating membrane, and denervated nictitating membrane of the cat, and a comparison with the action of adrenalin injected intravenously. In this and the following three figures, the top record represents the denervated nictitating membrane, the middle record the innervated nictitating membrane, and the bottom record the blood pressure. *No. 1:* 2 gamma mecholyl. *Nos. 2 and 4:* 10 gamma epinephrine. *No. 3:* 4 gamma mecholyl. *No. 5:* 6 gamma mecholyl.

in the anesthetized cat is shown by Figure 103. In this and the following figures the blood pressure and the contractions of the normal and acutely denervated nictitating membranes are recorded in an anesthetized cat while increasing amounts of mecholyl are injected. The innervated nictitating membrane indicates sympathetic discharges (and also the secretion of adrenalin); the denervated nictitating membrane gives a measure of adrenomedullary secretion.

Figure 103 shows that mecholyl induces sympathetico-adrenal discharges. With weak concentrations, often only the sympathetic discharges are present and cause a contraction of the sympathetically innervated nictitating membrane; with stronger concentrations an adrenomedullary discharge is also elicited, as seen in the contraction of the denervated nictitating membrane, which occurs after a longer latent period. Figures 103 and 106 also show that the neurogenic sympathetic response (indicated by the normal nictitating membrane) and the neurohumoral secretion (denervated nictitating membrane) increase with increasing concentrations of mecholyl. Moreover the bigger the dose, the more prolonged is the depressor action of mecholyl.

The sympathetic response begins when the mecholyl-induced fall in the pressure has become considerable. This response is thought to account for the quick return of the blood pressure after the injection of 2 gamma of mecholyl and to be involved in the rapid but partial restoration of the blood pressure after the administration of 4 and 6 gamma of mecholyl (Fig. 103). The second, slow phase in the return of the blood pressure seems to coincide with the neurohumoral phase. The injection of adrenalin, as shown in the figure, or of

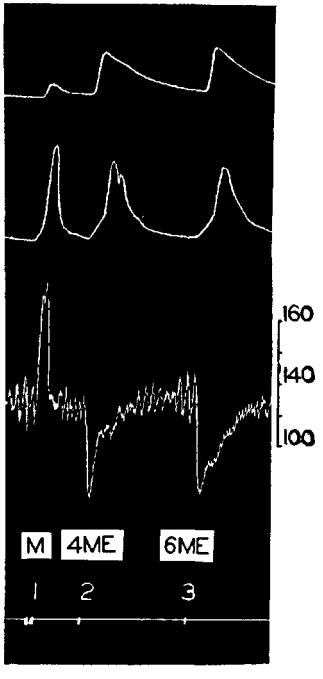

FIGURE 104. A comparison between the action of mecholyl and the effect of stimulation of the medullary sympathetic center on the blood pressure and nictitating membranes of the cat. *No. 1:* medullary stimulation of 4.4 volts, at 80 per second, for 10 seconds. *No. 2:* 4 gamma mecholyl. *No. 3:* 6 gamma mecholyl (intravenously).

nor-adrenalin elicits contractions of the nictitating membranes together with a pressor reaction.

If it is correct that mecholyl elicits a reflex excitation of centers of the sympathetico-adrenal system, direct stimulation of these centers may be expected to induce similar changes. Figure 104 illustrates that on stimulation of the medullary sympathetic center a sympathetic response (normal nictitating membrane) is followed by a neurohumoral response on the denervated nictitating membrane. The secretion of adrenalin was obviously greater after mecholyl injection than after medullary stimulation. This is evident from the greater amplitude of the contraction of the denervated nictitating membrane and from the longer duration of the contraction of the normal nictitating membrane. Similar effects were obtained on stimulation of the hypothalamus. Both autonomic centers also produced on weak stimulation a response on the normal nictitating membrane which was not accompanied by a contraction of the denervated nictitating membrane. The activation of the sympathetic centers through direct stimulation is thus similar to that induced reflexly by mecholyl.

A further analysis of the response to mecholyl and also of the reaction to adrenalin was made through tetraethylammonium chloride, which is known to block autonomic synapses, although it does not interfere with the reactivity of peripheral effectors. Consequently, reflexly induced activation of sympathetic and parasympathetic centers may be reduced or abolished by this drug. As was shown earlier,* sino-aortic reflexes are diminished or eliminated by it. These findings explain its action on the effect of adrenalin and mecholyl on the blood pressure and nictitating membranes. The weakening of the sino-aortic reflexes accounts for the increased pressor action to intravenously injected adrenalin (Fig. 105). On the other hand, the reactivity of peripheral structures such as the nictitating membrane is unchanged, as shown by the fact that the contractions of the nictitating membranes to injected adrenalin are not altered. Furthermore the action of mecholyl is changed fundamentally. Two gamma of mecholyl, which before TEA elicited a marked sympathetico-adrenal reaction, as indicated by the nictitating membrane records of no. 2, fails to do so after the administration of the autonomic blocking agent. The absence of the sympathetic hypercompensatory blood pressure rise in no. 5 as compared with no. 2 clearly shows the role of sympathetic discharges in the blood pressure response to mecholyl. In other experiments the diminution of sympathetic discharges by TEA resulted in a prolongation of the hypotensive action of mecholyl.

* P. 260.

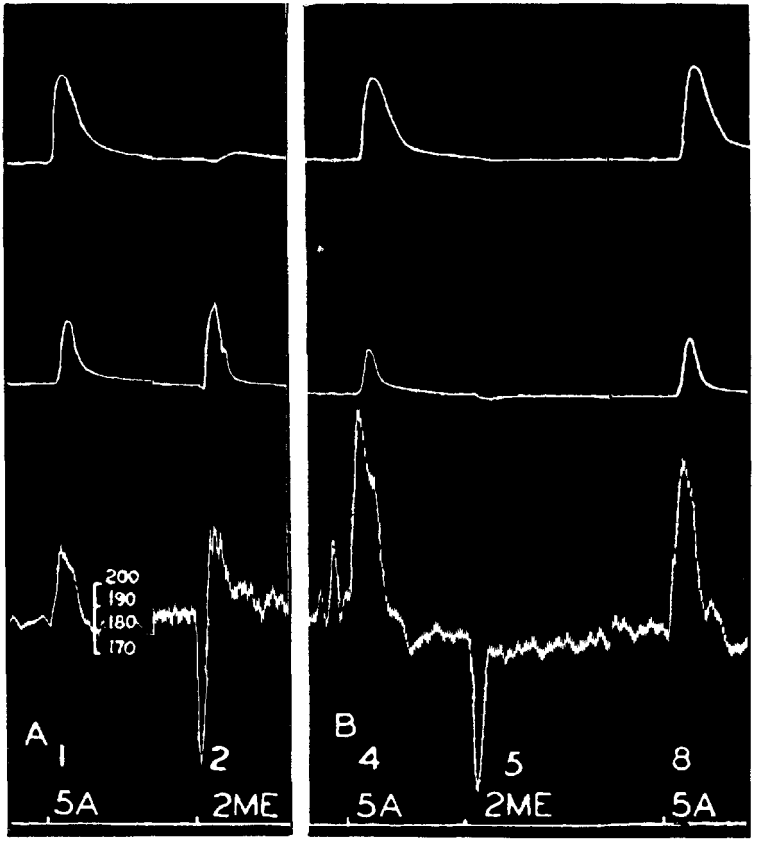

FIGURE 105. The effect of 10 mg. of tetraethylammonium chloride on the action of adrenalin (5 gamma intravenously) and mecholyl (2 gamma i.v.) on the nictitating membranes and blood pressure. *Nos. 1 and 2:* before TEA. *Nos. 4, 5, and 8:* after i.v. injection of TEA. *Nos. 1, 4, and 8:* 5 gamma epinephrine i.v. *Nos. 2 and 5:* 2 gamma mecholyl i.v.

In order further to clarify the role of sympathetic centers in the effect of mecholyl on the blood pressure and nictitating membranes, the influence of increasing degrees of barbiturate anesthesia was studied. It was found that with such an increase the hypotensive action of mecholyl was prolonged and the contractions of the nictitating membranes elicited by the hypotensive action of mecholyl were diminished. At the same time a diminished reactivity of the posterior hypothalamus to electrical stimulation was noted.

From these experiments it may be inferred that (1) mecholyl elicits a sympathetico-adrenal discharge through reflex stimulation of autonomic centers; (2) the degree of hypotensive action of mecholyl

is, other conditions being equal, indirectly related to the intensity and duration of the sympathetico-adrenal discharge. The various types of mecholyl-induced blood pressure curves observed in different groups of patients in response to mecholyl appear to be due to the fact that the centers of the sympathetic system show marked individual differences to reflex excitation.

Further work was devoted to the determination of the role of the hypothalamus in the reflex excitation of the sympathetic system by mecholyl. It appeared to us possible that the hypotensive action of mecholyl might lead to an excitation of the hypothalamus as well as of the medulla. Ample evidence exists that a fall in the pressure in the sino-aortic area evokes an increased sympathetico-adrenal discharge via the sino-aortic nerves. The vasomotor (and respiratory) centers in the medulla oblongata have long been recognized to be involved, but the role of the hypothalamus in this respect has not yet been investigated. It was thought that the participation of the hypothalamus in the reactions initiated by the injection of mecholyl could be proved if the destruction of this structure were found to alter significantly the mecholyl reaction.

Figure 106 illustrates the effect of a bilateral lesion in the posterior hypothalamus on the reactivity of the sympathetico-adrenal system to mecholyl. It is noted that 4, 6, and 9 gamma of mecholyl evoke in the normal animal a depressor response from which the blood pressure recovers rapidly. Only in the experiment involving 9 gamma of mecholyl is the restitution of the blood pressure delayed. Each mecholyl test is associated with a contraction of the normal and denervated nictitating membranes, indicating that a sympathetico-adrenal discharge is elicited in each experiment. It is further noted that the secretion of adrenalin is prolonged (see the sustained contraction of the denervated nictitating membrane in the experiments in nos. 3 and 4 in which 6 and 9 gamma of mecholyl were injected). In the test with 9 gamma of mecholyl the prolonged sympathetic discharge is associated with a rise in the blood pressure above the control level.

After the posterior hypothalamus has been partially coagulated, the electrical stimulation of this structure is much less effective on the blood pressure and normal nictitating membrane than in the preceding control test (compare nos. 1 and 5). The hypotensive action of mecholyl is prolonged and greatly aggravated. The interpretation that this change indicates a diminished responsiveness of the centers of the sympathetico-adrenal system to reflex stimulation is supported by the reaction of the nictitating membranes. Figure 106 shows that

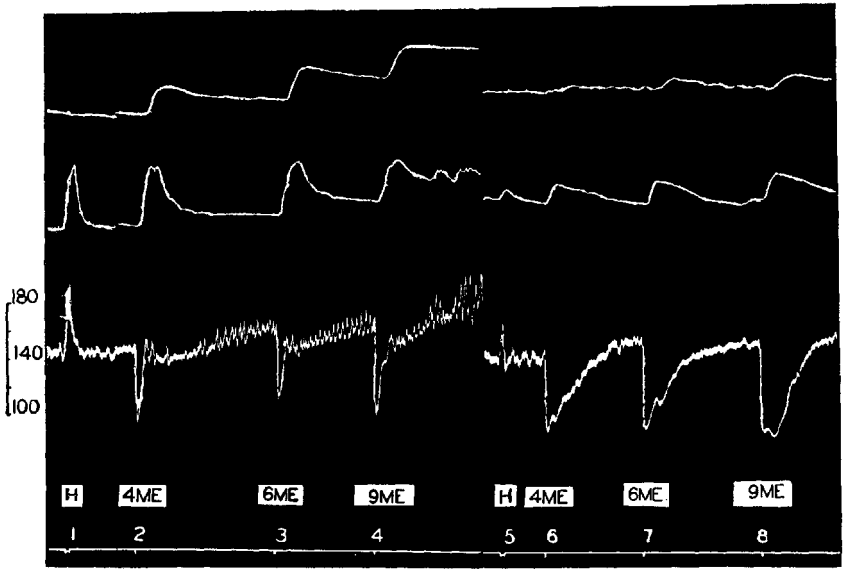

FIGURE 106. The effect of partial hypothalamic coagulation on the responsiveness of the blood pressure and nictitating membranes to mecholyl. (The effect of injected epinephrine was not altered in this experiment by the coagulation.) *Nos. 1 and 5:* hypothalamic stimulation of 1.5 volts, at 50 per second, for 10 seconds. *Nos. 2, 3, and 4:* mecholyl injected intravenously, 4, 6, and 9 gamma respectively. *Nos. 6, 7, and 8:* mecholyl respectively as in 2, 3, and 4, after coagulation of the posterior hypothalamus.

the contraction of the denervated nictitating membrane is minimal and that of the innervated nictitating membrane is also reduced. It follows from this experiment that *the degree and particularly the duration of the hypotensive action of mecholyl and the reflexly induced discharges of the sympathetico-adrenal system depend on the hypothalamus.*

The increased duration of the hypotensive action of mecholyl after hypothalamic lesions indicates that the type of blood pressure response to this drug depends on hypothalamic sympathetic discharges. Experiments in which through the injection of pentothal or procaine into the hypothalamus the excitability of this structure was diminished are in agreement with this interpretation. In this condition the hypotensive action of mecholyl was prolonged.

On the basis of this work one would expect conditions leading to increased discharges from the hypothalamus to influence the mecholyl-induced blood pressure curve in a manner diametrically opposed to that seen after hypothalamic lesions. Such a state of increased

hypothalamic discharges was produced by stimulating the hypothalamus with a near-threshold electrical stimulus. Although this stimulus failed to evoke contractions of the nictitating membranes and to alter the blood pressure significantly, it was found that mecholyl elicited stronger sympathetico-adrenal discharges than under control conditions. This was indicated by more marked contractions of the nictitating membranes and by a characteristic change in the blood pressure curve. Whereas the blood pressure returned to the original level following the hypotensive action of mecholyl in the control experiment, it rose considerably above this level when the hypothalamus was stimulated with a near-threshold current. Similar changes were brought about by the injection of minute quantities of strychnine into the hypothalamus. Apparently *conditions leading to increased sympathetic discharges of the hypothalamus as the result of electrical or chemical stimulation augment the responsiveness of the sympathetico-adrenal system to mecholyl and lead to a quicker return of the blood pressure and/or an overcompensatory hypertensive phase.**

That the hypotensive action of mecholyl is responsible for the activation of the hypothalamus is confirmed by the study of diencephalic and cortical potentials. It has been pointed out repeatedly in this book that excitation of the hypothalamus leads to an activation of the cortex. This statement holds for mecholyl-induced hypothalamic excitation. As the blood pressure returns to its normal level after the injection of mecholyl – i.e., at the time when the nictitating membranes contract and thereby indicate that a sympathetic discharge takes place – there occurs a distinct excitation of the hypothalamus and thalamus. At the same time a generalized excitation of the cortex is recorded. This effect is reduced or abolished by coagulation of the hypothalamus.†

Thus far the sympathetico-adrenal discharges resulting from the fall in the blood pressure induced by the injection of mecholyl have been discussed. In addition, the possible role of the parasympathetic system under these conditions should be considered. A lowering of the pressure in the sino-aortic area leads not only to increased sympathetic but also to diminished parasympathetic activity. It is conceivable that the reflexly lessened vagal action on the heart may contribute to the restoration of the blood pressure after it has been lowered by mecholyl or other procedures. In the light of previous work, however, it is extremely doubtful whether this action of the vagus plays a significant role. Bacq, Brouha, and Heymans (55a) have shown that sec-

* As in Funkenstein's patients belonging to Groups I and IV.

† Unpublished experiments with Drs. B. Sigg and W. P. Koella.

tioning the sino-aortic nerves, which induces an enormous hypertension in the normal animal, fails to alter the blood pressure in the sympathectomized dog. Similarly, it was found in this laboratory that the hypotensive action of mecholyl is not significantly altered by vagotomy. Neither was there any evidence that the sympathetico-adrenal discharge which occurs after the injection of mecholyl and which is indicated by the contraction of the nictitating membranes is changed by vagotomy.

Summary and Application

From these experiments the following facts may be concluded:

1. Increasing amounts of mecholyl call forth increasing degrees of sympathetico-adrenal discharge.

2. Conditions reducing or abolishing this discharge augment the hypotensive effect of mecholyl.

3. The degree and duration of the hypotensive effect of mecholyl are inversely related to the degree of sympathetico-adrenal discharges.

4. Conditions increasing the excitability of the posterior hypothalamus accelerate the return of the blood pressure to its normal level or lead to an overshooting of the level; conditions in which hypothalamic excitability is reduced cause a prolongation of the hypotensive action of mecholyl.

5. The mecholyl-induced hypothalamic excitation causes an increased "upward discharge" (generalized cortical excitation). This effect of mecholyl is abolished by coagulation of the hypothalamus.

6. Central parasympathetic discharges play no significant role in the blood pressure record resulting from the injection of mecholyl.

If we apply these facts to the various groups of Funkenstein *et al.*, which are based on the mecholyl (and the adrenalin) test, it may be said that in contradistinction to the control Groups II and III, Groups I and IV are characterized by a hyperreactivity of sympathetico-adrenal discharges in response to mecholyl, whereas Groups VI and VII show a hyporeactivity of this system.* Moreover, since it was found that the action of mecholyl on the blood pressure depends on sympathetic discharges of hypothalamic origin, it appears highly probable that the simple mecholyl test gives an indication of the degree of hypothalamic sympathetic excitability in the intact organism.

In the light of this discussion the relation between the clinical

* Group V likewise shows this hyporeactivity. It is not discussed because the diminished reaction to adrenalin (see footnote, p. 469) indicates further autonomic disturbances.

diagnosis and the groups established by Funkenstein *et al.* on the basis of the mecholyl test must be stated. The previously discussed idea that schizophrenia is characterized by a deficient central sympathetic reactivity applies only to a part of the schizophrenic group. Funkenstein *et al.* showed that *schizophrenia as well as other functional psychoses* may be associated with a normal, a lesser, or a greater reaction to mecholyl. In our interpretation this means that patients belonging to the last two groups show central autonomic (sympathetic) disturbances;* however, the latter are not characteristic for a certain disease entity. Thus schizophrenes may belong to Group I (sympathetic hyperreactivity) as well as to Group VI (sympathetic hyporeactivity). But – and this is in complete agreement with the work discussed previously – *only those schizophrenes (and other psychotic patients) who belong to hyporeactive sympathetic groups (VI–VII) benefit by shock treatment. In such successfully treated patients the altered mental state is associated with a change in their reaction to mecholyl so that they move in classification from Group VI to Group II or III; i.e., they show a normal sympathetic reactivity.*

From the point of view of the physiological theory presented here it is easily understandable that the hyporeactive sympathetic Groups VI and VII are improved by electroshock treatment, whereas patients with normal sympathetic reactivity (Groups II and III) are not altered clinically or autonomically. The few records on patients belonging to Group IV which have been published seem to show that shock treatment aggravates the sympathetic hyperreactivity so that the patients move in classification to Group I. This change is accompanied by clinical impairment. From these data it seems to follow that while *electroshock and other forms of shock therapy are indicated in patients with hyporeactive sympathetic centers, these therapeutic procedures are contraindicated in patients with sympathetic hyperreactivity.*

The fundamental observation of Funkenstein *et al.* that the prognosis of electroshock therapy is linked with a certain autonomic reaction (the prolonged hypotensive effect of mecholyl) – i.e., in our terminology, with a hyporeactivity of sympathetic centers, and not with the diagnostic classification based on clinical symptoms – suggests further applications. *Since sympathetic hyporeactivity and its psychological manifestations can be improved or cured by electro-*

* It is at present not known whether patients showing a normal reactivity to mecholyl are free from central autonomic disturbances or have disturbances not revealed by the mecholyl test.

shock – i.e., by a procedure increasing central sympathetic excitability – conditions involving sympathetic hyperreactivity should be improved or cured by procedures which specifically decrease the reactivity of sympathetic centers. Funkenstein's Groups I and IV, showing a sympathetic overcompensation to mecholyl resulting in a hypertensive effect following a brief and slight fall in the blood pressure, belong in this category.

It will be recalled that increasing the hypothalamic reactivity in the experimental animal causes a change in the mecholyl-induced blood pressure curve toward a type showing sympathetic overcompensation. On the other hand, diminishing the hypothalamic reactivity by an injection into the posterior hypothalamus of procaine or pentothal or by coagulation tends to shift the mecholyl-induced blood pressure curve toward the hyporeactive sympathetic type. Such an effect is also obtained from the administration of barbiturates.

Even in the present unsatisfactory state of our knowledge of how various drugs act on central nervous functions, it is quite obvious that sedatives such as barbiturates may be used to depress hypothalamic reactivity. A specific relation of these drugs to the hypothalamus was claimed by earlier investigators but has been denied in later studies. The methods used in the previously reported work on the action of carbon dioxide (Chapter 19) seem to yield data which clearly show that barbiturates depress the hypothalamus and hypothalamic-cortical discharges without interfering with the responsiveness to minimal acoustic stimuli of specific cortical projection areas such as the auditory area. Barbiturates cause a lowering in the frequency of the hypothalamic potentials and a diminution in background potentials of the cortex. But even in mild barbiturate anesthesia, in which these changes in neuronal activity are not very marked, the diminished responsiveness of the hypothalamus to nociceptive stimuli (or proprioception) is easily demonstrated.

Figure 107A shows that in the control condition, when the animal is very "light," a nociceptive stimulus causes an excitation of the cortex and hypothalamus. When additional amounts of pentothal are administered, the intensity and duration of the excitation diminish (Fig. 107B), and in Figure 107C excitation is confined to the motor area of the cortex, and finally disappears even in this area, although the cortical responsiveness to acoustic and optic stimuli is retained. This result is similar to that seen in experiments on the action of anesthetic concentrations of carbon dioxide on the hypothalamus and cortex.*

* See p. 458.

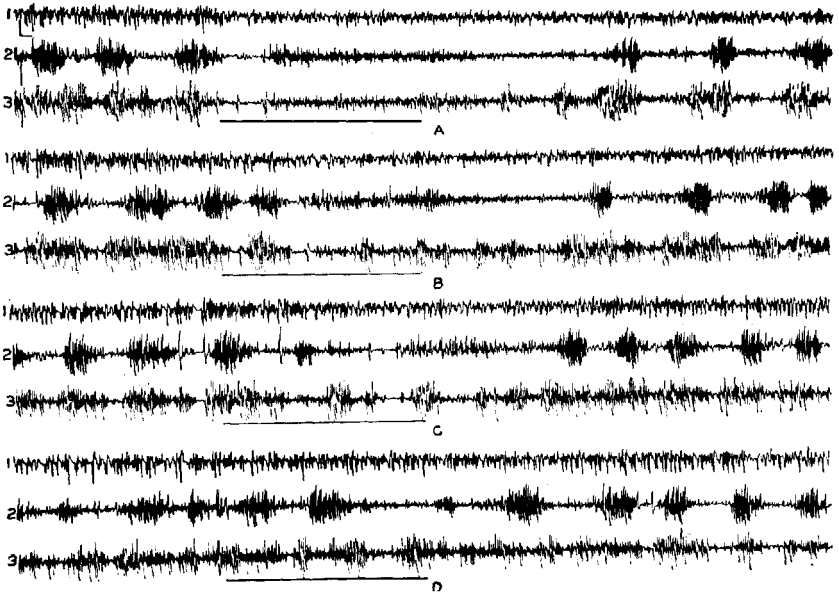

FIGURE 107. The effect of progressive barbiturate anesthesia on the responsiveness of the hypothalamic-cortical system of the cat to nociceptive stimuli (immersion of right hind leg in water of 60° C. for 20 seconds indicated by horizontal line). *Records A:* 31 hours after intraperitoneal injection of sodium pentothal, 35 mg/Kg, and 2½ hours after intravenous injection of 5 mg/Kg pentothal. *Records B:* 4½ minutes later, and after further i.v. injection of 1 mg/Kg pentothal. *Records C:* 4½ minutes after B, and after further i.v. injection of 3 mg/Kg pentothal. *Records D:* 30 minutes after C, and after further i.v. injection of 5 mg/Kg pentothal. Records 1 are from the right hypothalamus; records 2, from the left motor cortex; and records 3, from the sensory cortex (gyrus suprasylvius). With progressive barbiturate anesthesia there is a progressive diminution in the nociceptively induced excitation of the hypothalamus and cortex (464b).

As was mentioned previously, some patients show psychological disturbances but their autonomic reactions on the basis of Funkenstein's tests are normal (Groups II and III). Funkenstein *et al.* report that these patients are refractory to electroshock treatment. Theoretically one would expect electroshock to produce rather than to alleviate disturbances in these patients by changing the reaction type to that characteristic of Groups I and IV (i.e., sympathetic hyperreactivity). At any rate, electroshock is contraindicated on the basis of the physiological principles developed in this chapter. It is suggested that in these cases the diencephalon is not at fault and consequently that therapeutic procedures such as electroshock, insulin coma, and high concentrations of carbon dioxide, which act on the diencephalon

and alter autonomic balance, should not be applied. Perhaps psychotherapy, whose point of attack must be quite different, should be tried. The results of this discussion are summarized in Table 23.*

We are now in a position to answer at least in principle the three fundamental questions which were raised earlier in this chapter. In the light of our experimental work the mecholyl test can be used as a measure of hypothalamic excitability. The application of this test to patients afflicted with neuroses or functional psychoses allows one to get some idea of the hypothalamic disturbance in each patient and to correlate the clinical effectiveness of a certain therapeutic procedure with its action on the hypothalamus. Since changes in the hypotensive action of mecholyl are associated with changes in mental behavior, it can hardly be doubted that hypothalamic disorders or, more specifically, alterations in the responsiveness of the sympathetic division of the hypothalamus are intimately related to the disease process. The present work does not give any further clue to the nature of this relation, but this gap in our knowledge need not prevent us from pursuing therapeutic aims according to the physiological principles discussed in this chapter.

* In their most recent paper Funkenstein *et al.* (402a) no longer refer to the adrenalin test but confine their discussion to the mecholyl tests. They classify their patients into two groups. In the first (A), the hypotensive action of mecholyl is prolonged and the blood pressure fails to return to the original level within 25 minutes, while in the second group (B) mecholyl causes a slight fall in the blood pressure followed by a return to the original level within the 25-minute observation period. These two groups are obviously the same as Groups VI and VII and Groups II and III respectively. Group B is little improved by shock therapy, whereas the opposite holds true for Group A. Type A is believed to have an excessive adrenalin and type B an excessive nor-adrenalin resting secretion. This classification is derived from (as yet unpublished) experiments of these authors on the changes of the cardiovascular system in *normal* subjects who under the influence of stress showed adrenalin- or nor-adrenalin-like reactions. If those showing an adrenalin-like response to stress were injected with mecholyl, they reacted like Group A, while those with an apparently nor-adrenalin type of stress reaction reacted like Group B. Funkenstein *et al.* also mention that adrenalin-injected normal persons react to mecholyl like Group A and nor-adrenalin-injected normals like Group B. The data on which these observations rest are not yet available; but if correct they are certainly of great interest and represent an important extension of the work of Hickam *et al.* (647), who first suggested that emotional stress produces in different persons the liberation of adrenalin and nor-adrenalin respectively.

The application of these findings to psychotic patients, however, and the inference that such patients have a fundamental disturbance in the *resting* adrenomedullary secretion in the form of either an excessive production of adrenalin (Group A) or of nor-adrenalin (Group B) is thought to be improbable for the following reasons:

1. No evidence is presented that adrenalin or nor-adrenalin is present in excessive quantities in patients of Groups A and B.

2. Unpublished experiments from the writer's laboratory have shown on the

TABLE 23. Autonomic Reactions in Neuroses and Psychoses and Proposed Therapy

Funkenstein's Group	Result of Mecholyl Test	Result of Adrenalin Test
II & III	Slight hypotensive effect followed by return to normal pressure	Moderate or marked hypertensive effect
I & IV	Slight hypotensive effect followed by rise in blood pressure above normal	Moderate or marked hypertensive effect
VI & VII	Hypotension, marked and prolonged	Moderate or marked hypertensive effect

Funkenstein's Group	Type of Central Autonomic Disturbance	Suggested Therapy	Mechanism of Suggested Therapy
II & III	None	Perhaps psychotherapy	Action through the cerebral cortex
I & IV	Sympathetic hyperreactivity	High CO_2 therapy, possibly in combination with barbiturates*	Depression of posterior hypothalamus and of hypothalamic-cortical discharges
VI & VII	Sympathetic hyporeactivity	Electroshock; insulin coma	Increase in sympathetic reactivity with increased hypothalamic-cortical discharges†

* "High" CO_2 means CO_2 in anesthetic concentrations. Lower (10-per-cent) concentrations of CO_2 have been shown to increase the excitability of the sympathetico-adrenal system and to augment the hypothalamic-cortical discharge (464a).

† Increased hypothalamic-cortical discharges have not yet been demonstrated under these conditions. Their existence is inferred from the profound changes in conditioned reactions in animals subjected to "shock therapy" and particularly to repeated insulin comas (Gellhorn and Minatoya, 505).

basis of the action on the denervated spleen and denervated nictitating membrane that mecholyl elicits the secretion of nor-adrenalin.

3. Although the authors stress the elevated blood pressure in their Groups A and B, which could be related to the excessive secretion of adrenalin and noradrenalin, a study of their cases shows that the excessive mecholyl response in Group A (former Groups VI and VII) also occurs at normal blood pressure levels (see their cases 7 and 8 in their paper of 1951) – i.e., in persons who give no evidence of an increased resting secretion of adrenalin. Apparently the type of mecholyl response determines the effectiveness of the electroshock therapy, but the resting blood pressure level is not decisive for classification and prognosis.

The work of Funkenstein and his collaborators has further shown that the autonomic disturbance disclosed by the mecholyl test is not characteristic for a certain clinical disease entity. On the contrary, various autonomic disturbances (leading to a classification of the patients into different autonomic groups) occur in patients belonging to the same clinical entity. Apparently the type of autonomic disturbance does not determine the form of psychosis or neurosis.

It has often been pointed out in this book that hypothalamic discharges influence the cortex as well as peripheral (autonomic and somatic) structures and that these upward and downward discharges are changed in a parallel manner in different experimental conditions. In the light of these observations – clinical and experimental – it may be basically correct, although certainly incomplete, to state that cortical processes which determine behavior are fundamentally altered if the balance of the autonomic centers in the hypothalamus and the upward discharge which is intimately related to this balance are changed. Since a hypothalamic disturbance may give rise to various types of changes in behavior, it seems to follow that the specific behavioral change, the form of mental aberration, may be related to those cortical processes which, as yet not definable in physiological terms, are characteristic for the individual personality.

The proof of the dependence of normal and pathological "mental" processes on the central autonomic balance seems to us the most important theoretical conclusion which can be drawn from the investigations of the Harvard group. Their most significant practical result is the establishment of the fact that the quantitative response to mecholyl permits one to predict the therapeutic effect of electroshock. In our interpretation this means that certain types of central autonomic imbalance are revealed by the mecholyl test. Procedures which influence hypothalamic excitability in such a manner that autonomic balance is restored seem to have a restorative effect on those psychoses in which a hypothalamic dysfunction is primarily involved.

The experimental analysis of the mecholyl test presented in this chapter and the elucidation of the physiological action of carbon dioxide, electroshock, insulin coma, and related procedures given earlier may supply the blueprint for further investigations of the complex relations between autonomic reactions, mental disease, and a form of therapy based on clearly established physiological principles. The recognition of these fundamental relations seems to the writer more important than the effectiveness of the therapy suggested in Table 23. If, for example, it is correct that certain psychotics show sympathetic hyperreactivity of hypothalamic origin which can be

recognized by the mecholyl test and if it can be shown that carbon dioxide in high concentrations is effective in such cases because it reduces hypothalamic reactivity, a field of great potentialities is opened for neurophysiological research. Since the principles have been recognized, it will be possible to refine, on the basis of physiological experiments on animals, the diagnosis of disturbances in hypothalamic functions in man and to correct these disturbances with new and more effective therapeutic procedures.* The selection of the latter would be guided by physiological tests, and these would also determine at what time a certain therapy should be terminated. It is hardly necessary to add that future investigations must be concerned with the study of parasympathetic hypothalamic functions and their clinical significance as well.

This discussion has been confined to the physiological interpretation of the autonomic tests of Funkenstein *et al.* and their importance for the recognition of central autonomic dysfunctions and for the treatment of functional psychoses. That treatment of mental patients requires more than the administration of certain procedures which modify autonomic reactions is obvious. The importance of these psychological procedures is not underestimated, but their discussion is outside the frame of this book. It is not improbable, however, that the subtle techniques of psychotherapy are more successful after the basic disturbance in hypothalamic-cortical relations has been minimized or corrected through appropriate physiological procedures.

It is not unlikely that the application of autonomic tests † may be of great value for neurosurgery and neurology. The relation of the hypothalamus to the frontal lobe, and especially the effect of lobotomy and topectomy on the reactivity of the hypothalamus, is not well understood. By performing mecholyl tests before and after operation data could be obtained which would allow one to correlate clinical improvement with the autonomic reactivity of the patient. On the basis of such work it could be determined which type of operation would be the most suitable for a certain type of autonomic disturbance. Some preliminary observations suggest also that the diagnosis

* Repeated stimulation of the anterior or posterior hypothalamus through aseptically inserted electrodes may be a means of increasing central parasympathetic or sympathetic reactivity and thereby restoring central autonomic balance.

† Such tests were recently performed by Glaser (549a) on schizophrenes. Unfortunately the action of mecholyl was evaluated on the basis of the maximal fall in blood pressure; neither the area of hypotensive action nor the individual variations were taken into account as in Funkenstein's observations. Moreover the group consisted of deteriorated chronic schizophrenes who failed to improve through the operative procedures. Significant permanent changes in the reaction to mecholyl were likewise absent.

of neurological disturbances of the hypothalamus may be greatly aided by autonomic tests.

The investigations reported in this chapter offer new avenues of approach to numerous basic neurophysiological problems and are pregnant with clinical implications. The time may not be very far distant when the reactivity of the parasympathetic and sympathetic divisions of the hypothalamus and their balance can be determined in man. Therapeutic procedures directed at the restoration of the physiological central autonomic balance may result from the systematic study of the factors which alter hypothalamic excitability. Even the most important field of *preventive* psychiatry may benefit from the study of autonomic disturbances discovered in persons in whom neuropsychiatric disorders are not yet manifest.

The purpose of these lines is to arouse the interest of clinical investigators to apply the data presented in this chapter. Obviously a great deal of work will be necessary before tangible progress can be achieved in the treatment of mental disorders, but the task will be less difficult if the principles developed in this book are valid. The cynic may reject these anticipated developments as dreams, but he forgets that vision is as necessary an element in scientific achievement as is the carefully controlled experiment.

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