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Volume 3

Biology and Neurophysiology

of the

Conditioned Reflex

and its

Role in Adaptive Behavior

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Biology and Neurophysiology of the Conditioned Reflex and its

Role in Adaptive Behavior

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Editor's Preface

IT is a great privilege and a pleasure to present to English-speaking scientists the first English-language extensive summary of the experimental data and original concepts accumulated by Academician Peter Kuz'mich Anokhin for a period of some five decades of sustained creative scientific activity. Professor Anokhin, known as one of the most brilliant and productive students of I. P. Pavlov, has the distinction of having studied also with Vladimir Mikhailovich Bekhterev at the Brain Research Institute in Leningrad before transferring to Pavlov's laboratory. Anokhin was thus able to achieve a synthesis of Pavlov's basic conditioning studies with Bekhterev's clinical psychiatric and neurologic observations and pioneering studies on behavior modification techniques and group psychotherapy methods.

Anokhin also has the distinction of bridging the gap between the Pavlovian school and modern Western neurophysiology, experimental psychology, and cybernetics. As early as 1935, Anokhin developed the concept of the functional system as the fundamental unit of neurophysiologic integration, incorporating into this system the idea of "return afferentation," thus foreshadowing the development of the concepts of feedback, cybernetics, and the systems approach in psychobiology. This monograph depicts elegantly the development of these concepts and delineates suggestions for further research.

Anokhin was the first Pavlovian physiologist in the USSR to initiate in his laboratory extensive utilization of electrophysiologic methods in the investigation of the nature of conditional reflexes and their role in biological adaptation. Anokhin's contributions include: the development of secretory-motor techniques for studying conditional reflexes; investigation on subcortical-cortical interactions in conditioning, the nature of internal inhibitions, and the role of the frontal lobes in behavior.

On several occasions I had the opportunity to spend some time in Professor Anokhin's institute and to observe the exciting intellectual atmosphere in his laboratories and the highly sophisticated equipment and ingenious techniques utilized in the many interdisciplinary studies conducted by Anokhin and his industrious and distinguished collaborators. In the spring of 1970, I had an opportunity to lead an Ohio State University study tour devoted to psychology and psychiatry in the USSR. The day spent at the Sechenov Institute was a rare intellectual treat and left an indelible impression on all participants, opening up new horizons in psychobiologic thinking.

Apart from his distinction as one of the greatest Soviet scientists, Anokhin is also a

solid philosopher, a lover of and authority on classic Russian art, a humanitarian, and a wonderful, warm, and devoted friend. I hope that the readers of this book will derive as much intellectual stimulation and esthetic joy as those of us who were involved in translating and editing this volume.

I wish to take this opportunity to express my gratitude and appreciation to Joyce A. Alexander, Anne R. Coleman, Candace N. Corson, Marilyn F. Moeller, Barbara Decker Ritchey, Paul A. Robinson, and David C. Smith for their competent and devoted assistance with the manifold tasks of editing, typing, and proofreading. And last, but certainly not least, I want to express my gratitude to my wife and co-worker Elizabeth O'Leary Corson for lending her linguistic talents to help transform the translation into idiomatic English and for her indefatigable help in conducting and coordinating the numerous complex experimental procedures involved in our longitudinal interdisciplinary laboratory studies and thus offering me some respite for my editorial tasks. I shall be grateful to the readers for any comments, criticism, or suggestions.

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SAMUEL A. CORSON

Author's Preface to the English-Language Edition

IN recent years it has become increasingly apparent that the development of our knowledge in neurophysiology is going through a critical period. The situation is critical because the rapid increase in the number of investigations of every kind, which produce specialized and for the most part scattered results, considerably overtakes the attempts to interpret and generalize the accumulated data. As a result, we do not have a satisfactory theory either for explaining the available data or for formulating problems for future investigations. In a recent interview, Eccles very aptly characterized this critical state of the science of the brain. He said: "You've got to be in the experimental battle when it is being fought in order to realize just how inappropriate most experimental observations are for providing a sound basis for theoretical developments" (MacKay and Eccles, 1967, p. 82).

Essentially, everything said about general cerebral physiology is also valid for its most important branch: the study of the conditioned reflex.

Everyone agrees that Pavlov's discovery of the conditioned reflex is an event of enormous importance in the history of physiology. This is evidenced by the fact that at the present time almost all the neurophysiological laboratories in the world are taking part in one form or another in the elucidation and discussion of the basic functional laws of the conditioned reflex (Fessard, Eccles, Magoun, Corson, Razran, and others).

One cannot fail to see that the study of conditioned reflexes develops, in Pavlov's words, "extensively," that is, that it broadens. There is, essentially, a process of accumulation of diverse material on the basic forms of manifestation of conditioned reflexes (extinction, differentiation, experimental neurosis, etc.). An enormous number of data is gathered, which expand our knowledge about specific conditioned-reflex adaptations, and different variants are created for various already known manifestations of the conditioned reflex that had been first developed in Pavlov's laboratory.

Investigations naturally also exist in which attention is focused on *a deeper understanding of the actual phenomena of conditioned-reflex activity*. However, the biological nature of the temporary connection, as well as the physiological nature of the "coupling" of conditioned reflexes, still remain unclear. Particularly inadequate has been the study of the central phenomenon of the entire theory of higher nervous activity—"internal inhibition"—although it certainly is receiving emphatic attention in both Soviet and world literature. It suffices to refer to the substantial critical review of

this problem in the monograph of Solomon Diamond *et al.* (Diamond, Baldwin, and Diamond, 1963) and to our monograph on internal inhibition (Anokhin, 1958).

All this can be said in spite of the fact that there is a clear tendency to study detailed mechanisms. This general trend alone, however, is not enough: it is essential to develop overall fundamental views regarding the physiological architecture of the conditioned reflex and the integrative nature of its mechanisms.

It is becoming increasingly clear that the reflex theory in its original Cartesian form is no longer adequate as the fundamental basis for the explanation of complex forms of conditioned-reflex activity and behavior. Neurophysiologists are confronted by new problems, for which to a certain degree they had not been prepared.

It has thus become quite apparent that not a single complex behavioral act can appear under the influence of one stimulus alone, for example, of a conditioned stimulus. In the same manner, a number of other problems arose. It became clear, for example, that no behavioral act and, in particular, no so-called voluntary action can be performed without the critical mechanism to which modern science has given the name "decision making."

It also hardly requires mention that any behavioral act is carried out in such a manner that the characteristics of the future result or, to put it simply, the goal of the behavioral act is patterned in the brain before the implementation of this act has begun. Consequently, the entire behavioral act develops by no means linearly, that is, the excitation in it does not spread progressively from point to point.

It is also conspicuous that the reflex theory as a theoretical concept was developed only on the basis of reflex action, and therefore the *result* of the action was completely eliminated from it. This fact, which had not attracted the attention of physiologists in the past, considerably reduced the creative effect of the reflex theory on the understanding and study of the behavior of the animal as a whole. Only Pavlov's discovery of reflexes in man reduced this negative effect. The elimination of the result from the "reflex arc" first of all eliminated the possibility of using the theory of feedback in the system of the behavioral act. In fact, the presence of the result in the reflex would inevitably have raised the question of the adequacy of the result. This, in turn, could not be checked without special equipment for determining the degree of adequacy of the adaptive result.

All this clearly indicates that many long-held concepts in the field of higher nervous activity must be reexamined and brought into accord with the most recent data of neurophysiology, neurochemistry, neurocybernetics, and other borderline sciences, such as neuromorphology, especially electron microscopic neuromorphology.

The book we are now submitting to the English-speaking reader is an attempt to give a synthesis of the latest advances in the sciences of the brain and to develop on this basis certain new possibilities for the investigation of the conditioned reflex. In this respect I was greatly assisted by the many years of investigations by my collaborators, whose attention was specifically directed at the elucidation of the problems put forth above. Most of these investigations are of a complex nature and incorporate numerous advances from their borderline fields of science.

I do not think that our solution of certain aspects of this large problem is exhaustive

and ideal. It is likely that many of my colleagues will endeavor to provide improved concepts and a more efficient application of the latest advances for both theoretical and practical problems of neuropathology and psychiatry.

For example, the neuroses are at that point in the science of the brain at which the lines of the most diverse investigations and scientific disciplines intersect. In fact, the most widely held assumption that neurosis is the result of a "struggle between excitation and inhibition" meets the demands of modern clinical neurology less and less. The concept of a "struggle between excitation and inhibition" is also in conflict with the pedagogic and therapeutic tactics of educators and physicians.

It is, of course, a task too great for one person to overcome all these accumulated deficiencies and to develop a satisfactory scheme for all aspects of higher nervous activity. Nevertheless, such attempts must from time to time be made, and the new approaches must become the subject of extensive and friendly discussion.

For some forty years the author of this book has been developing new approaches to the solution of the basic problems of the conditioned reflex. I think that even earlier, still at the laboratory of my teacher I. P. Pavlov, I attempted to develop a somewhat different approach to a number of problems of higher nervous activity.

We have, for example, long ago proposed a modification of the concept generally held in Pavlov's laboratory regarding the onset and localization of internal inhibition. Our concept, which has been discussed quite extensively in the book by S. Diamond *et al.* (Diamond, Baldwin, and Diamond, 1963), is again analyzed in detail in a number of chapters of this book.

Perhaps the most important feature of the book we present to the English-speaking reader is that its central idea is the attempt to develop a unifying concept of the conditioned reflex and of higher nervous activity on the basis of the theory of the functional system, which we had proposed as early as 1935 (see Chapter 6).

This concept, which we formulated on the basis of our previous investigations about the compensation of disturbed functions, makes it possible to regard the conditioned reflex from the point of view of the systems approach to complex behavioral acts. As the reader can see, this approach, supported by concrete physiological mechanisms (afferent synthesis, the action acceptor, etc.), enables us to move to a new level in the investigation of complex behavioral acts.

Thus, the book combines the biological, neurophysiological, neurochemical, and neurocybernetic aspects, which all contribute to the development of a unified approach to the most pressing problems of higher nervous activity. It is my hope that the readers of this book will also find in it useful ideas regarding the further development of Pavlov's theory of conditioned reflexes.

I wish to acknowledge here the great help extended to me by my closest collaborators in the work on this book, both with their experimental data and with their participation in preparing the book for publication. I have in mind first of all my long-time collaborators A. I. Shumilina, I. O. Laptev, I. A. Zachiniaeva, Ia. A. Miliagin, E. L. Golubeva, F. A. Ata-Muradova, and others.

The general neurophysiological data for the analysis of the conditioned reflex were obtained by my collaborators K. V. Sudakov, V. A. Shidlovskii, and others. Further

data for the perfection of the concept presented in this book are now being collected by a large team of my collaborators at the Sechenov Institute of Physiology of the First Moscow Medical Institute.

I cannot fail to acknowledge here the enormous help given me in the publication of this book in English by my friend Professor Samuel A. Corson, himself an investigator in the field of higher nervous activity. With his advice and competent comments on a number of problems in connection with the publication of the book in English he did everything necessary to make our concepts and the overall line of thought of our work accessible to the English-speaking reader. I express my deep gratitude to Professor Corson.

ACADEMICIAN P. K. ANOKHIN

Author's Preface to the Russian Edition

In the literature of the past two decades, a great deal of attention has been given to the conditioned reflex as an integrated behavioral act. It has become apparent that this discovery of I. P. Pavlov is acquiring an ever widening significance in the most varied fields of life and culture. Efforts of many laboratories studying the behavior of animals and man, especially laboratories associated with psychiatric clinics, are devoted to the study of conditioned reflexes.

In fact, the conditioned reflex has become the object of investigation even in those neurophysiological laboratories which traditionally worked only on a detailed analysis of the nervous process itself. This is the reason for an increasing integration in the study of conditioned reflexes and the general physiology of the nervous system. This extensive use of the method of conditioned reflexes has been determined by the historical principles of the development of the general physiology of the nervous system.

In the nineteenth century, the analytical neurophysiologist was not confronted with the question of why the detailed processes he was studying are needed. It was thought that the nervous processes studied by analytical methods are indeed the very same processes which directly participate in the function of the central nervous system by creating adaptive reactions of the whole organism.

The development of electronic techniques turned the attention of neurophysiologists to still finer and more detailed processes of the nervous system as they occur in a single nerve cell and even at a molecular level. However, this progressive refinement of the analytical aspect of investigations harbored some basic contradictions which soon became apparent.

It turned out that the more profound and minute the processes are which the neurophysiologist investigates, the farther he departs from that which is the final aim of any neurophysiological investigation, namely the understanding of the function of the entire brain, of integrated behavior, of psychic activity, and *finally the control of the function of the brain under normal and pathological conditions.*

Naturally, then, the complex acts of behavior in animals, the neurophysiological units of integrative activity of the organism, gained the attention of many neurophysiologists.

Here it became apparent that the *one physiological principle of the function of the entire brain which explains the integrated behavior of animals and man is the principle of the conditioned reflex.* Gradually the concept became generally accepted that the finest processes of the

nervous system acquire their highest significance and occupy their true place in the architecture of integrated behavioral acts only if their study is continuously correlated with the formation and manifestation of the conditioned reflex. Thus, the way was prepared for the current development in the study of the conditioned reflex, wherein precise neurophysiological investigations and the study of the conditioned reflex became integrated in a single laboratory. It is interesting that the well-known series of international symposia on the study of the brain was entitled "Brain Mechanisms and Behavior." Moreover, paralleling the growing popularity of the conditioned reflex in neurophysiological laboratories, increased attention to the subject was paid also by clinicians and, what is even more significant, by the followers of Freud.

We should keep in mind the important fact that many working hypotheses and assumptions were necessarily proposed in Pavlov's school in the years of its rapid growth and expansion. This is a natural sign of the growth of the school. However, the logic of scientific progress is such that in the process of investigative work, hypotheses are subjected to experimental test; as a result of this they either become transferred into a class of "authentic" and firmly established truths, or else they do not stand up under experimental evaluation and are replaced by more acceptable working hypotheses.

In connection with the development of precise electronic methods of investigation of the nervous system, permitting intervention in any region of the brain and any cells of any nerve centers, during the past two decades the former neurophysiological concepts regarding the integrative processes of the brain and the nature of the basic nervous processes of excitation and inhibition have completely changed.

It is well known that Pavlov, having discovered the conditioned reflex, found it necessary to utilize the meager neurophysiology of his time for developing concepts on the concrete nervous mechanisms of the conditioned reflex (irradiation of the processes of excitation and inhibition, negative induction, cortical inhibition, etc.). One really had to be a genius in order to construct, on the basis of the quite imperfect neurophysiology of that time, those working concepts which for many decades have served as an impetus to productive scientific investigations. But these were, nevertheless, only hypotheses about the mechanisms of cortical activity which from various points of "input" and "output" intersected the mysterious mechanisms of the "black box."

At the present time neurophysiology has completely changed in character. Electronic methods have been developed for direct penetration into the "black box," new laws have been discovered regarding cerebral function and new concepts are being developed concerning the mechanisms of integration of the many processes of the brain.

The question naturally arises: are contemporary advances in the study of the physiology of the nervous system related to the studies of higher nervous activity? Can a connection be established between advances in the field of neurophysiology and the major concepts of the Pavlovian school?

There is little doubt that communication between the two approaches must be developed as soon as possible. The more time lost in this direction, the harder it will be later to create an organic unity between neurophysiology and the physiology of higher nervous activity. In this book we attempt to outline those basic problems in the

area of higher nervous functions which can be analyzed on the basis of recent advances in neurophysiology.

All that was said above concerns the relationship of higher nervous functions to the laws governing the functions of the "lower" central nervous system. These laws must serve as a natural foundation for higher nervous activity which, however, has its own specific features determining higher forms of behavior of animals and man. Furthermore, the physiologist of higher nervous function must have his own methods for utilizing contemporary neurophysiological material. We must remember that the conditioned reflex represents the highest integrative mechanism in the activity of the brain, subjecting and adapting to itself all the detailed processes of the nervous system which usually are the object of study by precise analytical methods.

It is also necessary to mention another connection of higher nervous activity, not downward but "upward," to psychology, to the study of psychologic phenomena and higher forms of conscious activity. It is sufficient to point out that Pavlov himself projected a number of problems of an interdisciplinary nature which could be approached from different directions. One can point, for example, to the "reflex of purpose,"* to the second signal system, etc. Indeed, are not the problems of the mechanisms underlying goal-directed activity of higher organisms worthy of the combined efforts of the physiologist and psychologist?

In this monograph an attempt will be made, on the basis of an analysis of contemporary scientific achievements, to formulate new concepts relative to some methodological problems of Pavlovian concepts. First I shall discuss the biological roots of the reflex per se and attempt to show that it is a biological reflection of the universal laws supporting the space-time structure of the material world.

Such an analysis of the origin of the conditioned reflex must inevitably lead to the transformation and expansion of the generally accepted reflex theory, the so-called "classical reflex theory," which had its origin mainly from Descartes. This theory has long ago become "primitive," according to Pavlov, and at the present time in its former architectural expression ("reflex arc") cannot promote further development of a neurophysiological foundation of the behavior of the animal as a whole.

It is hardly necessary to mention that the reflex theory formulated by Descartes played a revolutionary role in the development of the physiology of the nervous system. In the course of some 300 years, it has successfully directed thinking in thousands of investigations. Yet, at the present level of our knowledge, it limits the possibility of explaining the integrated behavior of animals and man.

In our laboratory we have tried to develop an expansion of the classical reflex theory. The theory of the functional system, formulated by us in 1935 (Anokhin, 1935), foreshadowed the development of cybernetic concepts by Norbert Wiener some thirteen years later (Wiener, 1948).

In this book we shall attempt to achieve a synthesis of cybernetic concepts and various neurophysiological disciplines, and to construct, on the basis of this synthesis, a perspective for future work. Such a task can be most successfully accomplished if the

* goal-directed behavior (*Editor*).

synthesis itself is conducted on the basis of two cardinal laws of the function of the brain as a whole: the law of the conditioned reflex and the law of internal (cortical) inhibition.

It is natural that the analysis of both these cardinal laws of behavior is also of great significance for elucidating the neurophysiological basis of what we usually designate by the term "learning." In the process of elucidation, an account will be given of some original neurophysiological concepts which were developed in our laboratory during the past forty years. Of special significance for this book is the concept concerning the biological specificity of the ascending activation of the cerebral cortex.

We hope that these concepts may help to bridge the gap between the integrative level of higher nervous activity and the fine detailed neurophysiological investigations, although the final judgment concerning the success of this must be made by the readers of the book.

P. K. ANOKHIN

Foreword to the English-Language Edition

It will be with great interest that the scientists of the English-speaking world will welcome this translation of the recent book by Academician P  tr K. Anokhin.

After a long period during which the advances in neurophysiology in the Soviet Union were almost unknown to the West, channels of intercommunication opened and, through the sponsorship of the Academies of Sciences and of Medical Sciences of the USSR, scientists were once again able to benefit from each other's knowledge.

The outstanding break-through for Western neuroscientists, instigated by the International Federation of EEG and Clinical Neurophysiology, was the International Colloquium on Electro-encephalography and Higher Nervous Activity held in Moscow in October 1958. Outstanding among the distinguished Soviet scientists in the achievement of this historic event was Professor Anokhin, whose interest in the Federation was unwavering.

From the English-speaking countries, four from the United States and one each from England and Canada were invited to participate in the Colloquium in Moscow, in addition to four scientists from Western Europe. All the Eastern European countries were represented, as well as China, India, Japan and Mexico.

The Westerners came with little knowledge of Soviet neuroscience other than that of classical Pavlovian physiology based, as it was, on observation of total animal behavior in controlled experimental conditions. In the West, influenced for over a century by the electrophysiology of Du Bois Reymond and its importance as a tool for exploring the nervous system, the focus of attack had been electrophysiological: i.e. the electrical concomitants of such behavioral states as wakefulness and sleep, arousal, attention and distraction. This Congress was instrumental in merging these two approaches to the study of behavior—leading to the electrical exploration within the brain of the behaving “Pavlovian” animal.

Pre-eminent in building this bridge between the two methodologies was, and has been continuously ever since, Professor Anokhin, a pupil of Pavlov and a skilled electrophysiologist.

The Westerners left behind them a deepened interest in what electrophysiology, even at the level of unit recording, can provide and a glimpse of the contribution that computers can make to the neurosciences. They returned to their own countries with a new knowledge of the powerful tool of conditioned reflexology developed so highly by the Pavlovian school. When the account of this period is written, the role of Anokhin

in reconciling the earlier and somewhat divergent methodologies prevalent in neurophysiology will place him in history.

But a far wider outcome of this historic event was the development of international relations in brain research, among the leaders of which again was Anokhin. This was the foundation of the International Brain Research Organization.

Planned during this week in Moscow by this small group, meeting together sometimes in the House of Scientists, sometimes in the Sechenov Institute in a quiet court behind the beautiful building of the Old Moscow University, with its walls of Peter's yellow, a proposal was drawn up and later brought into draft form for presentation to UNESCO in January 1959. As a result of this preliminary effort of a few dedicated scientists, IBRO came into being at a meeting in Paris in October 1960 with a strong Central Committee to guide it, Professor Anokhin being prominent among its leaders.

Since that date the line of communication in the Neurosciences between the 41 countries with membership in IBRO has never faltered and a younger generation who benefit from this free exchange of scientific knowledge should not forget one of its main movers : Pêtr K. Anokhin.

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MARY A. B. BRAZIER

CHAPTER 1

The Biological Roots of the Conditioned Reflex

STATEMENT OF THE PROBLEM

In most investigations the conditioned reflex is thought to be something definite. It is from this definitive concept of the conditioned reflex that many authors begin their analysis of its mechanisms and adaptive role in the life of animals and man. On the other hand, ontogenetic and phylogenetic investigations of conditioned reflexes are few. Finally, there is an absence of investigation into the *biological roots* of the conditioned reflex, i.e., the first appearance during evolution of those adaptive characteristics inherent in the conditioned reflex in its most pronounced form in lower and higher animals.

In the course of hundreds of millions of years, primordial life developed together with the evolution of the basic inorganic properties of the earth. At present there is no doubt that primordial living matter was able to "assert" its right to exist during its development only by adapting itself to external factors and developing reactions of a survival nature.

A number of questions immediately arise. To what external factors did primordial living forms need to adapt in the early stages of our planet's development? With the help of what mechanisms and processes were the earliest forms of life able to overcome harmful influences and thus survive? And did not these adaptive characteristics which acquired such a decisive significance in the conditioned reflex originate here during the first stages of life?

In order to answer these questions it is evident that we must, as thoroughly as possible, characterize the conditioned reflex as a specific form of the adaptive reactions of the organism. We must identify those parameters which are most specific for the conditioned reflex. The identification of each parameter, in its turn, will help to determine its origin and form in the "depth of ages." In other words, we may be able to discern to what living organism the adaptive element became useful for the first time.

Consequently, we need not consider by means of *what substrate* this parameter of adaptation is implemented and what kind of complex mechanisms of the organism ensure this form of adaptation.

Neither shall we use the level of somatic organization of a given species of animals as a decisive criterion. The decisive question must be the *form* of adaptation and its close connection with a specific feature of the inorganic world. For example, gravity as a fundamental physical factor, existing before the appearance of life on earth, necessitated

adaptation to itself in all animals regardless of their organization and zoological classification. Thus "weight," as the primary parameter of the external world, is essential for the fullest development of the capacity for adaptation of all organisms. Is there a similar parameter in the case of the development of conditioned reflex reactions? Do the adaptive characteristics reflect some kind of specific factor of the external world?

We can answer these questions only after an analysis of all those adaptive characteristics of the conditioned reflex which make it possible to separate it into an independent group of the organism's reactions.

ADAPTIVE FEATURES OF THE CONDITIONED REFLEX

In order to solve the problem of the primary characteristic of the conditioned reflex as a specific adaptive act, those characteristics which were formulated by Pavlov must be analyzed first.

Wishing to characterize this new physiological reaction, he first turned his attention to the fact that it is elaborated *de novo*, that it had not previously existed in the functional organization of the animal's brain. He also observed that this reaction appears only with a special combination of conditions which are essential for the development of the reaction, and which he therefore called *conditioned*.

According to this characteristic of being *developed* or *acquired* during the life of an animal, a distinction was made between the conditioned reflex and another form of adaptive reaction, *inborn* activity, accordingly called the unconditioned reflex.

We can, therefore, logically state that the criterion for separating the conditioned reflex into a special category is the fact that it is *acquired* rather than *inborn*. It follows that the introduction of the criterion of "acquiredness" is based on the premise that inborn or unconditioned reflexes are not developed in a given individual life but are presented, so to speak, in a final form. Acquiredness, then, is an essential feature of the conditioned reflex, for it characterizes the principal peculiarity in the adaptive behavior of the animal.

We saw that the concept of acquiredness inevitably assumes that the other form of behavior, the unconditioned reflex, is not acquired. We shall see later, however, that acquiredness must have two meanings. One of them must refer to the acquisition of conditioned connections in the individual life of the animal, while the other refers to those reactions which regularly appear on a basis of those neural structures "acquired" during phylogenesis, reflecting the corresponding ecological factors of a given species of animal. Otherwise, the appearance of complex behavioral acts or even systems of these acts in newborn animals could not be explained on a strictly scientific and deterministic basis. At the same time an impassable abyss would exist between inborn and acquired behavioral acts.

The second essential characteristic of the conditioned reflex is the changeability or *lability* of the acquired neural connection. It is gradually lost as soon as it becomes inappropriate for the newly established conditions, i.e., when the main reinforcing factor in the form of an unconditioned reflex disappears.

It must, however, be noted that this characteristic of the conditioned reflex is not as

peculiar as acquirability, inasmuch as the unconditioned reflexes also have a sufficient degree of lability. Thus, the unconditioned alimentary reflex disappears as soon as the alimentary excitability is decreased as a result of feeding. This decreased excitability by no means occurs because the "starved blood," as the primary exciting agent of the alimentary center, has changed its composition. We know from everyday experience that for such satiety a definite sum of afferent impulses from the lingual, esophageal, and gastric receptors is quite sufficient. We must recognize the presence of wide lability also in the unconditioned reflex, although quantitatively it is not of the same order of magnitude as in the conditioned reflex. In other words, lability is a relative rather than an absolute characteristic of the conditioned reflex.

The third characteristic of the conditioned reflex is its *signaling character*. It develops as an "anticipatory activity" in Pavlov's words, i.e., an *activity which anticipates the course of sequentially developing external events*.

Indeed, saliva secreted in response to a bell used as a conditioned stimulus appears not in order to "digest" the bell. Rather, it prepares, "in anticipation," conditions for the digestion of bread which will appear only in the future. On the basis of this characteristic and dynamic feature, Pavlov formulated the "principle of signalization" as the basic principle regulating the adaptive significance of the conditioned reflex.

If one compares the two most characteristic features of the conditioned reflex, "acquirability" and "signalability," then it is easy to see that in the adaptive sense the first feature is entirely subject to the second. Indeed, any kind of nervous activity in general is not individually acquired; what is acquired is the *mechanism which permits the anticipation of the course of future events for the purpose of achieving the best adaptation to the environment*.

It follows that signalability is the most characteristic and the most adaptive feature of the conditioned reflex. But what, in essence, is this signalization? We know that to signal means to warn about something impending. It is in this sense that Pavlov formulated the principle of signalization.

Since, however, the signal may refer only to a sequential development of external phenomena, we must emphasize its principal relation to the temporal aspects of those phenomena. *The parameter of time is the external factor on the basis of which and in connection with which conditioned reflex activity could historically originate.* This poses a new problem in physiology: to discover and characterize all the variations of temporal relationships which are an inseparable feature of the inorganic world that preceded the origin of life in the history of our planet.

THE TEMPORAL STRUCTURE OF THE WORLD

At the various stages of the development of science, ideas about space and time were based on different material foundations, depending primarily on advances in the field of physics. For example, several decades ago when the basic ideas of physics rested on the interaction of solid bodies, concepts were created about space and time in direct relation to the properties of solid bodies, with all the resulting limitations and deficiencies.

With the progress in the field of physics regarding the electromagnetic basis of all

forms of material bodies, there developed the concept of an electromagnetic "matrix" which links all forms of movement and states of the material world. In particular, the theory of relativity could arise only with the development of ideas concerning the universality of these electrical processes which fill the universe. It was therefore possible to formulate *new types of connections* between all material phenomena of the universe (Einstein).

From the point of view developed in this book it is important to state that space and time, taken as separate entities, do not represent as absolute a law of the universe as does the space-time complex.

However, for the evaluation of the component factors of the space-time complex, it is very important to realize that rarely do both factors play a role at a given moment and *to the same degree*. We often encounter the fact that some individual parameter at a given moment may acquire primary significance. In this sense we must distinguish between two completely different levels of evaluation of space and time—the general philosophical, gnosiological, and the correlative, *i.e.*, *space and time as factors of adaptation of living organisms*.

Indeed, since space and time as absolute factors of the material world existed during all times of transformation of the universe, then, on the scale of our planet, they naturally were the primary structure of the material world and possessed their absolute properties long before the appearance and development of living matter. From this it follows that even the primordial living forms were necessarily "inscribed" in these basic laws of space-time relationships; therefore, these laws became *absolute factors of the adaptation of living matter to the environment*. The space-time relationships had to become the inevitable foundation on which primordial life acquired its basic properties, and living organisms acquired their adaptive qualities up to the highest stage of evolution—man.

This concept can hardly be challenged by anyone : the very fact of the *primacy* of these laws determines their organizing role in the development of living organisms at the various stages of evolution. This cardinal fact of evolution basically changes our attitude toward the theory of space-time relationships. We cannot remain only on the level of the philosophical evaluation of the parameters of time, but we need to evaluate the whole diversity of the *time structure of the world* from the point of view of its significance for the progressive evolution of living matter.

Here we encounter properties of time which were never before taken into account. This is understandable. With the origin of life on earth, matter was enriched by an essentially new factor, the *active* relationship of living matter to all possible transformations of the space-time structure of the inorganic world, and consequently, to a living organism, time has acquired its own specific significance.

It was necessary to answer the question : in what manner could time, as a universal factor of the world, influence the development of living matter? How did organisms adapt themselves to the time factors of the movement of matter, and *precisely which parameters of time* proved to be the most decisive for life, ensuring its "survival" and progressive evolution?

Unfortunately, there has been comparatively little analysis of this central point of evolution in biological literature. Time as a factor in the evolution of living organisms

on earth and as the most important parameter in the development of their nervous activity, has hardly been subjected to serious analysis.

What is most important for us in the time relationships of animate and inanimate nature?

The first essential point is that the basic forms of movement of matter within the space-time framework existed also in inorganic nature long before the appearance of the first living organisms. This is, of course, an important factor which makes it evident that living matter, "inscribed" in the already existing space-time system of the world, could not fail to reflect the characteristics of the system, its architecture, provided that these characteristics had a relation to the basic characteristic of living matter itself, i.e., *survability*.

From the moment that life appeared, the relations to the individual parameters of the space-time structure drastically changed on the part of inorganic matter. The mountain, for example, as a form of inorganic matter, does not react selectively to climatic and meteorological factors which act upon it. For the mountain the problems of adaptation and survival do not exist. For living organisms the whole external inorganic world with all its diverse influences was "weighed" only on the scales of progressive evolution.

There appeared an *active relation to the external inorganic factors* and the inevitably resultant division of all factors into two major categories : *those harmful to life and those contributing to its preservation*. From this time on, all the diverse forms of the movement of matter within the framework of the temporal structure of the world began to be "arranged" by primitive living organisms according to this reciprocal scheme, and living matter began to reflect and strengthen these universal laws in its structure.

It follows that we must first of all determine *what concrete temporal parameters of the movement of matter* were encountered by primordial life. We must give a precise evaluation of the *temporal structure of the world*, i.e., of those varieties of the space-time movements of matter which may become factors forming the adaptive reactions of living matter. This makes it necessary to identify those special features of the temporal structure of the material world which were a kind of "absolute imperative" for the development of life on earth.

Here we see that in any attempt to concretize the space-time structure of the material world, we inevitably encounter a *sequential transference* of bodies in space, with *sequential influences* of one body on another, with a *sequential development* of phases of movement and transformation of matter.

In summing up these discussions, we can say from the point of view of dialectical materialism that the most essential feature of the space-time structure of the world determining the temporal relation of primitive organisms to the external inorganic world is the sequence of the influences of the outer world on these organisms, independent of the interval between these influences and of their forms of energy. In this way we identify the *temporal parameter* of the relationships of the organism to the inorganic world as a factor which, to a certain degree, is independent in the sense of its significance for adaptive transformations.

We now ask the question : what forms and variants of this basic time factor, *the sequence of influences*, does the organism encounter? In what manner does the all-encompassing

movement of matter distribute itself within the framework of the absolute temporal parameter, the sequence of phenomena? In other words, what *preexisting temporal structure* of the inorganic world (compelling adaptation to itself) have the primary organisms encountered?

We think that we have the possibility of identifying some temporal parameters from the basic form, the *sequential arrangement*, and of analyzing the significance which they could have had for the adaptive relations of primitive organisms.

The first variant is the existence of a number of such sequential phenomena, none of which is ever subsequently repeated in the course of the entire life of the organism. Symbolically, this series could be depicted as : a, b, c, \dots

It stands to reason, of course, that the factors of the inorganic world, a, b, c , etc., must be connected by cause-effect relations and develop in sequential order; there is also no doubt that all or some of them can exert sequential influences on the organism. However, according to stipulation, not one of these influences may ever have a repeated effect on the organism. Concretely, this can be a solar eclipse, a storm or tornado of unusual force, the passing of a comet close to the earth, etc. Surely, however, the unrepeated influences can also include those situated closer to the organism.

Some of these unrepeated influences of the environment could, of course, have some essential significance for the organism, either harmful or beneficial. The primitive organism could either resist this sudden action by means of possibilities already available in it, or be destroyed. However, these influences were always sudden and new for it.

There is possible, though, another time structure in the sequential order of external influences on the organism: certain individual factors of the environment can return and repeat their effect at definite intervals of time and consequently can be called a *repeating series of sequential influences*. Symbolically this second possibility can be depicted thus : $abcd, abcd, abcd, \dots, abcd$.

This scheme shows that in the inorganic world we can have this sequence of events which recur rhythmically in the same composition and in the same sequence of components. This may be, for example: day, evening, morning, or summer, fall, winter, spring, or cloud, lightning, thunder.

These series of sequentially developing and rhythmically or aperiodically recurring phenomena of the inorganic world have an absolute direction and are connected with astronomical, meteorological, and physical laws, although the duration of the rhythms in each case may differ. Consequently, the *recurrence* of these cycles may have a different significance for organisms with different life spans.

Until now we have taken as examples those series of sequentially developing events which have properties of absolute stability. Also conceivable, however, are sequential phenomena which, having the same parameter of recurrence or returning, at the same time have the property of *relative stability*. For example, a tree growing on the bank of a river and being of a certain age, can be a dwelling place for various kinds of animals only for a certain period of time, after which it may be replaced by other trees, the same or different. And yet, in the course of its life span, this tree will represent for its inhabitants a series of sequential, rhythmically recurring phenomena taking place at various times of the year, especially in northern latitudes.

Thus, both in the first case and in the second, we have one main temporal feature of sequentially developing events: *a recurrence which can be either absolutely stable or relatively stable.*

Of course, *the property of recurrence per se* of phenomena of the inorganic and later of the organic world, as a special parameter of absolute space-time sequential order, can have infinite variations in the duration of the rhythms themselves, in their stability, in the composition and length of the individual components, in their spatial localization, etc. In all these variants, however, the parameter of *recurrence* will be the most characteristic and specific.

TIME AND PRIMORDIAL LIFE

Thus far we have examined the sequential order of phenomena of the inorganic and partly the organic world with only one aim: to distinguish the various temporal parameters of the inorganic world which must inevitably have influenced organic matter even at its very inception. However, these temporal parameters (nonrecurrence, recurrence, duration, stability, variability, etc.) were set forth by us irrespective of another important quality which these parameters began to acquire upon interaction with living nature: their degree of *importance* for the support and preservation of the life process.

Undoubtedly even at the very first stages of the organization of living matter, perhaps at the stage of primary coacervates, the changes of external material conditions were "classified" by these rudiments of living substance as "harmful" or "useful" according to the criterion of their "importance" for the stabilization of polymolecular systems. This type of relationship of primary forms of living matter to external influences is particularly well described by Oparin (1953, 1957).

In spite of the relative constancy of the inorganic conditions under which life was generated (probably in primordial oceans), there was a successive change in the external influences on particles of primary living matter which could produce some kind of primitive "natural selection" of the most stable formations existing as "open polymolecular systems" (changes in temperature, reacting substances, chemical environment, currents, tides, etc.). This successive change of external influences gained particular significance at the moment when primary living organisms acquired the ability to multiply and disperse through various aqueous media with various ecological components.

A still greater number of variations of recurrence arose at the moment when the primary organisms acquired the ability to move actively. Then any recurrent movement near an *immobile* inorganic object, from a broad physiological point of view, led to recurring, more or less uniform influences from this immobile object on the organism. This type of repeated influence of the external world was of exceptional significance in the life of man as his potential for active movement developed.

At this point we wish to emphasize that in this period of the development of life the *temporal structure* of the inorganic world surrounding the organism remained the same and included at least four basic forms:

1. Action on the organism of relatively constant factors of the external milieu.

2. Action of sequential series of external influences recurring rhythmically or aperiodically.
3. Rhythmic or aperiodic influences of relatively constant and immobile external factors during active movement of living organisms.
4. Action of sequential series of never recurring factors.

All these external influences played a role in the preservation of life. Although these influences were only "harmful," "useful," and "neutral" nonrecurring episodes for living matter, in themselves they naturally were always links of continuous and sequentially developing phenomena in the general course of evolution of the space-time structure of the material world. They encountered the vital cycle of organisms, so to speak, at a tangent.

From this it follows that *these never recurring influences could not exert any decisive influence on the evolution of the higher forms of adaptation of living matter to surrounding conditions and, consequently, could not become factors of organization of the protoplasmic structure of living organisms.*

Let us imagine that the temporal structure of the inorganic world is represented only by this latter form of movement of matter, i.e., *by series of sequential and never recurring phenomena.*

Under these conditions could life, with its stabilized structures which always have an adaptive significance, develop on earth?

No, it could not. The living organism could not have a stable and firm structure, because the latter can appear only as a result of the reflection of *rhythmically and aperiodically recurring influences of the inorganic world.* And even the very concept of "adaptation" would lose all sense in such a world of ever new influences never before experienced by the organism.

It is quite obvious that in the general course of events of the space-time structure of the world, only *rhythmically and aperiodically recurring phenomena* could become the temporal basis for the development of adaptive reactions of primary organisms.

Thus we have reached a definite conclusion in regard to the evolution of organisms depending on constant properties of the temporal structure of the inorganic world. This conclusion can be formulated in the following manner: *the basis for the development of life and its relation to the external inorganic world was represented by the recurring influences of this external world on the organism. Precisely these influences, as a result of the initial properties of the space-time structure of the inorganic world, determined the whole anatomic organization and the adaptive functions of primordial organisms.* In this respect the organization of organisms represents in the true sense of the word the *reflection* of the space-time parameters of their concrete environment.

It is natural that the *relative constancy* of the space-time relationships of the organism with the external world can be considered as a variation of the recurring influence on the organism. It all depends on what concrete temporal relationships exist between the length of the life cycle of the organism and the duration of the external influence.

One may consider as a relatively constant influence one which encompasses in its duration millions of life cycles, such as the presence of oxygen in the atmosphere; an influence may be considered relatively less constant when it encompasses only thousands of life cycles, such as the natural features of a given locality; still less constant would be

the influence, for example, of some land reclamation or water diversion which in its duration may overlap only hundreds of life cycles.

Furthermore, even for primordial organisms, the rhythmic and aperiodic influences of the external world could have been of the same two kinds as those also required for higher animals. Some of them are rhythmic influences of external conditions on a sessile organism. Others, also rhythmic and aperiodic, depend upon recurring movements of the organisms itself. However, in both cases there is an essentially identical final process, a recurring influence of external factors on the organism.

SEQUENTIAL ORDER OF EXTERNAL INFLUENCES AND LIVING PROTOPLASM

From the analysis presented above, we may conclude that exactly this type of temporal relationship, *recurring sequential influences*, represents the universal relation of previously formed and individualized living organisms to their environment. This conclusion prompts us to discern the concrete mechanisms enabling the organism to adapt to these vitally important recurring influences. In what intimate processes of living protoplasm are these recurring influences of the external inorganic world reflected on already formed living organisms?

To answer this question we can utilize the generally accepted concept of modern biology and biochemistry that the simplest organisms of our planet represent "open systems" which were connected with the environment through a series of chemical transformations beginning at the boundary of living polymolecular protoplasm and continuing in the form of a whole chain of separate reactions, ending in a result either harmful or useful for life (Oparin, 1953, 1957).

Thus, we have reason to assume that, due to the special properties of protoplasm, each of the sequentially developing *external phenomena* is reflected in the protoplasm of the organism itself in the form of more or less long chains of chemical transformations. Such chains of reactions may have a metabolic character supporting the life of the organism and its reproduction, but there can also arise a chain of transformations which may prove harmful to this metabolism and consequently not support the life process. However, in spite of these two biologically opposite results, both of these influences by their very nature must evoke a series of sequential and regular chemical transformations. Coming to the fore here is the basic parameter of the space-time structure of the inorganic world which always plays a dominant role in the development of living matter, the *recurrence of phenomena and influences*.

One may speculate about the real consequences of these influences on the primordial organism, influences which had essential significance for its survival and recurred or were constant in the course of millions of years. It is generally accepted by biochemists that any external influence on primordial organisms inevitably served as a starting point for the formation of whole chains of chemical processes and interactions, leading either to the destruction of the organism or, on the contrary, to an increase in its metabolic stability.

At the same time, however, the same sequential series of influences *recurring many times*

inevitably led to a facilitated and accelerated catalytic type of development of these chain processes. Thus, the *dominant lines* of chemical chain reactions were finally created.

It is difficult to imagine that there could be ways of creating primary metabolic chains other than through the *recurring* influences of the external inorganic world on the organism. The *recurrence* of sequentially developing external influences essential to the organism was capable of creating an uninterrupted, successive, and to some degree stable chain of chemical reactions in the protoplasm.

On this basis in the evolution of life one very significant event occurred which in the course of many millions of years determined the chief features of the adaptive reactions of the organism. This event follows from the basic properties of the first living organisms as *open* formations with a polymolecular composition of the protoplasm. I have in mind their ability to react to changes in the surrounding world by more or less extensive chemical rearrangements, provided these changes establish a physicochemical contact with these formations.

It is natural, therefore, that if in the environment several specific events develop *sequentially* (for example, the seasonal rhythms, changes of temperature, currents in the oceans), then the organism must reflect *each one of them* in specific chemical rearrangements of its protoplasm, provided they reach a certain threshold of action. These specific chemical rearrangements can be related to the physical properties of each inorganic factor from among the long sequential series of such factors.

It is interesting that Oparin, in characterizing these relationships of primordial living matter with surrounding inorganic nature, also believes that the *sequential order and speed* of the reactions of the protoplasm are the decisive factors in the material organization of the first living organisms (Oparin, 1953, 1957).

Familiarity with the theories of the origin of life on earth shows that from the broad biological point of view as well as from the point of view of the above analysis of the role of the space-time structure of the world, *movement of matter according to sequential, rhythmically recurring phases is a universal law determining the basic organization of living organisms on our planet* (Oparin, ed., 1959).

The appearance of primordial protein bodies which later acquired an enzymatic function radically changed the whole process of the perfection of life. There arose the possibility for the development of dominant chains of reactions (i.e., with selective catalytic acceleration) and, of course, first of all the development of those reactions which, being essential for the preservation of life, recurred innumerable times under external influences. These influences could vary greatly; an example would be the periodic changes in the supply of substances necessary for the "open systems" of primordial organisms. However, it remains certain that the specific catalysis itself created the possibilities of the principal conditions for the development of these particular kinds of reactions.

This acceleration of reactions, as an analysis of some widely prevalent enzymatic complexes shows, can attain magnitudes of hundreds of millions, even billions, of times. In any case, at the first stages of the development of life this "principle of maximum rate" made it possible to form, on a background of more or less homogeneous coacervate formations, paths of the principal chains of reactions which develop at a tremendous

rate. Conditions were created, therefore, for the specific and appropriate responses of living organisms to definite external stimuli.

At this focal point in the development of organisms, one remarkable gain was made which later exerted a decisive influence on the whole development of the living world.

ANTICIPATORY REFLECTION OF EVENTS OF THE EXTERNAL WORLD IN LIVING PROTOPLASM

Between sequential influences of the external world and the reactions to these influences on the part of living matter, there existed one principal difference regarding temporal parameters. External influences on the organism could occur at the most diverse time intervals and originate from the most diverse sources; only the principle of sequential order unified them. At the same time all these influences converged on the same protoplasm of living matter and evoked qualitatively different chemical reactions performed within the limits of the same protoplasmic formation.

In this way all the conditions were created for the formation of one of the decisive processes of living matter which determined the further development of the animal world and the form of its adaptation to the external world.

Indeed, if diverse chemical reactions become possible (particularly at a very high rate) in a small lump of living matter constituting a polymolecular open system, then some external influences recurring in sequential order, even separated by great intervals, became capable of uniting and being reflected in the rapid chemical transformations of this substance in accordance with the physical or chemical qualities of these influences.

Gradually, relationships were formed in which the difference in temporal parameters was increasingly apparent for events occurring in the external inorganic world and for their reflection in the chemical rearrangements of living matter. For example, external factors could influence the organism in a *continuous sequential order* in a circadian rhythm (degree of insulation, tides, etc.). Consequently, various kinds of chemical reactions in organisms corresponding to each of these influences also developed in a circadian rhythm. The fact, however, that these individual chemical reactions developed in a sequential order in a small but very complex polymolecular formation, led to the closest interactions of these reactions and to the formation of *continuous and interdependent chains of reactive changes*.

Consequently, the same properties of primordial living formations—polymolecularity, catalytic acceleration of reactions, and possibilities for the reflection of external influences—ensured both the progressive development of organisms and the reflection in them, in the chemical rearrangements of their protoplasm, of the sequentially recurring influences of the external world.

As a result of these real interactions, at this stage there was formed one *universal law in the adaptation of the organism to external conditions*, which later developed rapidly in the course of the entire evolution of the animal world, i.e., *an extremely rapid reflection (in chemical chain reactions) of the slowly developing events of the external world*.

To further elucidate this process I shall attempt to illustrate this law schematically.

Let us assume that in the external world there develops a sequential series of certain phenomena which we designate as A, B, C, D . Let these phenomena act on the organism for considerable periods of time, for example, for 12 hours. Each of these phenomena evokes in the protoplasm of the organism a sequential series of chemical transformations which we will designate correspondingly by the symbols a, b, c, d . Let us assume that the series of external influences on the organism A, B, C, D (Fig. 1.1) systematically recurs for a period of many years and has an essential positive significance for its metabolic processes, establishing more perfect chains of chemical reactions, i.e., promoting the stabilization of the life process. Then, as a result of prolonged and repeated reproduction in the protoplasm of the living matter of this specific series of chemical reactions, an organic connection is established between the individual links which converts the whole series of transformations $a \rightarrow b \rightarrow c \rightarrow d$ into a continuous and rapidly developing chain of chemical reactions (Fig. 1.1a).

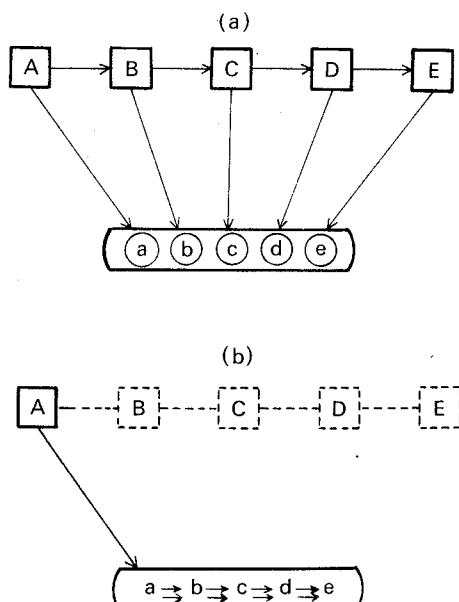


FIG. 1.1 Transformation of the slow sequence of phenomena in the environment (A, B, C, D, E) into rapidly proceeding protoplasmic processes of the living organism (a, b, c, d, e).

(a) Action of consecutively unfolding events of the environment on the organism during the first times that the organism encounters these events. Circles at the corresponding points of the organism show that every phenomenon of the environment evokes protoplasmic changes corresponding to it ($A \rightarrow a; B \rightarrow b; C \rightarrow c; D \rightarrow d; E \rightarrow e$).

(b) The same sequence of environmental phenomena after numerous repetitions. It can be seen that the protoplasmic processes in the organism (a, b, c, d, e), which before were developing separately, have established among themselves a very close chemical connection which is achieved with much greater speed than the actual phenomena of the environment. By means of these relationships, even the first link in a chain of environmental phenomena (A) may start the entire cycle of chemical interactions from a to e . This constitutes the basic law of the accelerated and anticipatory reflection of environmental phenomena in the protoplasm of primordial living beings. It is the prototype of the temporary connection and the conditioned reflex in higher animals.

As the data of biochemists of primordial life indicate, of decisive significance in the formation of these chains of reactions was the formation of specific catalysts which determine the main course of the chemical chain reactions in a given direction.

All these conditions, created at the very earliest stages of the evolution of living matter, led to the ability of protoplasm to acquire the potentiality to reflect in the *micro-intervals of time* of its chemical reactions those sequential events of the external world which by their nature can develop only in *macro-intervals of time*.

Gradually, then, primary organisms developed the ability to *reflect the external inorganic world not passively, but actively, with an anticipation in its protoplasm of sequentially and recurrently developing phenomena of the external world.*

In the protoplasm of the living organism there had been established a continuous chain of chemical reactions which formerly was evoked by the sequential action of external factors *A, B, C, D*, which may have been separated by considerable intervals of time. Now the action of the first factor *A* alone is capable of initiating and bringing into an active state the whole sequential chain of chemical reactions.

Historically, in living protoplasm, conditions inevitably had to be created under which the rate of the chemical reactions of the protoplasm ensured the organism's anticipation of the development of sequential, frequently recurring external influences (see Fig. 1.1b).

Thus, from our point of view, at a very early stage evolution discovered this universal and only possible way for the organism to adapt to the external world. The deep significance of this new property of the primordial organism lies primarily in the universality and rapidity of the chemical reactions of its protoplasm in response to the slowly developing influences of the environment.

First, all the originally separate chemical reactions of the protoplasm occurring in response to external influences are chemically united into a single chain and form, as a result of numerous repetitions, a "path" developing chemical reactions proceeding at high speed ($a \rightarrow b \rightarrow c \rightarrow d \rightarrow e$).

This is the new feature acquired by the primordial organism during the formation of a polymolecular substance, i.e., protoplasm. However, the events of the outside world ($A \rightarrow B \rightarrow C \rightarrow D \rightarrow E$) are occurring as slowly as before.

What happens now, after the chemical interactions of the protoplasm have changed?

Now the chemical reactions of the protoplasm $a \rightarrow b \rightarrow c \rightarrow d \rightarrow e$ constitute a *single entity*. All that is needed, therefore, is to evoke the process *a*, which corresponds to the first component *A* in the series of events of the external world, and the entire chain with its very high rates of microchemical reactions "explodes," with the process of excitation almost instantaneously passing through the entire course of the interactions from *a* to *e*. This was the cause for the high reaction rates and, consequently, for the anticipation of the course of a sequential series of external events ($A \rightarrow B \rightarrow C \rightarrow D \rightarrow E$) in the chemical processes.

It must be emphasized that this molecular chemical process was developing at the dawn of life on the level of the protoplasm of a unit, perhaps even of microscopic size.

Due to this marvelous property of living protoplasm, its chemical process, e.g. *d*, develops long before the external factor *D*, which had been evoking it in the past, sets in.

Living matter gained great advantages from this form of reaction to recurring series of sequential influences. As a matter of fact, without this *anticipatory* development of chains of chemical reactions it is difficult to imagine even such a simple act as, for example, the swallowing and digestion of a small piece of food by the amoeba or the seizing and digesting of bacteria by the bacteriophage.

The whole history of the development of the animal world clearly demonstrates the perfection of this universal and most ancient law, which could be called an anticipatory reflection of reality, i.e., an enormously accelerated development of chains of chemical reactions which in the past reflected sequential and slow transformations of this reality.

Returning to the initial premise of this problem, we could say that the *anticipatory reflection of reality is the basic form of adaptation of living matter to the space-time structure of the inorganic world, in which sequential order and recurrence are the basic temporal parameters.*

Up to this point no *qualitative distinction* has been made between the sequentially occurring events of the external world. They simply followed each other in a definite order. However, in the real life of an organism this is never the case. Every sequence is always interrupted by some *essential* event, vitally important to the organism. Actually, any sequence of events in the life of an organism consists of vitally important events interspersed with "indifferent" influences.

Let us assume that in our example (see Fig. 1.1), the events *A*, *B*, *C* of the external world are indifferent for the animal; for example, *A* refers to the opening of the door into the room where the dog is, *B* to the entrance of a man with a dish, and *C* to the movement of the man toward the dog. *D*, however, is the intake of the food from the dish by the dog.

If this sequence is repeated many times, then in the protoplasm of the nerve cells of the brain an intimate chemical connection is established not merely on the basis of the sequence alone, but also due to the reinforcing action of the vitally important stimulus, i.e., the reverse chemical *influence of the reinforcement* on the preceding processes from the preceding events (the stimuli). In our example these are *A*, *B*, *C*.

It follows that with such a sequence of factors (a recurring sequence), the chemical process evoked by factor *A* (or by any earlier factor) is not retained in the structures *a* alone, but spreads immediately all the way to the chemical complex *d*. As is evident, in this case the chemical process *d*, which corresponds to the phenomenon *D* of the external world, will develop in the cells of the brain or in the protoplasm of a primordial organism sooner than the actual phenomenon *D* sets in.

This is the chemical process of the protoplasm (or the excitation) which *anticipates* the course of the external events that occur considerably more slowly. Thus, the living protoplasm has become a unique "accelerator" of the course of external events.

From this anticipation, however, it follows that in the series of sequentially occurring events of the external world, the factor *A*, which evokes a chain of processes including the process *d*, becomes a signal for the approaching, but as yet not present factor *D*. In this case the actual chemical process *d* constitutes an "anticipatory reaction" with respect to factor *D*.

Consequently, the very fact of the appearance of "signalization" and "temporary connections" can be accepted as one of the most ancient laws in the development of

living matter. In this sense one must understand Pavlov's expression that "temporary connections constitute a universal phenomenon of nature."

Accompanying the origin and perfection of living matter and being a natural result of the space-time structure of the world, this law was fixed by natural selection and was further established in the stabilized structures of protoplasm. Consequently, the principle of anticipation of impending external events in the protoplasmic processes of the organism can be considered as the basis for the creation and fixing of all those structures of the organism which purposefully adapt it to the external world on the basis of signalization and temporary connections.

It is, therefore, hardly surprising that this particular function of the organism, providing the greatest potentialities for adaptation and progress, soon began to specialize in a particular substrate whose main function became the rapid chemical coupling of all simultaneously and sequentially developing chemical reactions. The nervous system became such a substrate.

From this broad point of view the primary neural substance, and subsequently also the central nervous system, can be regarded as a substrate of high chemical and structural specialization which developed the capacity for *the maximum and fastest anticipation of sequential and recurring phenomena of the external world* (Anokhin, 1956d).

ANTICIPATORY PROCESSES OF PROTOPLASM AND THE CONDITIONED REFLEX

In one of our previous publications we showed that the attendant approaching the dog with food from the first floor to the third constitutes a definite sequence of stimuli (Anokhin, 1962a). This approach of the attendant demands considerable time because it occurs within the physico-mechanical limitations of space.

We have quite different relationships in the neural substrate of the animal's brain. The processes in the receptors and in the neural substance occur in milliseconds. Consequently, as early as the action of the first agent of this whole series of external events (the sound of the door on the lower floor) the brain can *immediately reproduce the entire chain of chemical reactions previously fixed by these slowly proceeding events of reality, provided the same sequence of these events has recurred many times*.

In this fact one cannot fail to see the vast achievements of evolution which proved to be capable, on the basis of primary protoplasmic chains of chemical reactions, of creating a mechanism which permits achieving a greatly accelerated reflection of reality and anticipating the sequential course of actual phenomena of the external world.

The different rates at which phenomena occur in natural reality and in the neural substance of the brain are the prerequisites for the spread of this anticipatory excitation.

If we compare the different levels of organization of living matter discussed above, we see that in the whole course of the evolution of living matter, the *principle of anticipatory reflection of the external world is an inalienable part of life and of its adaptation to surrounding conditions*.

The brain, as an organ specialized in this direction, has no limits to this anticipatory reflection of reality. It has the ability to reflect in micro-intervals of time chains of events which may occupy many years.

Comparing the anticipatory reflection in primitive organisms with the highly specialized form of anticipatory reflection of the external world which is manifested in the conditioned reflex in higher animals, we by no means remove the qualitative difference between these two phenomena. We must only remember that the comparison and the classification of many phenomena inevitably demand a *guiding criterion*.

Therefore, naturally, we must ask : *what is the most characteristic feature of the conditioned reflex, which determines its essence?* Of all its possible qualities, that of "anticipation," or "signalization," concerning imminent, i.e., future events of the external world, is the most distinguishing. Neither variability nor stability nor acquiredness, etc., can compare in their significance with this biological quality. Since animals have the ability to *prepare in response to a signal for as yet only impending links of sequentially developing events*, this major discovery by Pavlov became the central point of progressive evolution.

If, however, this basic property (parameter) of the examples discussed is the most ancient, then consequently, according to this property, we can fully consider the adaptive potential of lower and higher animals.

It is natural that the structural and quantitative complexities of the mechanisms which ensure more extensive signalizations have led to further qualitative changes in the behavior of animals. However, *signalization*, as a universal parameter of adaptation to the external world, has not lost its principal significance.

Consequently, the conditioned reflex of higher animals, evaluated according to the parameter of signalization, is only a particular case of highly specialized forms of the *anticipatory reflection of reality*, i.e., adaptation to future events (Anokhin, 1949c) ("anticipatory activity" according to Pavlov).

In the light of the above historical laws on the development of the biological bases of conditioned reflex activity, the complete artificiality of an entire series of questions referring to the conditioned reflex becomes evident, such as : When in evolution did the conditioned reflex appear? Do protozoa and plants have a "conditioned reflex"? Can an inborn activity be signaling? etc.

From this point of view, the universal principle of all forms of adaptation of an organism to the conditions of the surrounding world is the anticipatory reflection of sequentially and recurrently developing events of the external world, an "anticipatory" adaptation to forthcoming changes of external conditions or, in a broad sense, the *formation of preparatory changes for future events in response to a signal*.

As we have seen, this principle was operating even from the first stages of the formation of living matter. Therefore, the question can only concern the *form and concrete mechanisms* in which this principle of anticipatory reflection of the external world is present at a given level of development. In protozoa it occurs in the form of chains of chemical transformation of protoplasm which anticipate the development of a sequential series of external events. In higher animals it appears in the form of the participation of specialized neural apparatuses which give a tremendous advantage in perceiving the external world and in the rapidity of anticipation. However, in all cases this form of anticipatory reflection has one decisive feature—signalization. For animals which have a nervous system, this is the conditioned reflex.

In view of what has been said, the second question also loses its sense, namely : can a

temporary connection be elaborated in protozoa and plants? Since both represent living formations with a complex molecular and cellular structure, and since they are subject to constant series of sequential and recurring influences (especially the plants), one can definitely state that natural signal changes have taken root in both protozoa and plants, or that these changes can be developed *de novo*. It is only necessary to observe the requirements stated above: *prolonged recurrence and a sufficiently well-chosen essential factor for the life of a given plant or protozoan.*

It should be recognized that *not a single plant could exist, as it would immediately be rejected by natural selection, if it reacted only to an existing factor of the environment, i.e., only to that which acts at a given moment, and did not react according to the principle of anticipatory reflection.*

INBORN SIGNALIZATION IN HIGHER ANIMALS

The answer to the third question concerning inborn reactions of the signaling type also becomes clear. We have already said that *signalization* is the most characteristic feature of the conditioned reflex. The *anticipatory reflection of reality* has acquired in the conditioned reflex the most pronounced and most specialized form. However, according to the generally accepted classification, inborn, i.e., unconditioned, reflexes cannot have this most characteristic property of the conditioned reflex, i.e., a *signal* meaning.

Experimental material from our laboratory on the study of the ecological conditionality of the first behavioral acts of the newborn has shown, however, that this question cannot be solved so easily.

Investigations by Miliagin, one of my collaborators, have shown that immediately after hatching, the nestling rook invariably reacts by lifting its head and opening its beak, i.e., with a reaction of preparation for the intake of food. It is remarkable that the reaction arises in response to stimuli which, in themselves, in no way have any alimentary significance (motion of air, the sound kar-r-r, jarring of the nest).

An analysis of the natural ecological situation in which the rooks live during the first days after birth has shown us that all three agents mentioned above have ecological significance and serve as *signals of the impending introduction of food by the father rook into the open beak of the nestling* (Miliagin, 1951, 1954, 1957, 1958) (see Fig. 3.6).

It is quite evident that we have in this example a paradoxical case: an "inborn conditioned reflex" which, though obviously inborn, has at the same time all the features of a signaling function.

Analyzing this phenomenon from the point of view of the general biological law of the "anticipatory reflection of reality," the case of the nestling proves to be especially important for understanding the evolution of this law from lower to higher organisms which have a well-formed nervous system.

We have noted above that the prolonged repetition of sequential series of external influences evokes in the protoplasm of the organism a chemical reaction specific for each influence. These reactions, if they are repeated in the course of many centuries, are finally fixed by natural selection in stable protoplasmic structures of a given organism, reinforced by tremendous acceleration by means of specific catalysts, and selected as the most rapid and perfect form of adaptation of the animal to external influences. From

this broad biological point of view, all organized protoplasmic structures can be recognized as the result of the fixation of constant, sequential external influences upon the living organism, provided they have been of essential significance for the preservation of life.

Thus, in the life of many animals, especially birds, the presence of air and the movement of this air is an almost absolute factor of the external world, accompanying the evolution of all life on earth. It is not surprising, therefore, that in the process of development of adaptive reactions in the rook, the movement of air, as a result of the movement of the mother's wings, was included in the process of the historic formation of such a specialized labile substrate as the nervous system.

Thus, on the basis of the historic recurrence of sequential changes of the neural substrate which precede the moment of feeding, *the fixation by heredity of those structural connections which now ensure the anticipatory reflection of external events was accomplished, i.e., in principle the same thing occurs here as was shown above for primordial protoplasmic formations.*

Indeed, the movement of air is not a "food product," it is not an unconditioned stimulus in the sense in which we understand it in the usual interpretation of the Pavlovian school. It is a true *signal* of feeding, but at the same time all structural premises for the perception and realization of this stimulation have fully matured only on a morphogenetic basis during the period of embryogenesis.

Here a critical question arises : why does this excitation of the cutaneous receptors of the nestling by the movement of air go specifically to the central nucleus of the alimentary functional system and form the above-described reaction of preparation of the nestling for food intake? No doubt we have here an impressive example of the fixation, in the labile neural substrate, of that chain of consecutive chemical reactions which reflect the actual *sequence* of influences of the external world on the nervous system of the nestling in the ecology characteristic for it. This sequence, which ends in feeding, consists of the following factors : (a) the mother's leaving the nest and the uncovering of the nestlings, (b) the recurring sound kar-r-r, (c) the fanning of the nestlings by the mother's wings, (d) the arrival of the father and the jarring of the nest from his settling on its edge, (e) the placing of food into the open beak, (f) the stimulation of the taste receptors and the receptors of the digestive tract, (g) the secretion of juices and the digestion of food.

I have not mentioned many other factors which actually precede this series of phenomena. As a matter of fact, the father comes with food and alights on another tree so that he is *within the limits of the visual field of the mother sitting on the nestlings*. Seeing the father rook, the mother gets up from the nest and, flapping her wings, commences the above-described series of sequential phenomena.

It is quite obvious that the stimulation of the nestling's skin by the moving air is not only *one of the intermediate stages of a long series of sequential agents* but also a stage which acts on the nervous system of the nestling together with other factors (sound kar-r-r, jarring of the nest). Therefore, although the stimulation of the skin, for example, is not an alimentary stimulus, the excitation from it, *due to having preceded feeding over many centuries*, proceeds with tremendous speed (30 msec) and along prepared (inborn) synaptic connections, to the alimentary center : the nestling lifts its head and opens its beak. Here nature has given an especially lucid example of an *anticipatory reflection* of sequential

events of the external world and its adaptive significance in evolution. This propagation of excitation anticipating reality was fixed by heredity in the neural structures and acquired a most important adaptive significance for the nestling rooks. Up to the moment of hatching, if the neural connection between the stimulation by air and the alimentary center had not sufficiently matured, i.e., if one or two of the most important synapses did not prove to be ready, then such a nestling must immediately be rejected by natural selection.

It is interesting that careful electrophysiological investigations of the auditory faculties of the rook have shown an amazing adaptation of the embryonic development to its postnatal ecology. It was found that in the auditory receptor, up to the moment of hatching, *only those cells which are able to perceive the sound kar-r-r mature* (see Fig. 3.7).

One can cite striking examples of these anticipatory reflections of external events from various ecologies. Moreover, in each individual case this has a tremendous adaptive significance and corresponds exactly to the ecological factors of a given species of birds, i.e., to sequences of phenomena preceding feeding which, in the final analysis, are characteristic for it.

The pied flycatcher (*Muscicapa hypoleuca*), for example, hatches its nestlings in a hollow tree where the sun's rays enter only through the small opening through which the mother and father pass *before they can feed the nestlings*. Naturally, when the mother or father pushes its head into this small opening, the initially slight illumination of the hollow disappears and for a moment there is complete darkness. These events are the natural and inevitable results of physiological conditions which have arisen on the basis of physical laws and must precede feeding. Indeed, the parents have no physical possibility of feeding the nestlings without first shutting out the light. It is this temporary darkness which serves as the strongest stimulus for the nestlings of these birds: with one accord they all immediately stretch out their necks, open their beaks, and are ready for the intake of the food. The mother then gives each of them its due portion (investigations by my collaborator Khaiutin, 1963a, 1963b, conducted under natural conditions) (see Fig. 3.8).

A number of observations show that the *temporary and necessary obscuring of the ray of light* by the parents became the central ecological factor for the newborn nestlings, and that to it was "attached" the whole ontogenetic behavior of the nestlings.

For example, the nestlings are fed regularly and uniformly because they move counterclockwise in such a manner that the nestling next in turn is in the zone of the light ray. This remarkable rotation compensates well biologically for the fact that it is physically impossible for the mother to regulate the sequence of feeding in the given ecology.

However, if the nestlings are deprived of food for some time, i.e., if their alimentary excitability is increased, *then immediately there begins among them a "quarrel" and a struggle for the place onto which the light ray falls through the opening of the hole, since this place is ecologically the strongest signal for feeding*.

In all these cases with diverse ecology (I could cite many more examples) there is a manifestation of the same law. The natural recurrence of sequential external phenomena in the course of many centuries is *reflected* in the nervous system as a sequential

series of processes. This series, resulting from the action of the nearest preceding links by a type of explosive mechanism, makes it possible for the animal to anticipate the course of phenomena of the external world and to prepare beforehand a reaction which adapts it to a future link of the sequential chain. Therefore, this consecutive series of processes is of vital importance to the newborn.

Thus, *anticipation of the events of the external world* is a universal phenomenon of life which has determined all forms of the adaptive behavior of the animal: "inborn," "signaling," and "conditioned reflex." Considering this law, any component of a sequential series of influences of the external world can become a signal for that vitally important reaction which terminates the series.

Examples similar to those discussed can also be cited from the general physiology of the brain, in its capacity as the substrate of the most rapid associations of sequentially

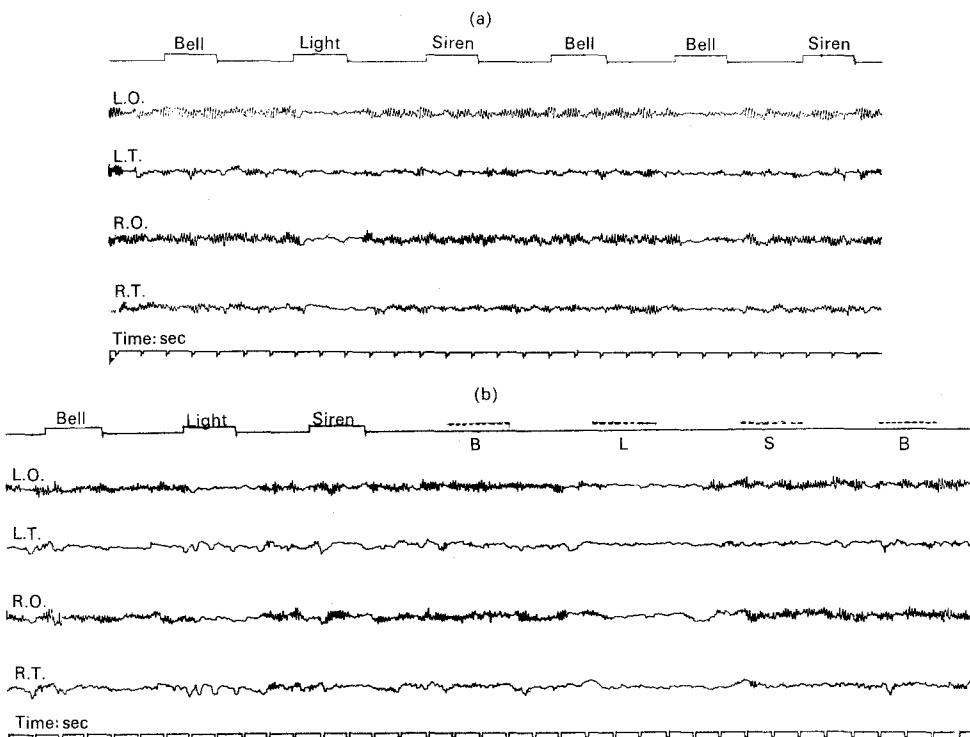


FIG. 1.2. The significance of anticipatory excitation, which spreads over the cerebral cortex irrespective of the presence of an inappropriate stimulus. The electroencephalogram shows that on the 5th test of a bell, instead of light, the bell evokes the same desynchronization of electric activity as if light had actually been presented (a). In another case the presence of anticipatory excitation is demonstrated even more convincingly. The stimuli were not presented at all (broken lines). Nevertheless, at the point where light should have been presented, desynchronization occurs (b). L.O., left occipital cortex; L.T., left temporal cortex; R.O., right occipital cortex; R.T., right temporal cortex.

proceeding chemical reactions. For example, it is well known (Jasper and Shagass, 1941a, 1941b) that if sound and light are presented consecutively for a long time, then in the cerebral cortex of the animal this recurring sequence fixes the relations of the type of *anticipatory reflection* of reality, i.e., of the applied stimuli. After a large number of pairings of "sound + light," it is only necessary to present the sound alone, and in the brain, precisely in that section where the stimulus of light is perceived, *exactly the same phenomena develop as if light had already been presented, although the light will only be turned on several seconds later.* Here the anticipatory reflection of external phenomena is quite obvious, due to the fact that the excitation from the auditory area of the cerebral cortex spread into the visual area before the light arrived there. In this elementary physiological event there appears with exceptional distinctness the fundamental function of the central nervous system of associating those molecular chains which, according to the above-described law, promote the anticipation of those events which are only to occur later. The neural substrate is, however, according to this law, a substrate which has specialized in the rapid "chemical coupling" of those molecular processes which arise *sequentially* from an action of *sequential agents* of the external world.

A collaborator of mine, A. D. Simonenko, by means of electroencephalographic recordings, studied the electric reaction of the brain to the standard triple stimuli (bell—siren—light). After applying this stereotyped series of stimuli dozens of times, it could be seen that the reaction characteristic for light (the inhibition of the alpha rhythm in the visual area) begins *even when one substitutes the bell for light*, which does not usually evoke this inhibition (Fig. 1.2a). This is an electroencephalographic manifestation of what Pavlov called the "dynamic stereotype." In this experiment we observe directly the processes of the substrate of the brain. Investigations have shown that in the mass of the brain, after frequent repetition of the same sequential complex of stimuli, such stable chains of interneuronal contacts are established that even the presented stimulus (bell) cannot overcome their inertia; therefore, at this point in the stereotype, *a reaction develops to light, the anticipated stimulus* (see Anokhin, 1957a).

It is also possible to show that this capacity of the brain to fix in new molecular bonds the sequentially recurring influences of the external world goes even further. One can completely stop presentation of this stereotyped group of stimuli, but the characteristic changes in the brain mass *at the same intervals of time* will continue to appear several times yet (Fig. 1.2b).

This phenomenon is a remarkable example of the fact that the brain substance is a specialized embodiment of the basic law of living matter which we called *anticipatory reflection of the external world* and which is the result of the absolute properties of the space-time structure of the world, *sequence and recurrence*.

To avoid misunderstandings in the comprehension of our point of view, it is necessary to discuss in more detail the *similarities and differences* between these two levels of associative activity at the level of primitive life and at the level of the conditioned reflex. It is important to formulate exactly that criterion or parameter which allows a comparison of these two categories of phenomena.

As a basic parameter for comparison, we shall use the decisive biological criterion: the forms and mechanisms of reflection in both phenomena of consecutively developing

external events, since sequence per se is a universal law of the inorganic and organic world. As is known, the development of the sense organs in animals is connected with the necessity for a more perfect adaptation to the external world. The sense organs transform qualitatively different external energies into a single neurochemical process. Even in response to a single stimulus, then, a specific system of neurochemical reactions at various levels of the central nervous system is established. Even one such stimulus evokes a system of specialized chemical reactions consisting of millions of points. This system has a definite architecture and gives extensive information to the entire organism, not only about *what* stimulus was presented and in which way, but also about *where* and *when* this stimulus was presented.

Thus, already upon the first contact of various organisms with external factors, there appears a tremendous difference in the amount of that information about the external world which they receive from even a single stimulus. Therefore, according to the *parameter of complexity* of the distribution of microfoci of chemical reactions, the brain undoubtedly cannot be compared with the chemical results of stimulation, for example, of an already formed but still primitive organism. In the latter case the chemical excitation is primitive; it proceeds throughout the protoplasm, in which the specificity of chemical valences and catalysis keeps this chemical reaction on a more or less limited course. How intricate is by contrast the architecture of microchemical foci in man under highly complex special conditions in the formation of enormous numbers of connections involving the storage in memory of both past experience and grandiose plans for the future.

However, if these phenomena, i.e., the anticipatory reflection of reality in primitive organisms and the conditioned reflex in higher animals, are compared strictly on the basis of the parameter of reflections of sequentially developing phenomena of the external world, then we come to the conclusion that the mechanism of the formation of the anticipatory reflection of reality in both proceeds exactly according to the diagram given above (see Fig. 1.1).

The chemical unification of separately, sequentially, and repeatedly occurring chemical reactions and the subsequent launching of this whole chain of reactions from the first link constitute the common parameter for both phenomena of adaptation, which are so different in their level of development.

At the same time this is also a historic basis for the development of *all forms of signaling adaptations, i.e., the preparation of the organism for future events.*

The laws examined above and their illustrations further establish the credibility of the concept that the conditioned reflex in its basic biological and neurophysiological mechanisms is a particular and *very specialized case* of the universal law which, in the primitive form of stabilization of chemical chain reactions, had already appeared at the phylogenetic stage of primitive organisms.

Until now we have considered the conditioned reflex as a highly specialized form of activity of the nervous system which gives an extremely accelerated anticipation of events sequentially and recurrently developing in the external world. This allows the highest adaptation of the higher animals to their environment.

There is another still broader philosophical aspect to this problem. Before Pavlov, the physiology of animals dealt with two categories of time: the past and the present. Both

these categories were represented by appropriate processes fitting well into our concepts of the reactions of animals. Everything concerning the third category of time, the future, was relegated to the purposeful behavior of man and was almost exclusively the domain of idealistic psychology.

Adaptation to future events, "anticipation of the future," was the prerogative of man and was a sign of the most purposeful processes of the brain.

In formulating the conditioned reflex as an "anticipatory" function, i.e., a *function of adaptation of the animal to impending events*, Pavlov thereby introduced into physiology the third category of time, the future. Thereafter, the "future" in the life of organisms became the object of the same objective scientific investigation as the other two categories of time. Thus the discovery of the conditioned reflex was an event of tremendous importance for physiology, and herein lies one of the reasons for such great achievement in the study of the behavior of animals from this point of view.

The more material accumulated along this line, the more extended became the relevancy of the conditioned reflex. At the present time we can confidently say that Pavlov found the cardinal and universal feature of the historic development and perfection of the animal world.

The conditioned reflex is a specialized form of the very same process which, in the chains of elementary chemical reactions of the primordial protoplasm, ensured life at the first stages of its development in the form of *anticipatory reflection* of the space-time movement of inorganic matter and the formation of stable structures of the organism on this basis.

Billions of years were needed for this primitive form of chemical chain reactions to be fixed and to develop into the most perfect form of living matter, neural substance.

However, in spite of this entire magnificent course of evolution and the considerable transformations of the very forms of anticipation, its basic law of evolution remained valid : the anticipatory reflection of sequentially recurring series of external phenomena.

For implementation it has acquired a special tool, the brain, the substance of which is highly specialized to the "*chemical coupling*" of *sequential and recurring influences of the external world*. This permitted the broad and perfect mastery of the *future* as we see in the behavior of the higher animals and man. The energetistic aspect of reflection, i.e., the transformation of external energies (light, heat, chemical agents, etc.) by the organism into appropriate information to the brain about the material properties of the external world, is undoubtedly one of the immediate problems of neurophysiology. At the present time this *primary form of reflection* can be studied at a very high level, provided that for this purpose the whole arsenal of modern scientific advances is applied (biophysics, information theory, coding theory, etc.).

There is also, however, another form of reflection in the properties of the organism. This is the reflection of the *temporal structure of the world*, which is the subject of our present work. We saw that the main leitmotif of this form of reflection is *anticipatory reflection*, which gives the brain at the highest stage of development completely appropriate information about sequential and recurring series of phenomena of the external world. Here it must be noted that on the basis of this form of reflection, the brain itself was

formed and specialized as the organ of psychic activity, i.e., *the organ of universal reflection of the world in the thinking activity of man.*

Thus, the *anticipatory reflection of reality*, i.e., of the sequential course of external events, as illustrated by a number of examples in this chapter, is only one of the forms of the reflecting capacity of living matter.

CHAPTER 2

The Nature of the Unconditioned Reflex

SIGNIFICANCE OF THE TEMPORAL RELATIONSHIPS OF CONDITIONED AND UNCONDITIONED REFLEXES

What is significant about the nature of the conditioned reflex is its relation to the unconditioned reflex, which is the invariable basis for the formation of the conditioned connection. Pavlov understood unconditioned reflexes to be inborn, i.e., to appear *unconditionally* as soon as an appropriate stimulus is applied. Consequently, the decisive feature of the unconditioned reflex was acknowledged to be its inbornness.

However, from the preceding chapter we have seen that any structure of the organism and any form of reaction, regardless of its simplicity, must pass through a historic course of development in which the external factors stereotypically repeated their action on the protoplasm of the organism during a period of many millions years. Some of these physical factors (light, temperature, gravity, circadian and seasonal variation, etc.) have scarcely changed the nature of their influence from the beginning of life to the present. On the other hand, others (supply of oxygen, atmospheric pressure, specific effects of the aqueous medium, etc.) arose *de novo* and had a prolonged but temporary action on the organism, appearing in connection with a change in the conditions of life.

Comparing the characteristics of conditioned and unconditioned reflexes and knowing what conditions facilitated their appearance, we can say that "anticipation" or "signalization" cannot be used as the decisive criterion for the differentiation between the two activities. We have seen that even during the early stages of the development of life, an *anticipatory* adaptive character of the formation of any structure of the organism appears. This makes it impossible to accept *signalization* as a differentiating feature of the conditioned reflex, since any inborn activity already has the properties to adapt the organism to forthcoming stages of sequentially developing events of the environment.

Therefore, the only criterion for comparative investigation is the *inborn* and *acquired* nature of signal interactions of the organism with the environment. We must focus our attention on how "inborn" signalization differs from "acquired" signalization, and on the basis of what principles functional interactions develop between these signalizations.

Thus, we must first understand how the unconditioned reflex develops as an inborn activity during the period of embryonic development, and due to what properties it, being "elaborated," becomes the foundation for the acquisition of new associations

during the process of phylogenesis. Before solving this problem we must characterize the unconditioned reflex as a basis of higher nervous activity in the most accepted form in which the latter is visualized.

The unconditioned alimentary and defense reflexes are usually used as the unconditioned reflexes on the basis of which new conditioned connections are elaborated. In the former case an indifferent external stimulus of any sensory modality is paired several times with reinforcement by food in the form of bread crumbs or a meat and bread crumb mixture. In the practice of the Pavlovian laboratory the most common food reinforcement is a meat and bread crumb mixture. In previous experiments on digestion at Pavlov's laboratory, it was established that the *crumbs* have the most marked effect on stimulating salivation. This provides a convenient method for obtaining a conditioned salivary reflex which is great enough for use in further analysis.

The second unconditioned reflex which is often used in the practice of elaborating conditioned behavioral reactions (but less often in Pavlovian laboratories) is the *defense reflex*, or, more explicitly, the avoidance response to a nociceptive stimulus.

Both these "unconditioned reflexes" are in fact highly developed unconditioned activities involving a vast number of apparatuses and mechanisms which develop successively until the full realization of the adaptive end effect. For example, eating a meat and bread crumb mixture may include licking, chewing, etc., which in themselves, in their physiological essence, are independent, inborn, and to some degree acquired reflexes. However, the sum total of simultaneously and consecutively developing reflexes ends in the intake of food.

Unconditioned reflexes of the alimentary and defense type are not the only ones used in the practice of elaborating conditioned reflexes as a basis of reinforcement. The "blinking reflex" is also used, with blowing air on the cornea as the unconditioned stimulus. The knee-jerk reflex and many others are used in addition. It is important that in all these cases a defense activity with a positive end effect for the organism must be brought about.

Unconditioned reflexes connected with any kind of vegetative activity comprise a special group. In this case there is no defense activity in its true sense. Rather, a type of vegetative activity originally evoked by an appropriate unconditioned stimulus is reproduced in the form of a conditioned reflex.

Introduction of water into the stomach, for example, and consequently into the blood, leading to a decrease in its osmotic pressure, stimulates renal activity and increases diuresis (Bykov, 1942; Bykov and Kurtsin, 1952, see English translation, Samuel A. Corson, ed., 1966; Corson *et al.*, 1960, 1962; Corson, 1966). If this activity of all the involved systems is taken as a reinforcing "unconditioned factor," and the sound of a bell, for example, as an indifferent signaling stimulus, then an increased conditioned diuresis can be evoked by the bell alone after several pairings of the bell with the introduction of water into the stomach.

Regardless of what is used as the unconditioned reflex, the sequence of the presentation of stimuli must be quite definite: the indifferent stimulus must always *precede* the unconditioned stimulus, i.e., become the *signal* of the natural need for the given unconditioned activity. As can be seen, those initial features of any signaling activity which

have historically become a reflection of the natural sequence of external events retain this sequence (see Chapter 1).

In Pavlov's laboratory, repeated attempts were made to establish just how essential it is for the elaboration of the conditioned reflex to maintain the indifferent→unconditioned sequence of stimuli (Anokhin, 1926a; Maiorov, 1926, 1928; Rait, 1926, 1928). Experiments were conducted by the method of "covering," i.e., at first food was given, and then several seconds later the indifferent stimulus was applied. As a rule, only questionable results were obtained and never was a distinct conditioned reflex obtained. On the basis of these results the hypothesis was advanced that, at the moment of action of the unconditioned stimulus, a considerable alimentary excitation develops which by negative induction inhibits any newly applied indifferent stimulus, i.e., one that has no signaling significance.

This explanation is physiological, i.e., it emphasizes those relationships of processes which at a given moment actually exist in the neural substrate. However, as it turned out, another approach to this problem is possible: the biological approach, which is expressed in Pavlov's principle of signalization.

Indeed, if the basic requirement for elaborating a conditioned reflex is that the indifferent external stimulus become the signal for the approach of some kind of events essential to the organism, then it is quite obvious that for the distorted sequence, "feeding→bell," the bell no longer is the signal of a stimulus essential to the organism, and therefore its anticipatory significance is nil.

In this biological approach one may suppose that purely physiological relationships (negative induction from the stronger alimentary excitation) need not play a decisive role. They could be fully subordinated to the biological sense of a given situation. This assumption concerning the *decisive role of the relationship between the signals*, i.e., concerning the anticipatory character of the sequential development of external events, was verified in a special series of experiments. As a matter of fact, according to the conditions of the classical Pavlovian experiment, any distortion of the sequence of the indifferent and unconditioned stimuli inevitably leads to the loss of signaling qualities by the indifferent stimulus, for it no longer signals anything and does not precede an essential, i.e., unconditioned, activity of the organism.

The special features of our secretory-motor method with bilateral feeding of the dog made it possible to set up this experiment in a somewhat different way (see Chapter 15 and Fig. 15.1). Indeed, since we could reinforce the stimuli on the right as well as on the left side, we could impart a signaling character to the stimulus being "covered" without changing those relationships which were utilized in previous experiments in Pavlov's laboratory: indifferent→unconditioned. The only difference was that the indifferent stimulus applied on the background of an already operating action of the unconditioned stimulus *on the right* side of the platform had become the signal for feeding *on the left* side of the platform. With this experimental setup, as in the early experiments of Pavlov's laboratory, the indifferent stimulus was applied under conditions of assumed negative induction. However, in this new form of the experimental variant, the indifferent stimulus now signaled feeding on the opposite side of the platform.

Specifically, the experiment was conducted in this way: a bell was used as the conditioned stimulus for feeding on the right side, and the animal ran to the right feeder and ate the food. At this time, while the dog was eating, the indifferent stimulus (a tone) was presented, and after several seconds the feeder on the left side, i.e., on the opposite side of the platform, was offered. Usually the animal *interrupted* its eating from the right feeder, ran to the left side, ate the food there, and then ran back to the right side and finished the remaining food.

After a number of such pairings the animal began to interrupt its eating on the right side in response to the originally indifferent stimulus of the tone alone. Interrupting its eating, the animal rushed to the left side and stopped at the feeder. Here I would like to call attention to a very interesting phenomenon which significantly contradicts our previous views. The animal leaves *real food*, and runs and waits for *food that is only being signaled*. Thus, while retaining the natural *signal* relations between the tone and reinforcement, the previously assumed negative induction did not keep it from becoming a fully adequate conditioned alimentary stimulus (Anokhin and Strezh, 1934).

Since in this experiment we had two different conditioned stimuli (bell and tone), the question arose concerning control experiments in which the *same* conditioned stimulus would be applied on the background of eating, i.e., in which the same "cell" of the cortex would be stimulated, but in which this stimulus would have a different signal meaning. This stimulus would have to be placed under conditions of "negative induction" without losing its signal meaning.

This problem was solved in the experiments of a collaborator of mine, Strezh, in the following manner. The tone was used as the conditioned signal for eating bread crumbs. After the dog had begun to eat the bread crumbs, the tone stopped. Ten seconds later, i.e., with continued eating, the same tone was given again, but several seconds later the dish with the unfinished food was taken away from the animal. After a number of such pairings, in response to the second presentation of the tone, on the background of eating, the dog began to show a pronounced *anticipatory reaction*: in great haste it began to take into its mouth all the bread crumbs found in the dish, and without chewing them, it first put them on the platform and then quietly finished eating them.

We also see that in this case the same stimulus, presented for the second time under conditions of eating, i.e., in spite of conditions of assumed negative induction, became a conditioned stimulus *as soon as it became the signal anticipating changed conditions of feeding* (Strezh, 1937).

All the above-mentioned experimental variations indicate that the requirement for establishing a conditioned stimulus is that it precede an unconditioned stimulus. This occurs in exact accordance with the biological role of the unconditioned stimulus as an essential factor in the life of the organism, setting in after a number of sequentially developing external events.

As we saw from the material of the first chapter, these properties of the central nervous system have developed historically as a reflection of the time structure of the external world which existed before the appearance of life on earth.

**FIXATION OF SEQUENTIAL ORDER WITHOUT THE FACTOR
OF REINFORCEMENT**

Among the many phenomena involved in the elaboration of new connections on the basis of unconditioned stimuli, there is one group of phenomena which seemingly contradicts the principle of signalization in the sense of signaling of factors essential to the life of the organism, i.e., unconditioned stimuli.

I have in mind the so-called "electroencephalographic" conditioned reaction. As we know, the presentation of a sound does not cause desynchronization in the occipital region of the cortex. However, it does cause desynchronization if the sound is paired several times with light, considering sound as the "indifferent" and light as the "unconditioned" stimulus. This combination of "sound + light" becomes to a certain degree similar to the combination "indifferent + unconditioned." However, all investigators agree that after repeated use of this combination, the sound ceases to evoke the "conditioned" reaction of desynchronization (Jasper and Cruikshank, 1937; and others).

How should we interpret the above-described phenomenon of the "electroencephalographic conditioned reaction"? I have previously explained this from the neurophysiological and biological points of view (Anokhin, 1958a).

With a profound understanding of the whole evolution of the animal world, one will conceive the origin and development of the higher forms of the central nervous system as the development of the capacity for the most precise and rapid "chemical couplings" of those changes in the neural substrate which correspond to sequentially developing phenomena of the external world. The chemical evolution of the central nervous system proceeded in this direction. It is not surprising, therefore, that the most characteristic property of nerve tissue is the securing of sequentially developing changes in it. This is a *constitutional* property of nerve tissue. Only on the basis of sequentially developing events do these changes appear. However, these connections become secured only if they eventuate in factors essential to the life of the animal. In the case of the combination "sound + light" there is no such factor essential to life, if one disregards the adaptation of the eye to light; therefore, this connection, arising only as a manifestation of characteristic properties of nerve tissue, subsequently disappears. And yet this connection can be maintained indefinitely, provided one again gives it some type of signal meaning, i.e., makes it in some respect essential to the given organism.

Karazina, a collaborator of mine, conducted experiments especially for this purpose and thereby convinced us of the correctness of the above reasoning. Like other investigators, she systematically paired sound and light. However, in her experiments "light" was presented as a flash of several different luminous figures, for example, a circle, a square, or a triangle. With respect to luminosity, these figures were identical. As in the case of the experiments of the other investigators, the sound soon began to evoke a desynchronization *characteristic of the forthcoming light*. When this combination was repeated several hundred times, the conditioned desynchronization in response to the sound disappeared.

In this sense our results fully agree with all the results of previous investigators.

However, we subsequently changed the experimental setup. On a table before the subject we placed several small figures which were duplicates of the luminous figures in the combination "sound + light." The small figures actually were switches for the appropriate signal in the room of the experimenter. According to instruction the subject was to press the same figure which flashed in the combination "sound + light." Thus, the neutral combination "sound + light" acquired a signal meaning. Each time upon the presentation of any figure in the combination "sound + light," an orienting-investigative reaction preceded the correct solution of the problem, i.e., pushing the corresponding figure-button.

In this experimental setup the reaction of desynchronization in response to the sound no longer disappeared. One could present up to a thousand and more combinations with distinct desynchronization in response to the sound preceding the flashing of the figure (Karazina, 1958a, 1958b).

The above-described series of experiments leads to one particular conclusion: the reinforcing factor is absolutely necessary for the stable unification of a series of sequential influences from the external world on the organism. These influences may consist of more or less long series of phenomena, but at some stage of this sequence they must receive "reinforcement," i.e., a factor essential to the life of the organism must appear.

Thus, we may conclude that the elaboration of a conditioned reflex according to the usual classical method is an imitation of natural relationships in the external world, where series of recurring and sequentially developing phenomena become signals for some future factor essential to life.

All the other physiological features in the interrelation of indifferent and unconditioned stimuli (for example, inductive interactions) are subject to this universal law of signalization. Therefore, a temporary connection may fail to develop, not because unfavorable relations of induction have occurred, but because the basic principle of signalization is broken, as the result of the *sequential development of phenomena in the external world*.

Thus, we face a most important question in the physiology of higher nervous activity: what does the unconditioned stimulus bring with it into the newly formed temporary connection? As a vitally important stimulus, why does it have a "cementing" force which is directed toward the more or less distant influences of the external world which preceded it? Is the concept of its "greater force" sufficient for understanding the profound meaning of its qualities which stabilize the temporal connection?

These questions naturally touch upon the very essence of the formation of the conditioned reflex. Therefore, we will return to them after we have examined in detail the neurophysiological bases of the factors involved in the process of coupling of the conditioned connection.

Now we shall attempt to understand the afferent properties of the unconditioned stimulus, i.e., those centripetal currents of afferent impulses which arise upon the occurrence of an unconditioned stimulation and are the source of its capacity to stabilize the conditioned connection.

THE AFFERENT STRUCTURE OF UNCONDITIONED STIMULATION

In practice the study of conditioned reflexes usually does not raise the question: what is unconditioned stimulation with respect to the structure of its afferent impulses? By "unconditioned stimulus," the investigator generally assumes something definite, homogeneous, and qualitatively indivisible. At the present time this question becomes increasingly urgent when, for the understanding of the neurophysiological mechanisms of the conditioned stimulus, the *fate* of the unconditioned stimulus in the central nervous system acquires a decisive significance.

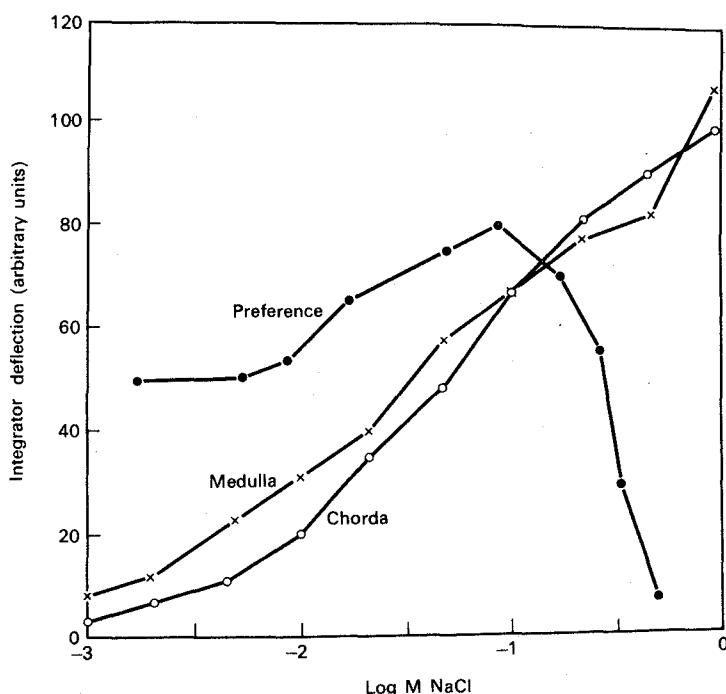


FIG. 2.1. A composite graph showing the rise of impulses in the chorda tympani and in the medullary taste area plotted as the integrator deflection in arbitrary units corresponding to the increase in sodium chloride concentration. Both impulse curves are correlated with the curve of preference for the salt solution. Preference behavior is plotted as a percentage of the total fluid ingested during a 48-hour period. It can be seen that at a certain point in the increase of concentration, the preference breaks off, whereas the impulses continue to increase progressively. From Pfaffmann *et al.* (1961, p. 468).

Because the basic concepts concerning the conditioned reflex developed on the basis of *alimentary reinforcement*, it is best to examine the afferent structure of this particular unconditioned stimulation.

Such an analysis of the afferent structure of the unconditioned alimentary stimulation is further necessary because it is universally accepted as the reinforcing factor, i.e., the factor which completes the sequential series of phenomena. Which features of the

unconditioned stimulation have such a decisive force in the process of the formation of a temporary connection?

It is quite natural to think that the constituents for this decisive influence of the unconditioned stimulation can be supplied only by those afferent formations which are stimulated by food. From recent systematic investigation it is known that the sensory formations of the tongue which mainly participate in the coding of the unconditioned stimulus include several kinds of individual receptors. The properties of these receptors have been studied by means of precise electroencephalographic methods, including the discharges of individual receptor elements and individual nerve elements on the pathway: receptor→medulla oblongata→thalamus (Zotterman, 1961; Pfaffmann, 1959, 1960; Pfaffmann *et al.*, 1961; Landgren, 1960a, 1960b, 1961).

The total number of these systematic investigations is now very large. However, we do not need to consider all the results of these investigations. We need to examine briefly only those results which enable us to come closer to the problem which interests us at present, the *afferent structure of the unconditioned reflex*.

First it must be noted that all investigators agree on some important propositions. It is recognized that there is quite a wide scale of chemical sensitivities which include all possible chemical effects on the tongue from the environment.

The second proposition is that there are receptors with various ranges of chemical sensitivity. For example, there are receptors which respond with discharges to several chemical agents (NaCl, sugar, etc.), but there are also receptors which respond only to a specific chemical agent, for example, to NaCl. Moreover, the higher the concentration of the stimulus, the more discharges the receptor fires (Fig. 2.1).

An important concept ensues from the experiments of Pfaffmann, who compared the electrophysiological effects of stimulation of the lingual chemical receptor at various stages of the propagation of impulses into the central nervous system: into n. lingualis, the medulla oblongata, and the thalamus. The result of this comparison proved to be somewhat unexpected and even paradoxical. The quantitative characteristics and the general configuration of impulses arising from stimulation of the lingual receptors by chemical substances remain constant regardless of the stage of propagation at which they are recorded (Pfaffmann, 1960; Pfaffmann *et al.*, 1961). These observations emphasize that a single specific channel of propagation of afferent impulses cannot be considered as the basis for explaining the end result of taste perception and taste differentiation.

This conclusion becomes especially plausible in view of the complex investigation of Pfaffmann *et al.* (1961). These investigators evaluated the increase of nervous impulses in the chorda tympani and the medulla oblongata in response to a gradual increase in the intensity of stimulation of the chemoreceptor by means of an increase in NaCl concentration. A striking similarity was found in the increase of the total electrical effect in both the chorda tympani and the medulla oblongata. The two curves nearly parallel one another. The investigators compared this increased electrical effect of various chemical substances with the curve of preference by rats for a solution of sodium chloride. This curve of preference was superimposed on the same scale of concentrations as the total electrical effect (see Fig. 2.1).

The figure shows that, in spite of the continued increase of the total electrical effect corresponding to the increase in sodium chloride concentration, the curve of preference by rats for the sodium chloride solution breaks off and sharply decreases with a further increase in concentration (Pfaffmann *et al.*, 1961, p. 468).

This interesting experiment reveals that the final *behavioral* effect does not coincide with the *electrophysiological* effect which we can observe on individual pathways of the propagation of nerve impulses. There is good reason to believe that neural and especially subcortical formations participate considerably in the final synthesis of all incoming afferent impulses. *Only with their participation* can some form of behavioral act be decided. This will be discussed in greater detail in Chapter 6.

From the data presented it follows that investigations of the propagation of nerve impulses *on one ascending pathway* cannot give us an understanding of the final effect of a given stimulation, e.g., unconditioned stimulation.

This conclusion is supported by the experiments of Landgren (1961), who compared the cellular discharges in the thalamus with the cerebral cortex in response to thermal stimulation of the tongue. He demonstrated that there are no essential differences in the discharges of single elements, either in the thalamus or the cortex in response to thermal stimulation of the tongue. If these data are compared with the data of Pfaffmann *et al.* (1961), who showed that there are no differences on the main pathway (chorda tympani → medulla oblongata → thalamus), then it becomes quite clear that *under no circumstances can we expect that unconditioned alimentary stimulation would have specific characteristics to establish new connections on these isolated pathways*.

Apparently the unconditioned stimulus does not acquire its most characteristic properties on these "specific" pathways. Most probably the impulses evoked by the unconditioned stimulus enter the reticular formation, where there occurs a dispersion of these impulses into the main subcortical formations, especially into the area of the hypothalamus. This has been shown by the experiments of Shuleikina (1963) in which electroencephalographic recordings were made during alimentary reactions in newborn kittens. The specific nucleus of the thalamus (according to Landgren, the specific afferent pathway from the tongue) exhibited a completely *identical* slow electrical activity in *different* biological situations: hunger, satiation, and transitional stages. On the other hand, the reticular formation of the midbrain (nonspecific pathway from the tongue, according to Landgren) and the medial hypothalamus gave a *different* electroencephalographic manifestation of all the above-mentioned biologically different conditions: the EEG of hunger differs markedly from that of satiation.

Thus, the nature of any form of unconditioned alimentary excitation is determined not by specific (in this case thalamic) structures, but by the system of reticular formation + hypothalamus. It appears that every kind of biological quality of adaptive behavior is patterned by these formations.

Located here are those neural formations which send the series of ascending impulses to the cerebral cortex, especially to its frontal lobes (Sudakov, 1962, 1963; Sudakov and Uryvaev, 1962). As may be seen from the cited literature, all the experimental data are basically concerned with the characteristics of individual receptors involved in unconditioned stimulation and with the relation of these receptors to separate points of a

specific pathway of conduction of impulses to the cerebral cortex. Only in some cases do they also include an evaluation of the behavioral effect of impulses arriving during alimentary reactions.

Most of these experiments quite obviously indicate that the presence of lingual receptors is absolutely necessary for the complete adaptive alimentary behavior of an animal (Richter, 1942). However, the lingual receptors alone are not decisive in the formation of a central system of impulses. They act as special triggers which *select* the suitable stimulus from the environment, whereas the final form of behavior depends on the situation which exists in the internal milieu of the organism in the sense of the presence or absence of suitable substances. Therefore, the final form of the behavioral act or selective alimentary behavior ("motivation") is related to this internal milieu of the organism or, figuratively speaking, to its "need" at a given moment (Wilkins and Richter, 1940; Richter, 1942).

We shall return to these experiments when we evaluate motivation as one of the factors of behavior. At present it is important to note that in all the above-mentioned publications, the question which interests us most was not discussed. We are concerned with what qualities of the alimentary stimulus are important during the action of food on the lingual receptors for it to become an *unconditioned stimulus*, with what form and at what points of the central nervous system the impulses arrive, and what constitutes their final synthesis. In other words, we are interested in the *neurophysiological basis of the reinforcing action of the unconditioned stimulus*.

An important feature of unconditioned reinforcement attracts our attention. Investigators tend to overlook the fact that food in experiments with conditioned reflexes acts only as a *sensory factor*, and its actual utilization in the metabolic processes is separated from the moment of its intake by a considerable interval of time. We are dealing here with the striking phenomenon that *food can become a reinforcing factor because of its sensory qualities alone*. There follows, then, the importance of studying the mechanism and composition of the afferent impulses arising from the intake of food, as well as their action in the central nervous system.

There is no doubt that the *moment of intake* of food and its utilization after several hours in the metabolism of the organism are connected by a continuous chain of processes, stimulations, and changes along the entire digestive tract. Consequently, we again encounter the question concerning the *sequential action* of external factors on the organism.

Indeed, under natural conditions a situation never occurs in which food begins its action on the organism from the lingual receptors. The mechanics of food intake are such that the organism unmistakably sees the food or feels it with the tactile receptors of its extremities, or smells it, etc. This chain of continuous sequential actions continues further.

Under natural conditions of feeding there was never a case in which food acted on the esophageal receptors before acting on the lingual receptors, or on the gastric receptors before acting on the esophageal receptors, etc. Thus, stimulation of the lingual receptors is connected by a continuous chain of afferent processes with the last stage, tissue metabolism, terminating this chain of consecutive transformations.

From the point of view of the theoretical considerations which were developed in Chapter 1, we can say that in this sequentially developing series of phenomena, each member of this series may potentially become the signal for the following one, inasmuch as this sequence is invariably repeated in a given animal or man throughout the course of his life.

The best example of such signal actions within the limits of a series of processes is the secretion of the "triggering gastric juice" during mastication of food (Pavlov, 1897, see Pavlov, 1951a, pp. 106-126; Pavlov, 1911-13, see Pavlov, 1952, p. 138). Unfortunately, this entire area of signal relationships along the digestive tract, so exceedingly important both theoretically and practically, has not received adequate consideration in experimental investigation.

For the problem we are studying at the moment it is important to emphasize that, considering the organism as a whole, the utilization of the ingested substance in tissue metabolism is truly unconditioned, i.e., a *true reinforcement*, for here is the determining point for accepting or rejecting a given food substance for the life process.

Why, then, does the moment of the action of food on the lingual receptors have such a reinforcing power? Why does it become such a valuable and universal representative of the interests of the tissue? The answer to these questions lies in the field of the phylogenetic principles of the development of organisms and in their relations to the external world.

The lingual receptors are the first point of contact where the organism may refuse anything inedible or harmful. It is due to this peculiarity of the oral cavity as the *initial selection stage* that it acquires such a decisive role in the alimentary relations of the animal to the external environment. The lingual receptors and the subjective taste sensation from a given food evoked by these receptors in the brain have, during evolution, become adequate informers about the true needs of the tissue metabolism and the acceptability of various foods to the organism. At the same time, each action of an unconditioned alimentary stimulus on the taste receptors must be subsequently *reinforced* by the processes of tissue metabolism necessary to the organism.

Thus, from the point of view of a continuous series of food transformations, the unconditioned stimulation can become an appropriate signaling stimulus for future tissue transformations. In this process we can see the principle common to all organisms, a principle which has developed during evolution on the basis of the invariable sequence of events and their frequent repetition (see Chapter 1).

All the above considerations make the study of the *structure* of the unconditioned stimulus and its central action especially important. Only by knowing the precise mechanisms of action of the unconditioned stimulus can we also understand both its reinforcing role in conditioned reflex activity and its relation to the metabolic processes of the entire organism.

In our laboratory my collaborator, Laptev, has undertaken systematic oscillographic investigations of the lingual receptors with regard to the diversity of information which they send to the central nervous system. By eliminating the action of various parameters of food stimulation, each in turn, he could show that at least three types of receptor formations must be combined, in view of their action on the central nervous system.

First, the tactile receptors must be singled out. These receptors give the initial discharges which are recorded after a brief latent period, and have a high potential, short duration, and a rapid propagation along the fibers of the lingual nerve. Since, under the conditions of our experiment, the tactile receptors were always first to discharge *when a drop with any given chemical composition would fall on the tongue*, one may suppose that they give information concerning the instant of contact and the consistency and form of the alimentary substance, regardless of its chemical properties (Laptev, 1949a). The thermal impulses are next in appearance. They, too, have a high potential and high rate of propagation (Fig. 2.2). Slowly propagating impulses of low amplitude appear later than all the above-described discharges. They discharge continuously over a long period of time and, judging from their character, they are impulses arising in the lingual chemoreceptor formations (Laptev, 1949a).

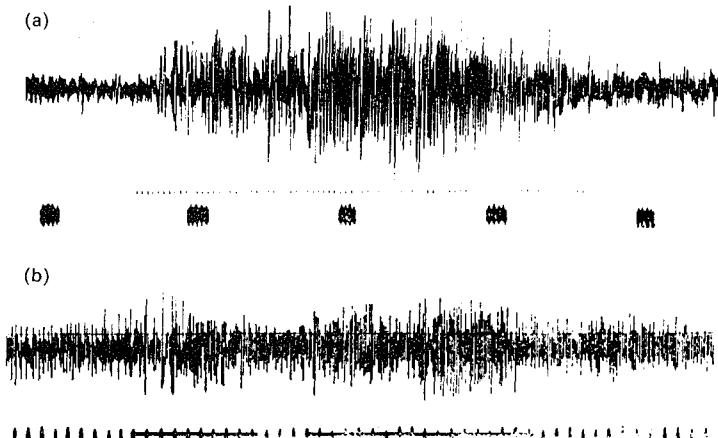


FIG. 2.2(a). Lead from a branch of the lingual nerve of a dog. Time recorded in 1/5 sec. Strong mechanical stimulation with the smooth end of a glass rod.

(b) Lead from a branch of medium diameter of the lingual nerve of a dog. Time recorded in 1/100 sec. Mechanical stimulation of the tip of the tongue with a glass rod. The tongue is in water brought to a temperature of 70°C.

It can be seen that, on a background of constant thermal impulses, the stimulation of the tactile receptors produces an additional rise and intensification due to tactile impulses.

Our recent data on the successive reception of tactile and thermal impulses by the central nervous system could not determine any *specificity* of these discharges with respect to the chemistry of the substance applied to the tongue. However, they change greatly in frequency and duration depending on the concentration of the applied solution.

If the technical difficulties in the application of the stimulating substance can be overcome, then the distribution in time for the appearance of the tactile, thermal, and chemical impulses generally takes up to 0.1 sec and, in some experiments, up to 0.2 sec.

These data on the successive entrance of sensory impulses of various modalities into the central nervous system were recently confirmed by Landgren (1957b, 1961) for the cerebral cortex. This interval between the application of stimulus and appearance of

impulse was somewhat less than what we obtained (up to 40 msec). We attribute this to the difference in the technique of applying the stimulus.

Of most importance in this investigation is the fact that *the impulses evoked by different parameters of the unconditioned stimulus arise with different latent periods and have different rates of propagation* toward the central nervous system. Due to their temporal relation, they enter the central nervous system "in pursuit," one after the other. The result, then, is that the central nervous system receives *sequential* information concerning the essential properties of the food which has acted on the tongue.

A number of questions arise regarding the essence of the unconditioned reinforcement.

First, in what manner are these impulses, diverse in time of origin and rate of propagation, integrated into the central nervous system and perceived as a single, fully-defined alimentary stimulus? What are the interrelations of the individual types of impulses and can they somehow influence each other? We can say little to answer the first question, since we do not know the localization of projection for each of these impulses. Electroencephalographic investigations give us reason to believe that each type of impulse has its own zone of projection (Anokhin, 1940a; Laptev, 1949b). Recently, Pfaffmann (1959, p. 510) also expressed the same point of view, although Landgren (1961) notes a rather limited zone of the cortex for all impulses.

If further, more exact investigations show that these impulses are, after all, projected into different points of the cortex, we shall then have to explain this remarkable process of afferent synthesis in which *a physiological integral of a stimulus is formed de novo as a single sensation of a given kind of food from the projections of the various parameters of a single "unconditioned stimulus" which are separated and scattered over the cortex*. Experiments indicate that it is highly probable that the impulses from the chemical parameter most decisive for the animal's evaluation of the quality of a food are projected neither directly nor exclusively into the cortex; rather, they are projected also into individual structures of the limbic system and especially, as we shall see later, into the hypothalamus.

At present, we can more fully answer this question: what are the interactions and what is the role of individual series of nerve impulses from the various lingual receptors?

There seems to be no doubt that in some special situations individual parameters of an unconditioned stimulus can acquire an independent physiological role. One of our experiments showed that tactile receptors clearly inhibited the efferent influence on the secretion of the salivary glands. The experiment involves artificial anastomosis of heterogeneous nerve trunks.

After suturing the central stump of the vagus nerve to the peripheral stump of n. lingualis dex. and n. lingualis sin., and after regeneration of the sutured nerves, an uncontrollable salivary secretion continues day and night. Some dogs lost up to 9 liters of saliva during a 24-hour period.

An analysis of this phenomenon showed that salivary secretion is due to both the constant tonus of the vagal nucleus and incoming stimuli from the lingual receptors. However, the animal itself "discovered" a means of overcoming this disturbing salivary secretion. In their mouths, the dogs continually grasped the chains with which they were tied to the stands. Putting their tongues under the chains, they hung onto them for a long time. Secretion then stopped (Fig. 2.3). Clearly shown in this experiment is the



FIG. 2.3. Photograph of dog "Zona", which found a method of inhibiting continuous, profuse salivation. Seizing a chain with her teeth, she could stand for hours in this position. During this time the salivation stopped.

inhibitory action of impulses from only the lingual mechanoreceptors on the secretory impulses arising in the cells of the vagal nucleus.

The fact that impulses from various lingual receptors sequentially enter the central nervous system with an interval between the tactile and chemical impulses of about 0.1 sec suggests still further possibilities for this complex information concerning the unconditioned stimulus. Due to this break in time, conditions are again created for a constant and recurring sequence of stimuli: tactile → thermal → chemical; and *under proper conditions, the tactile impulses may become the signal for a forthcoming chemical stimulation of the lingual receptors*, just as a sound becomes the signal for a forthcoming light.

The possibility of such signaling relationships within the limits of individual parameters of a single "unconditioned stimulus" was, of course, interesting to observe. It

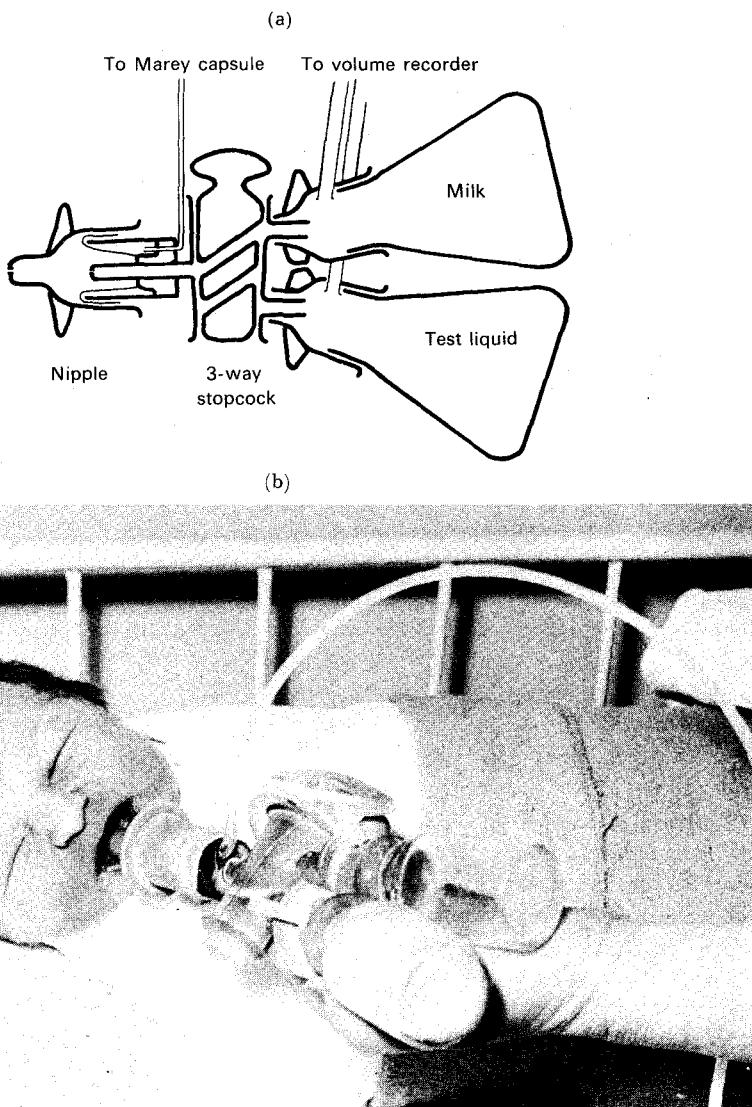


FIG. 2.4. Apparatus for studying the reactions of a newborn infant to sudden replacement of milk by ascorbic acid (a). The infant during observation (b).

was necessary to select those conditions under which it would be possible to check the tactile component in two situations : when it is still indifferent and when it is becoming a signal. The most suitable subject for such verification was a *newborn baby who had not as yet had a single feeding*. As a consequence of the lack of feeding, the tactile impulses could not have become a signal, since there was still no chemical component of the unconditioned stimulus.

Under the experimental conditions, we suddenly had to replace the milk with some other liquid, entirely neutral (i.e., of no special significance) and harmless to the infant. It was necessary to construct a special apparatus which would make this exchange possible. Shuleikina (1959a), a collaborator in my laboratory, constructed such an apparatus and conducted investigations which clearly answered the above question (Fig. 2.4a).

The following is the order of observations: the newborn infant, having *not yet sucked*, was given milk which was then suddenly replaced by a 2 per cent solution of ascorbic acid. At the same time, the sucking movements were recorded. In almost all cases the ascorbic acid evoked an inhibition of the sucking movements and a spitting out of the liquid, frequently accompanied by an appropriate facial expression and crying. Under the same conditions and in the same infants, milk evoked a positive reaction of sucking and swallowing (Shuleikina, 1961) (Fig. 2.4b).

By means of what receptor formations was the ascorbic acid perceived as a substance to be rejected and so sharply differentiated from the milk?

In this experiment the tactile and thermal receptors were placed under identical conditions, since the mechanical properties of both liquids are almost identical, and the temperature was specially stabilized at the same level. It is quite evident that the differentiating factor in this observation could only be the specific peculiarities of the *chemical parameter* of the two liquids, milk and ascorbic acid. I see no other possibility of explaining this initial ejection of the unpalatable liquid.

Supporting this point of view are Jensen's data, also obtained by using newborn infants. By adding salt to the milk in increasing amounts, he found that the infant immediately spits out the milk when there is a salt content increase of only 0.225 per cent to 0.3 per cent (Jensen, 1932a, 1932b).

Returning to our observations, we can say that in a newborn infant *which has had no previous experience in sucking*, the only *sure* criteria for distinguishing unconditioned stimuli are the chemical parameters of the stimulation. Thus, the newborn infant has a central mechanism very precisely organized in embryogenesis for the differential evaluation of afferent signalizations coming from the tongue. The function of this mechanism may be stated in this way: the *lack of coincidence* of the peripheral chemical impulses with any kind of inborn synaptic organization at the level of the hypothalamus and the reticular formation gives preference not to the swallowing complex of the effector mechanisms, but to the opposite complex—the ejection of the substance.

After these procedures we changed the method of observation. We took an infant 8–10 days old, i.e., one which had already had considerable experience in sucking, and tested a sudden replacement of the *milk familiar to him* with the same ascorbic acid as used in the previous experiment. Completely different results were obtained. Now the baby did not reject the ascorbic acid immediately, but made a number of sucking movements, and only after prolonged sucking of the ascorbic acid did it stop sucking (Fig. 2.5a, b).

Such a change in behavior with respect to the substance to be rejected may be explained in the following way: practice in sucking during the first 10 days after birth radically changed the specific significance of the individual parameters of the uncondi-

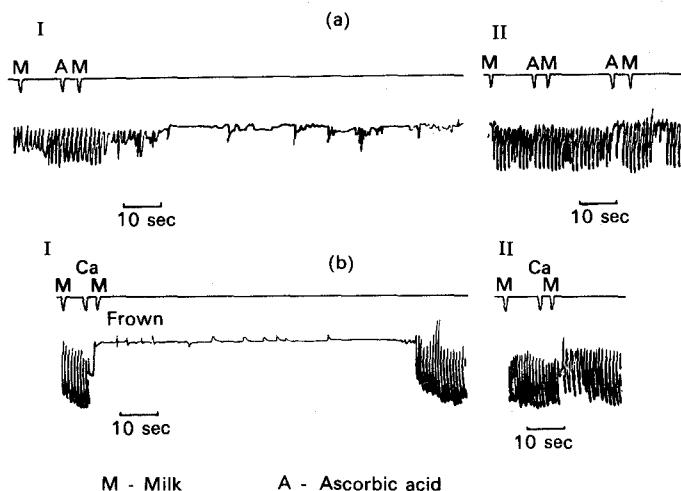


FIG. 2.5. The effect of replacement of milk with ascorbic acid (a), and of milk with a solution of calcium (b). After replacement of milk with ascorbic acid, there occurs a prolonged delay in sucking movements in a newborn infant, even when milk is given again (a-I). However, on the tenth day after birth, under the same experimental conditions, there is no cessation of sucking movements (a-II). Similar relations also exist in the case of replacement of milk with a solution of calcium (b-I), (b-II). More detailed explanations are given in the text. M, milk; A, ascorbic acid; Ca, calcium.

tioned stimulus. The first sucking movements immediately after birth result, of course, in stimulation of the tongue by the tactile, thermal, and chemical properties of the given substance. However, as we have seen, only the chemical properties of the substance can be the parameter which determines the nature of the effector complex (swallowing or ejection).

It is another matter when the newborn infant has already practiced sucking and swallowing of milk for several days. As a result of such practice, the parameters of stimulation which act with the shortest latent period and at the greatest speed of propagation (tactile), being essential and invariable forerunners of the chemical action, acquire a signaling role with respect to the central mechanisms of the act of sucking. In our opinion, this is why, after an 8-day experience of sucking, it is sufficient for the ascorbic acid merely to come in contact with the tongue in order to initiate immediately the sucking mechanism. Only after several such movements, when the chemical action becomes sufficiently distinct, the decisive action of the chemical nature of the substance takes place with the subsequent formation in the centers of the appropriate response, i.e., ejection of the substance.

Thus, the experience of sucking for only 8 days completely changed the significance of the individual parameters of the unconditioned stimulus by shifting the signaling role to the tactile stimulus which, during these 8 days, naturally and *invariably preceded* the chemical stimulus.

This explains the difference in the reactions of a newborn infant to the same unacceptable substance during the first hours after birth and on the eighth day of life. In the

first hours of its life the reaction more truly reflects an adaptive relation to the unacceptable substance, since in this period only the chemical properties, which are directly involved with the metabolic processes of the body, form the decisive factor. After 8 days of sucking milk the infant has acquired the following fixed sequence of experience: "tactile→positive→chemical," and therefore the tactile afferent component, acquiring a signaling meaning, becomes the impetus for the beginning of sucking movements. The sucking may proceed *for some time* in spite of the presence of a particular chemical stimulation only because the tactile signal has already succeeded in creating in the central nervous system a dominant state (preference in excitability) for the elements of the sucking reaction.

Evidently this above-described situation, which depends on different periods of stimulation of different receptors and on different rates of propagation of impulses from these receptors, occurs not only in the case of an unconditioned alimentary stimulus. One must suppose that an unconditioned nociceptive stimulus also has a distribution in time of the individual series of impulses constituting the stimulus. Indeed, we know that a nociceptive stimulus spreads towards the central nervous system considerably more slowly than a tactile stimulus. And yet, with any form of nociceptive stimulus, especially mechanical, it is the tactile receptors which are first excited. Considering the speed of propagation of the latter impulses, we can say that with any nociceptive stimulus the central nervous system receives first the tactile impulses and then the true nociceptive impulses. It is true that Gasser (1943) has shown that there are comparatively rapidly conducting nociceptive fibers, but even in this case the tactile impulses must reach the central nervous system first. We can make one general conclusion concerning all unconditioned stimuli: *each unconditioned stimulus already has an integrated structure in its receptor component. Therefore, in spite of the apparent homogeneity of the stimulation, the central nervous system receives a complex of sequential impulses of diverse physiological qualities.*

It is easy to see the immense biological significance of sequential and qualitatively diverse impulses. Due to such a distribution in time, *each preceding series of impulses can be a signaling stimulus for the following one* only if the latter constitutes an essential aspect in the life of the organism. The tactile impulses in this sense are in an especially favorable position. By nature they must be a universal signal for all the other qualities of the unconditioned stimulus, acting on the lingual receptors after initial contact. It is, therefore, not surprising that the "tactile" properties of a given type of food become firmly coupled to its true alimentary, i.e., chemical, properties according to the principle of *conditioned signaling*.

A remarkable example of the rapidity of appropriate tactile signaling is the swallowing of food by an axolotl. As we know, the intake of food by an axolotl entails several stages. "Moving food" in the shape of a bloodworm creates a movement of the liquid and probably disseminates the appropriate chemical substances which are an alimentary stimulus for the axolotl. In response to this stimulus the axolotl almost imperceptibly moves towards the moving prey. Upon approaching its prey, the axolotl makes a sudden lunge forward, seizes the food and immediately swallows it. The seizing and swallowing of the food succeed each other so rapidly that it seems that the axolotl does

not assess the qualities of the prey, i.e., that after the seizing of the food, reverse afferentation cannot appear. Actually this is not the case. If one moves a piece of rubber shaped like a bloodworm and imitates its movements in front of the axolotl's mouth, the axolotl approaches the piece of rubber and characteristically seizes it just as it would a real bloodworm. However, almost immediately the axolotl forcefully ejects it.

This observation convinces us that between the very rapid seizing of the prey and the equally rapid subsequent swallowing, an important action occurs in the axolotl: *an evaluation of the subtlest differences between real food and accidental inedible objects perceived by the receptors*. Most probably this ability to evaluate involves the differentiation between the subtlest tactile variations. It is quite possible that in a fraction of a second the axolotl's central nervous system evaluates the active movements of the seized object. However, in any case this can be an evaluation of tactile stimuli only, since thermal stimuli are eliminated in an aqueous medium, and there is hardly sufficient time for chemical stimuli to be effective.

The study of war injuries has given us additional information showing that the different qualities of the unconditioned stimulus (mechanical properties, temperature, chemical composition) constitute sensory integration and not some kind of homogeneity of receptor impulses. In some forms of trauma in the facial area, when the wounding instrument strikes some sensitive branch of the trigeminal nerve, peculiar sensory disturbances can be observed. The patients may completely lose their sense of taste. In an attempt to attain at least some taste sensation while eating food, they added large amounts of pepper, mustard, and salt to their food, thereby developing gastritis, and yet they still did not have any sensation of taste. It is remarkable, however, that the *tactile sensations from the mucous membrane of the tongue remain almost completely intact*.

Such a dissociation is not the result of a partial injury to the lingual nerve. As I have already noted, the injury in such cases often does not involve it at all. In a case which I observed in the Tomsk Hospital of Stomatology, for example, the disturbances were connected with a surface trauma in the facial area. A bullet had gone through the cheek, knocked out a tooth, and slightly injured the left edge of the tongue where it lost its penetrating power, and the patient spat it out. As can be seen from this description, the lingual nerve was completely unaffected.

I shall not discuss in detail the central physiological mechanisms of such a disturbance of sensory function, for this has already been done elsewhere (Anokhin, 1942a, 1942b). At present it is important to note that the intricate complex of various impulses, arising in response to stimulation of the lingual mucosa by alimentary substances, is a true sensory integration which has adaptive significance.

Summarizing these considerations concerning the afferent structure of an unconditioned stimulus, we must first point out that the very nature of the lingual receptor apparatus emphasizes the extraordinarily complex system of coding all the detailed physical and chemical parameters of the unconditioned agent. Thus, the characteristics of the receptor structures make possible, on the basis of an *invariable sequence* in the stimulation of the lingual receptor mechanisms, the establishment of signal relationships at some time between the individual parameters of the unconditioned alimentary stimulus.

Moreover, it is not by chance that both the tactile receptors and tactile impulses acquire the significance of an outpost. Indeed, during any action of *contact* stimuli on the organism, regardless of their chemical properties and subsequent importance, they must first *touch* some surface of the organism. This absolute law of the relation between the organism and the environment has also been reflected in the exceptional sensitivity of the organism, and especially of the lingual mucosa, to any contact.

Attention must also be given to the fact that the unconditioned alimentary stimulus is not a true reinforcement in the sense of a final metabolic process of the organism itself, but is only the *most reliable, appropriate signal* for the future satisfaction of tissue needs, which is a normal stage in the continuous development of the consecutive processes of digestion and assimilation. This role of the unconditioned stimulus will be described more thoroughly in the last part of this chapter.

Now we must emphasize one more characteristic of the unconditioned stimulus as an *integrated afferent formation*. The pathway of propagation through the thalamus to the cortex, which may be called specific, does not determine the most decisive *reinforcing* properties of the unconditioned stimulus. A definite need has arisen to include in the investigation and explanation of the nature of unconditioned stimuli those numerous collateral channels along which it branches from the specific pathway. These collateral channels of unconditioned afferent impulses include the regions of the reticular formation, the vast area of nuclei of the median line, and finally the highly integrated neural formations of the lateral and medial hypothalamus (Fig. 2.6). The importance of these interrelationships lies in the fact that the "collateral" channels of propagation of unconditioned impulses impart a *biological quality* to the cortical integration of nervous processes, as well as to the integrated reaction of the organism.

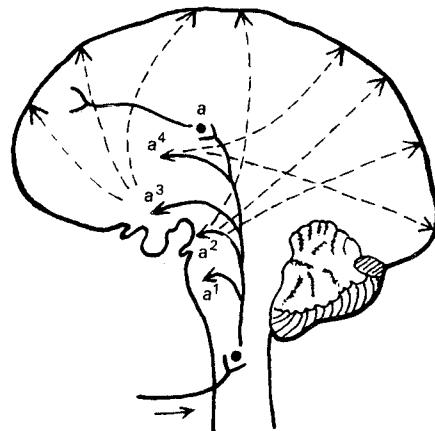


FIG. 2.6. Diagram of the relationship between a specific excitation reaching the cerebral cortex along a specific pathway, i.e., through the specific thalamus (a), and the streams of excitations ascending from the subcortical nuclei also to the cerebral cortex (a^1 , a^2 , a^3 , a^4). A final synthesis of both kinds of excitations is essential for the evaluation of the gustatory qualities of a particular unconditioned stimulus.

In the final analysis, from all the channels of propagation of impulses evoked by an unconditioned stimulus, many impulses converge in the cerebral cortex; they are different in quality and distributed along various specific synaptic formations. Most of these impulses are of a generalized nature, some being less so than others. And, as was shown by means of the microelectrode technique (Jung, 1961; Fadeev, 1965), individual sensory modalities are strictly localized in the cortical area.

Such is the complex appearance of what Pavlov long ago called the "cortical representation" of the unconditioned stimulus. In view of this complexity, can we analyze and understand the interactions of conditioned and unconditioned stimuli at the level of the cortex and subcortex? In the following section we will concentrate on answering this question.

THE BIOLOGICAL NATURE OF REINFORCEMENT

We indicated earlier that a "reinforcing factor," i.e., an unconditioned stimulus, is absolutely essential for the elaboration of a new conditioned connection. This circumstance demonstrates that reinforcement is essential for uniting *simultaneously and sequentially excited neural elements in the brain*.

At the same time it is well known that an inverted sequence, i.e., applying the reinforcing factor first and then the indifferent stimulus, either precludes the establishment of an associative connection between the indifferent stimulus and the reinforcement, or forms a highly unstable connection. This law of the formation of conditioned reflexes emphasizes that the arrival in the cerebral cortex of indifferent impulses first, and then of impulses from the reinforcing factor, is an essential condition for any "coupling" of a conditioned connection which has adaptive importance for the animal. What, then, does the reinforcing factor contribute to the cerebral processes? Which of its qualities are decisive in the formation of a new and stable connection between the excited elements?

We shall more fully discuss the process of coupling in regard to its intimate nature in Chapter 4. Presently it is necessary to examine the biological and physiological evaluation of the reinforcing factor per se.

From a broad biological point of view, during its entire life an organism is continuously influenced by *sequentially developing external and internal factors of its existence*. At this point we are specifically interested in the role of the sequence of external factors in transformations of the internal conditions of the organism.

Indeed, any attempt to isolate a particular external influence from other similar influences must end in failure, since the given influence on the organism is invariably preceded by some other influence, and the latter is preceded by still another influence, etc. A sufficiently thorough analysis may even prove that an action as elementary as the opening of a door may be separated into hundreds of individual events which are quite closely connected with each other *in time*. Nevertheless, from this series of mutually connected influences on the nervous system, we will single out some main events that acquire certain adaptive qualities for animals and man.

To illustrate, let us analyze the following example. My being in my office and my

being on a noisy street are, of course, two qualitatively different conditions, depending on the totality and distinctiveness of external as well as internal influences. However, these two conditions are connected by a continuous chain of influences, starting with opening the door, descending the stairway, passing through the courtyard, etc., and ending with the influence of the entire setting of the noisy street.

These intermediate links may in turn be broken down into thousands of still smaller and briefer influences. For example, while passing through the courtyard, I sequentially receive dozens of stimuli from spatially stable factors and objects. This analysis can be extended to elements of stimulation so fractional that we encounter an amazing overlapping of these stimuli in space and time, which invariably results in a similar overlapping of the influences and chemical states evoked by these factors in the central nervous system.

This characteristic of the environment and of our behavior in relation to the environment is of present interest. The external stimuli act upon the central nervous system continuously, and the intervals between the stimuli turn out to be much shorter than the temporal parameters of the excitation itself, which is manifested by the receptors and the nervous system. As a result, the central nervous system, especially the cerebral cortex, is subjected to something comparable to a large moving picture in which all the frames become organically united, with one basic difference: the frames of a film never "overlap," whereas the influences of the environment and the impulses evoked by them are invariably united and overlap in the neurochemical processes.

However, there is one criterion which refutes the apparently continuous uniformity of the stimuli. This criterion is the *biological, vital significance of an external influence*—its value for the survival of a given organism in a given state and under given conditions of existence.

A flying bird is undoubtedly a "stimulus" for a predator. A bird, however, that has been taken into the mouth of a predator is actually already a part of its organism, *an absolutely certain factor of survival*. Indeed, it is difficult to imagine that food could ever be taken from the mouth, much less the stomach, of a predator.

It is therefore quite natural that "probable" and "certain" features of food, from the point of view of their relation to the most basic condition of life, survival, are of great importance for behavior and are therefore variously manifested in the hereditary structural features of the central nervous system.

On the basis of this alone, gustatory stimulation by food *that has already entered the mouth* can become a "reinforcing factor," since among the numerous probability factors of the environment ("indifferent" in laboratory terminology), gustatory, i.e., unconditioned, stimulation is a *reliable* signal of the introduction of food into the organism and consequently a signal for subsequent processes of metabolism and the preservation of life. I must mention an important point in the technique of elaborating conditioned reflexes and its generally accepted physiological interpretation. According to the concept accepted in Pavlov's laboratory, stimulation of the taste receptors of the tongue by food is an unconditioned, i.e., a *reinforcing*, stimulus. We have seen how this stimulation differs from other stimuli from the biological point of view: it is a signal ensuring survival and has the capacity to remove the distressing sensation of hunger and to bring

the animal through a number of positive alimentary reactions to a state of satiety.

These decisive properties of the unconditioned alimentary stimulus contribute to its importance as a "reinforcing" factor. Let us assume an imaginary case in which the mammalian esophagus branches into five separate channels but food enters the stomach through only one of these and subsequently becomes a metabolic factor. The remaining four channels take the food outside, and therefore it does not become a metabolic factor. In mathematical terms, the probability of the utilization in metabolic processes of food taken into the mouth would be only one-fifth in such an animal. Under these conditions, could the mere entrance of food into the mouth be a *reinforcing factor*? Of course not. If that were so, the organism would be placed in a difficult position from the point of view of survival: it would experience satiety when its actual metabolism was in a state of "hunger" with no insurance of its satisfaction.

This physiological nonsense convinces us that the reinforcing significance of alimentary stimulation is most intimately connected with the certainty of the incorporation of food into the metabolism of the organism. This certainty, however, arises when food is already in the mouth, and thus within the organism. Here two evolutionary factors are obviously manifested in conjunction: the anatomical reliability of the progress of food in the organism and the physiological role of the alimentary stimulus in the mouth, which in the process of evolution has acquired a reinforcing significance.

I must now emphasize a remarkable observation that has attracted attention. The generally-known reinforcement which we discussed above is not actually a true metabolic factor promoting the preservation of life. It is well known that the metabolic factor does not become involved until several hours after the entrance of food into the mouth, when the digested food enters the blood and is assimilated by the tissues. Thus, the reinforcing power of the actual entrance of food into the mouth is an evolutionary result of the fact that *the action of food as a complex gustatory stimulus is connected in the closest and most ensuring relationships, through sequential stimuli, with the end result of its utilization in metabolism*. All these relationships and the sequential influence of stimuli on the central nervous system take place on the basis of inborn structural relations.

Consequently, in its biological essence, eating serves merely as a *maximally reliable signal of future metabolism*. However, this signal is part of a sequential series of processes which have not changed in the course of hundreds of millions of years. Direct experiments with section of the esophagus and elimination of the last metabolic link in the series of reinforcing stimuli confirm the validity of these propositions.

Returning to our postulate of the continuous action of external conditions on the organism, we can now say that this continuous chain of influences on the organism is such that individual stimuli of the environment gradually pass onto the internal pathways of the organism and terminate either in the preservation of life or in its destruction. These are, so to speak, the *vital junctions* of natural continuity which determine the biological value of the factors closest in sequence for the organism and, consequently, also determine the relation of the organism itself to these factors.

Thus, the selective relation of the organism to sequential series of external factors takes shape. Those closest to the reinforcing factor, i.e., to the action of food through the mouth, turn out to be the most significant for the organism, whereas the distant ones,

and especially those that are not at all in the given series of sequential influences, are not essential for the vital processes. They are not conditioned signals of prospective feeding.

It must again be emphasized that these continuous external actions *overlap* in their stimulating influence, and consequently the processes evoked by them in the brain, which interact over short intervals of time, also have the possibility of entering into chemical and functional interaction with each other.

Generally speaking, the reinforcing strength of the alimentary influence from the receptors of the tongue spreads into the environment through a continuous series of preceding influences with a gradual decrease in this strength, in exact correspondence with the *probability value* of these remote links for the vitally important functions of the organism.

Until now I have discussed only the reinforcing significance of stimulation of the receptors of the mouth, the esophagus, and the stomach by unconditioned alimentary stimuli. I have also shown that they are merely *signals* of the true and final unconditioned process, metabolism, which, although occurring much later, is nevertheless connected with the moment of food intake by a number of continuous stimuli that are received by the receptors along the entire digestive tract.

I have intentionally not touched upon another extremely important and, unfortunately, rarely considered factor : the appearance of a specific emotional condition which is defined in all languages as *satiety*. It is universally known that the intake of food is connected with a "gustatory sensation" terminating in "satiety." Moreover, every one of us has observed this phenomenon of satiety in a newborn infant in an especially illustrative form. But how is this satiety achieved? What neural mechanisms are responsible for this specific condition which ultimately leads to the rejection of food?

The rejection of food by an animal or a human being primarily means that the food has lost its reinforcing significance for them in the series of sequential stimulations of the organism by external factors. From the experience of Pavlov's laboratories it is well known that a sated dog responds neither by a salivary nor by a positive motor reaction to conditioned alimentary stimuli. There is no sufficiently excitable substrate in the central nervous system to redirect these stimuli to the central mechanisms of the alimentary system and evoke an integrated response.

From these observations it obviously follows that to reveal the concrete neurophysiological mechanisms of satiety means to be able to decipher the nature of the reinforcing action of unconditioned stimuli, or at least of the unconditioned alimentary stimulus.

In this field we do not have any satisfactory concept to allow us to understand the physiology of this basic activity of the organism. It is therefore not surprising that Brobeck, evaluating the contemporary status of the problem of hunger and satiety, observes : "There is no hypothesis which explains quantitatively how the organism regulates either eating or drinking on the basis of sensory experience" (Brobeck, 1960, p. 1197).

In connection with this problem a number of investigations were undertaken in our laboratory which to a considerable degree have revealed this mechanism, removed the veil of mystery from the condition of satiety, and permitted us to formulate one important physiological rule, which applies not only to the intake of food, but also to many

other vitally important functions of the organism which are connected with an initial humoral stimulus (motivation).

We first directed our attention to one disturbing paradoxical phenomenon for which no explanation had been found. It is well known that we experience a sensation of satiety before leaving the table. Moreover, the very process of eating continues up to the moment when we begin to experience satiety.

The situation is exactly the same for quenching thirst. Our thirst is quenched before we take the glass of water away from our lips. In each case, the amount of food or water ingested corresponds, as a rule, to the degree of the previously experienced hunger or thirst. These observations are certainly paradoxical in relation to the theoretical concepts on the basis of which we explain the onset of the sensations of hunger and thirst.

Long ago the concept appeared that the most likely cause for the onset of the sensation of hunger is a depletion of nutrients, which are gradually removed from the blood due to the metabolism in the tissues. Pavlov always spoke with complete certainty about "starved blood." This is indeed true, since the most reliable and rapid information about a depletion of nutrient reserves in the blood would be information from the blood itself.

Anand *et al.* (1955), Andersson and Jewell (1957), and Brobeck (1957, 1960) have demonstrated that the most probable point of the central nervous system to be related to the onset of the sensation of hunger and to the intake of food is an area of the hypothalamus, namely, its lateral and medial nuclei. As we know from the publications of these investigators, destruction of the lateral nucleus of the hypothalamus leads to a complete loss of food-procuring reactions and to cessation of food intake. Following destruction of this area of the hypothalamus, animals may die of starvation while sitting beside food. Destruction of the medial nucleus of the hypothalamus, on the other hand, leads to extreme voracity during which the animals cannot stop eating if the food is not taken from them (Brobeck, 1957; Andersson and Jewell, 1957; Anand *et al.*, 1955).

Experiments compel us to assume that the lateral nucleus of the hypothalamus produces the sensation of hunger, whereas the medial nucleus inhibits eating and, consequently, its function must correspond to evoking the sensation of satiety. But how does this take place? Until recently there was no sufficiently clear physiological solution to this problem. In our opinion, characterizing the nature of the reinforcing action of food during the elaboration of conditioned alimentary reflexes depends on solving this problem. All we know is that this mechanism is related to the peculiarities of the relationship of the hypothalamus to the cerebral cortex. Previously, the only specific experiments which revealed the actual mechanisms of these relations were those on motivated behavior (see below).

Sudakov (1963) performed experiments dealing with this problem in our laboratory. In an experiment on a cat under urethane anesthesia, it was discovered that a 2-day fast before the experiment caused a well-defined desynchronization in the anterior areas of the brain (Fig. 2.7a). As the figure shows, this desynchronization is maximal in the frontal lobes of the cortex, whereas in other cortical areas there occurs the slow electrical activity characteristic of an anesthetized condition.

If the state of electrical activity in a sated animal (Fig. 2.7b) is compared with the

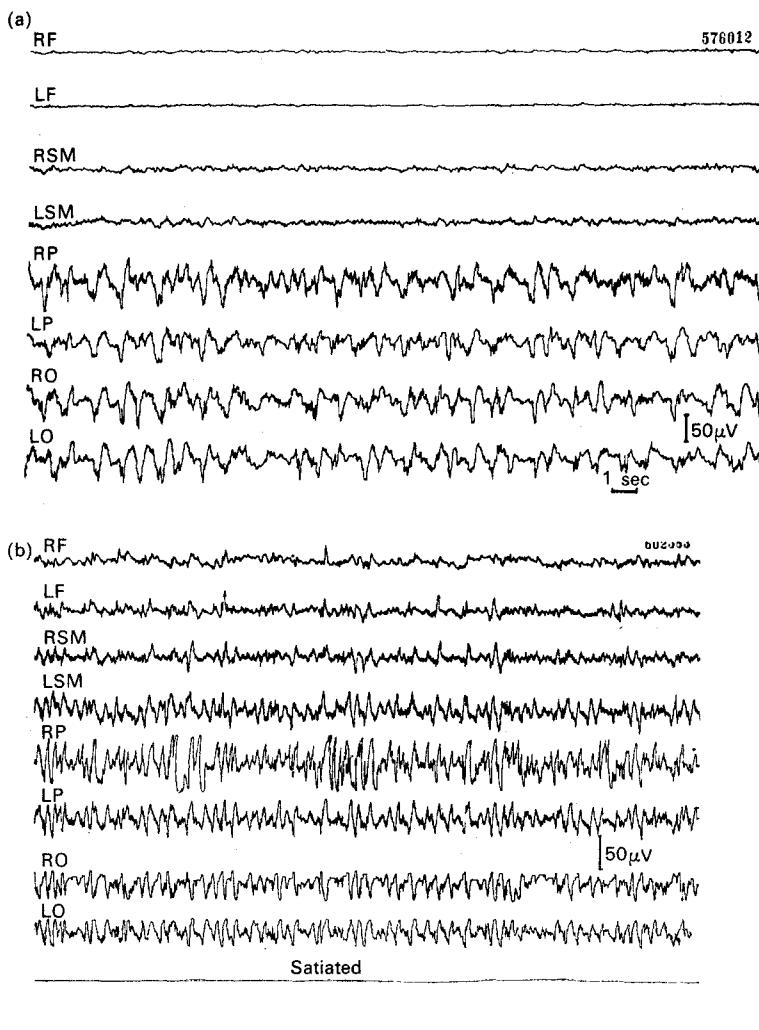


FIG. 2.7. Two electroencephalograms, recorded from the anterior areas of the cerebral cortex of a cat.

- (a) Before artificial feeding under urethane anesthesia.
- (b) After artificial feeding.

The electroencephalographic indices change from an active state (a) of the anterior areas of the cerebral cortex (RF, LF, RSM, LSM) to a slow electric activity (b). RF, right frontal region; LF, left frontal region; RSM, right sensorimotor; LSM, left sensorimotor; RP, right parietal; LP, left parietal; RO, right occipital; LO, left occipital.

activity in a fasting animal, it will become quite clear that hunger was the cause of this local desynchronization in the cerebral cortex. The electrical activity of the lateral hypothalamus, if it is simultaneously recorded with the cortical electrical activity, also exhibits considerable activation (Fig. 2.8). This experiment suggested that the hypo-

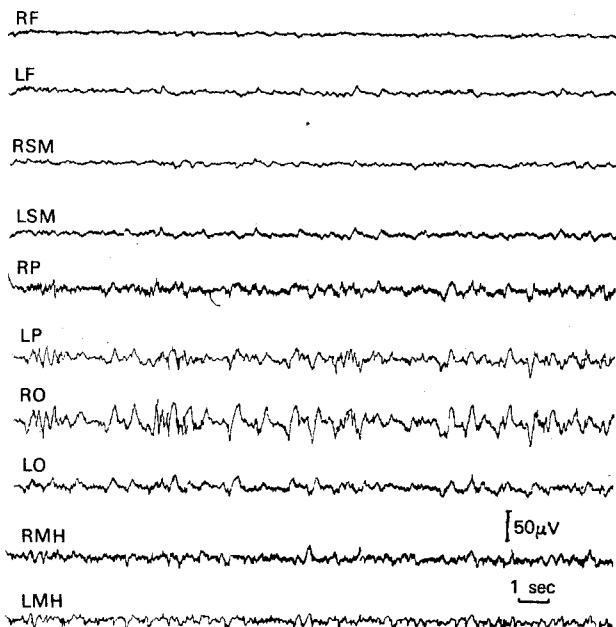


FIG. 2.8. This figure shows the coincidence of the activated states of the frontal areas of the cerebral cortex with the medial parts of the hypothalamus. RMH, right medial hypothalamus; LMH, left medial hypothalamus; other abbreviations the same as in Fig. 2.7.

thalamic region initiates the local activation of hunger in the anterior areas of the cerebral cortex.

These considerations were tested by coagulating the lateral nucleus of the hypothalamus with direct current. Immediately after the coagulation of those areas of the hypothalamus which exhibited desynchronization when the animal was fasting, the slow electrical activity corresponding to that of a sated animal was restored in the frontal areas (Fig. 2.9a).

Subsequently this procedure was improved. A simple anodic block of the lateral centers of the hypothalamus was quite sufficient for eliminating the activation of the frontal lobes and transforming the electrical activity into the slow type (Fig. 2.9b) (Sudakov, 1963). Thus, we acquired a means of reversible action on the hypothalamic alimentary centers, which in essence corresponded to surgical extirpation in the experiments of Anand and of Andersson, while considerably expanding the possibilities of experimentation.

The above-described phenomenon of the activation of hunger made it possible to confirm our propositions in special, somewhat unusual experiments which led to a solution of the problem under natural conditions. We decided to "feed" the hungry cat *under urethane anesthesia*. We reasoned as follows: if the fasting condition of the cat can cause an activated state in the frontal lobes of the cerebral cortex under urethane anesthesia, this means that the anesthetic, while blocking the neural substrate which

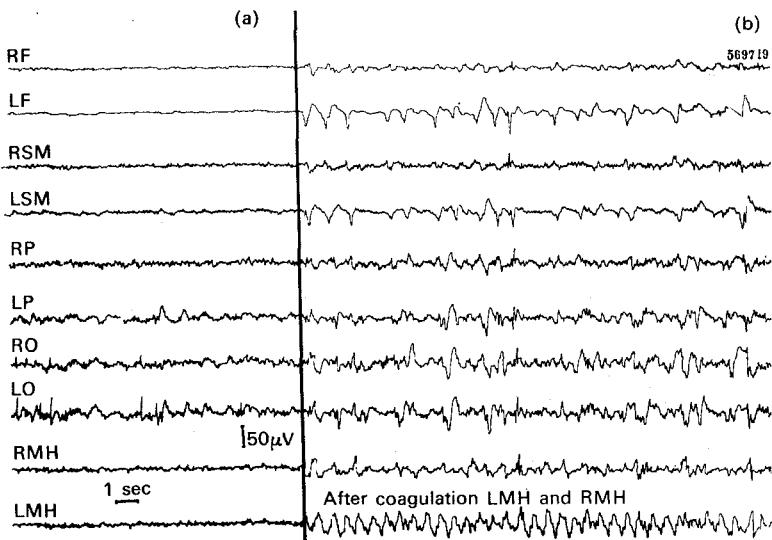


FIG. 2.9. Dependence of the activation of the anterior parts of the brain on the active state of the medial areas of the hypothalamus (relations of the pacemaker type).

- (a) Starvation activation of the anterior parts of the brain before coagulation.
 - (b) Recording of electric activity from the same points after anodic coagulation (1 ma for 0.5 min).
- Abbreviations the same as in Fig. 2.7.

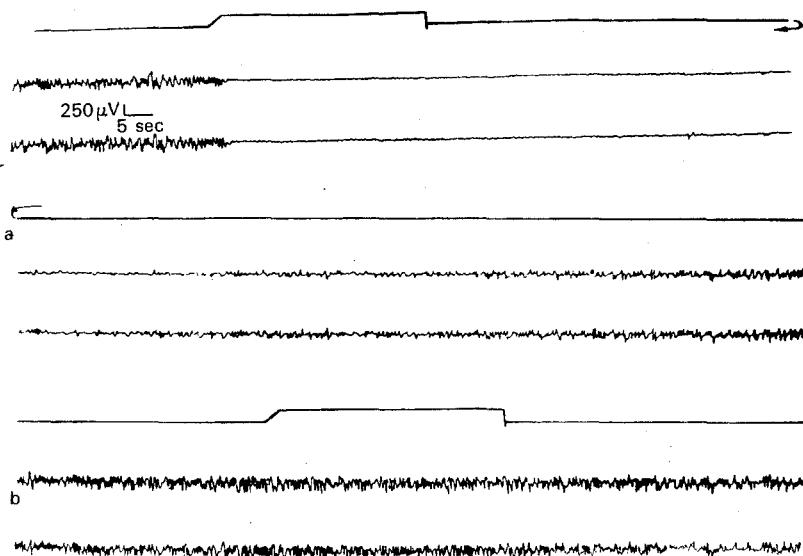


FIG. 2.10. The effect of nociceptive stimulation under urethane anesthesia. The stimulus evokes a distinct desynchronization over the entire cerebral cortex (a). The same nociceptive stimulation, applied on a background of the action of chlorpromazine, does not produce activation of cortical electric activity (b).

maintains wakefulness, does not block the substrate which at the cortical level evokes alimentary activation directed from the hypothalamus to the frontal lobes of the cerebral cortex.

This selective blockade of one quite specific activation ascending to the cortex, while leaving other ascending activities untouched, was not new to us; we had first observed it in the experiments of my collaborator Agafonov. It was shown in his experiments that in certain dosages urethane can block the ascending activation of wakefulness, yet at the same time allow nociceptive influences to pass freely to the cerebral cortex without waking the animal (Agafonov, 1956) (Fig. 2.10). These results, later supplemented by modified experiments of Shumilina (1956), Gavlichek (1958), Makarov (1960, 1961), and others, made it possible to formulate the concept of the biological specificity of ascending activations (Anokhin, 1958a).

Therefore, it was natural to think that if urethane anesthesia does not block the ascending alimentary activation which is generated in the hypothalamus, then the specific alimentary afferentation accompanying the intake of food can also be detected in the hypothalamus.

Experimentation has shown that these observations are correct: irrigation of the oral cavity with a food substance (milk), its introduction into the stomach, and intravenous injection of glucose, i.e., an attempt to imitate eating, resulted in elimination of the activation of the frontal lobes and its replacement by slow electrical activity. Thus, purely "afferent" satiety was produced, similar to our own satiety at the dinner table (Fig. 2.11). Once more I emphasize that this "satiety" was entirely produced under urethane anesthesia.

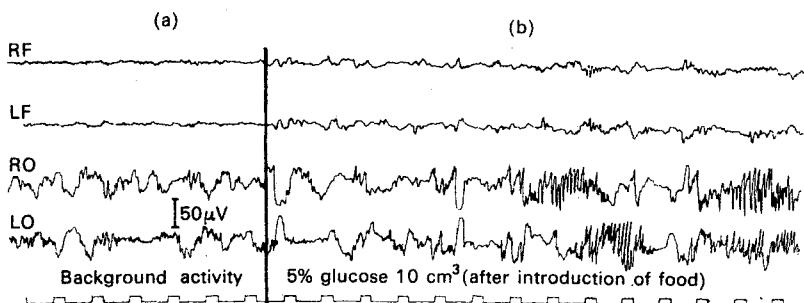


FIG. 2.11. After the introduction of milk into the oral cavity and into the stomach, together with the injection of glucose, there appears in the frontal parts of the brain a slow electric activity (b), whereas previously (a) there was a distinct activation in the frontal areas of the cortex. Abbreviations the same as in Fig. 2.7.

Since the alimentary activation of the frontal lobes was undoubtedly of a specific nature and was functionally connected with the neural substrate which was not blocked by urethane, we may justifiably conclude that this substrate, like the substrate that causes desynchronization by pain, differs radically in its *chemical properties* from the subcortical substrate which determines our waking state by its ascending activation.

This chemical characteristic of the hypothalamic mechanisms that maintain the alimentary activation of the anterior areas of the brain was particularly evident in experiments comparing the conditions of nutrition and pain in an animal (Fadeev, 1965).

As already mentioned, in a sleeping, fasting cat the desynchronization encompasses only the anterior areas of the brain, while in the remaining part of the cortex the usual slow electrical activity takes place. If on this background a nociceptive stimulation of the sciatic nerve is produced, the desynchronization becomes generalized over the entire cerebral cortex. Therefore, in evaluating this phenomenon, we may say that after nociceptive stimulation we have a summation of specific activations.

The injection of chlorpromazine under these conditions brings about a very clear dissociation of the two types of activation, emphasizing their chemical distinctiveness. After the injection of chlorpromazine, nociceptive activation no longer appears in response to nociceptive stimulation; on the other hand, the regional desynchronization of the frontal lobes that appeared on the basis of the fasting condition remains just as before (Fig. 2.12).

Thus, in the above-described kind of experiments it was obviously shown that unconditioned alimentary excitation has its own specific chemical basis, distinct from the chemical basis of the unconditioned defense reflex. Spreading in an ascending direction, this specific excitation acquires a definite physiological architecture which involves the cortical synaptic organizations on the basis of selective connections with the subcortex in accordance with the biological quality of inborn emotional states, and also on the basis of previous life experience which has expanded this architecture. Consequently, in this sense hunger is a specific biological condition which develops on the basis of the above-described biological principles and assumes the nature of a *distressing urge* to eliminate this condition ("food-procuring behavior").

Here it is most appropriate to ask the question: in all its stages is the development of hunger always connected with the same substrate? Does this substrate not change with the extent of food deprivation and with other factors?

In our laboratory experiments involving various periods of fasting, performed under urethane anesthesia, have shown that there is indeed a characteristic "dynamics of transformations." If the animals have been without food for two days, they usually exhibit the form of regional desynchronization which was described above (Sudakov, 1963). However, if the period of fasting is increased to 5 days, this desynchronization becomes generalized over the entire cerebral cortex (Panfilov and Loseva, 1964).

We began to suspect that the difference in the degree of generalization of ascending alimentary excitation over the cerebral cortex was related to a change in the interactions of the subcortical and cortical areas of the brain. The bases for this suspicion are quite obvious and follow from biological observation. Upon examination of a predator (which the cat is, by the way) in various stages of fasting, one will understand that hunger may be satisfied in different ways, with different amounts of effort, often with aggression and struggle. This means that these conditions must include the sympathoadrenal system as a system of stress, a system of action. If that is the case, then the secondary, i.e., generalized desynchronization, which appears after 5–6 days of fasting,

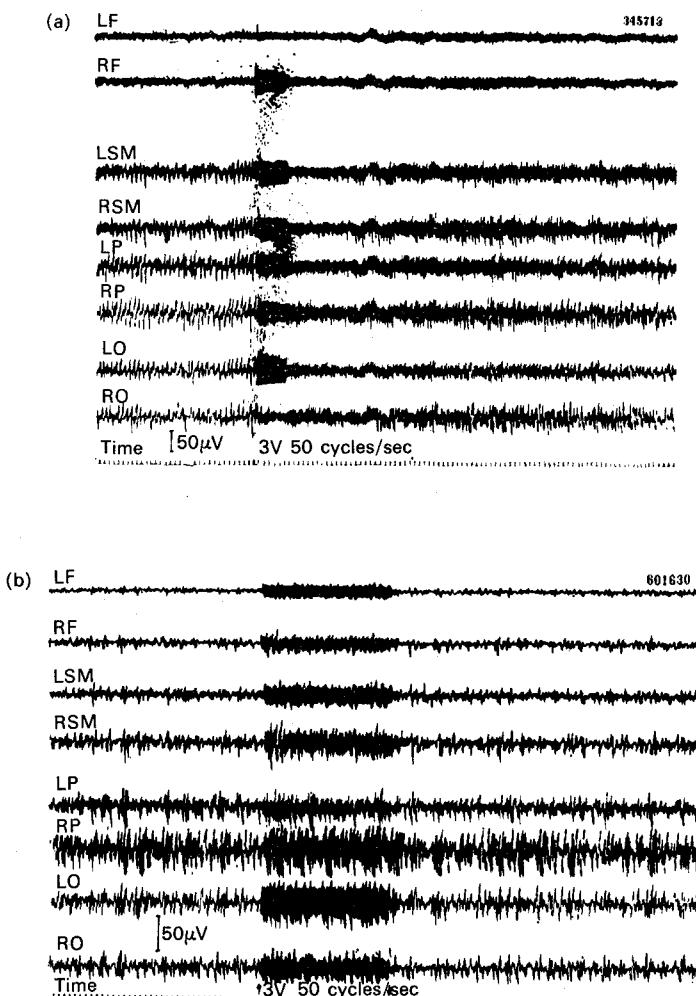


FIG. 2.12. The appearance of generalized activation after brief stimulation of the sciatic nerve by electric current (a). The same stimulation, however, does not evoke a generalized desynchronization after the injection of chlorpromazine (b). It is remarkable that chlorpromazine, while blocking pain activation, does not block the alimentary activation of the anterior parts of the cerebral cortex, and it remains the same as before the injection of chlorpromazine (explanations in text). Abbreviations the same as in Fig. 2.7.

must be of a different neurophysiological as well as neurochemical nature.

In order to verify our reasoning, we selected that test which was described above and which had revealed to us the *neurochemical differences between the unconditioned alimentary and defense reflexes*.

The reasoning for designing the new experiments was as follows: if the generalized desynchronization after 6 days of fasting is of an adrenergic nature, it should be blocked

by chlorpromazine, whereas on the basis of experiments by Panfilov and Loseva (1964), we should expect that regional, i.e., frontal desynchronization would remain unblocked.

These experiments have demonstrated that all the considerations presented above were correct. Chlorpromazine, administered under urethane anesthesia during the stage of generalized fasting desynchronization, blocks this secondary generalized ascending activation (desynchronization), transforming it into slow electrical activity, whereas the specific alimentary activation in the frontal lobes of the cortex remains unchanged (Fig. 2.13).

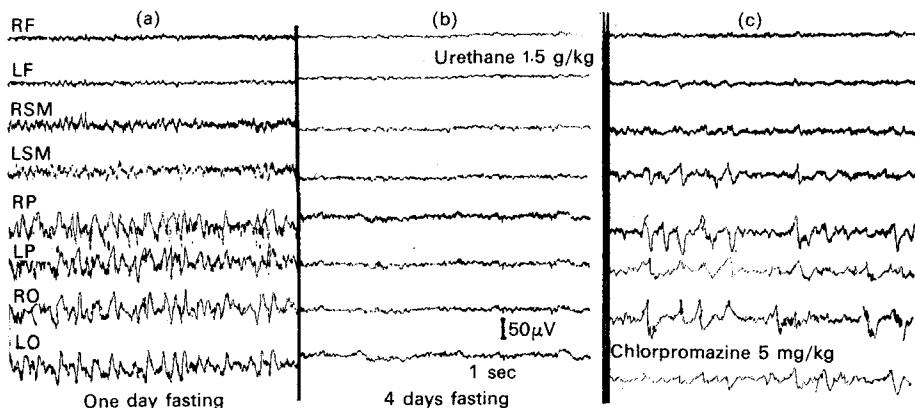


FIG. 2.13. Composite of electroencephalographic recordings, showing :

(a) One-day fasting; limited activation can be seen in the anterior parts of the cerebral cortex and slow activity over all remaining regions of the cerebral cortex.

(b) Four-day fasting; generalized activation can be seen over all regions of the cerebral cortex.

(c) The administration of chlorpromazine eliminates the generalized activation and leaves, as before, the alimentary activation of the anterior parts of the cerebral cortex. Abbreviations the same as in Fig. 2.7.

These results have shown an interesting principle in the patterning of integrated behavioral acts. It is quite possible that many specific biological reactions originate from their own specific pathways possessing definite chemoreceptor properties of the neural substrate. However, in the case of the development of any biologically negative condition, there occurs an involvement of those mechanisms of a predominantly adrenergic nature which, because of their universality, encompass all "troubles" of various origins. An important condition for this transformation is the appearance of some factor threatening the integrity of the organism. The transformation apparently takes place concomitantly with the transition from a condition of appetite to a condition of marked hunger.

The results of these experiments are instructive in another respect. They show that outwardly *uniform* desynchronization of cortical electrical activity may result from qualitatively diverse physiological conditions. Moreover, considering only the visible aspect of the generalization of the activated condition of the cortex in the case of a prolongation of fasting, it may be assumed that this generalization is of an intracortical

nature. This deduction follows from the generally held opinion that the origin of such an intracortical generalization may be a primary regional activation in the frontal lobes of the cortex. In any case, the traditional concepts concerning the spread of excitation over the cortex imply that this process is of a *horizontal* nature.

However, the results of the above-described experiments lead us to think that this generalization is of a *vertical* nature, due to the transfer of excitations from the specific alimentary center (hypothalamus) to the mechanisms of adrenergic activation (reticular formation), i.e., even at the level of the subcortex. This reveals one of the possibilities for the formation of cortical activity on the basis of multilateral subcortical interrelations.

Let us now return to our central problem of the reinforcing role of satiety (in the case of alimentary reinforcement) or of the satisfaction of any biological need in the elaboration of a conditioned reflex. On the basis of many experiments in Pavlov's laboratory, we can assert that the *reinforcing strength* of an unconditioned alimentary stimulus becomes greater with its increasing ability to *satisfy* the animal, i.e., to relieve the initial need.

What, then, are the physiological mechanisms of satiety?

The fact that satiety sets in during eating, before nutrients have reached the bloodstream, leads us to an important conclusion. We must admit that the afferent impulses that arise in the receptors of the tongue and digestive tract are alone sufficient to eliminate the sensation of hunger which preceded the intake of food. This satiety is afferent and may be called "primary" in contrast to "secondary," true satiety which sets in with the transfer of nutrients from the blood into the tissues.

This "afferent satiety" is especially evident in the newborn infant which quite suddenly ceases to suck, leaves the breast, and falls asleep. It is clear that this satiety is not caused by the direct action of the nutrients on the lateral hypothalamus, since the mother's milk is still in the stomach of the child. This is an example of *summational inhibition* of the cells of the lateral hypothalamus by the afferent impulses accompanying food intake.

From the physiological point of view, we must reason that the sum of the afferent influences from food intake must, in the form of unconditioned excitation, invariably inhibit those neural elements which in the state of excitation were the source of hunger. Many experiments have demonstrated that the lateral nucleus of the hypothalamus, excited by "starved blood," is such a "pacemaker" of hunger. Moreover, we should assume one more fundamental principle: the afferent (gustatory, esophageal, gastric) impulses arising from food intake correspond exactly to the extent of the initial excitation of the hypothalamic center; the sum of these impulses is capable of inhibiting the excitation of the hypothalamus, regardless of the strength of the excitation.

Thus, we can formulate an extremely important physiological proposition: *the afferent impulses arising from food intake proceed through a number of intermediate points toward the lateral nucleus of the hypothalamus and, overcoming the excitatory effect of the "starved blood," inhibit the cells of this nucleus.* As a consequence of the suppression of this "pacemaker" in the hypothalamus, an immediate disintegration of the entire alimentary functional system occurs. This system had maintained an integration of the vast number of sub-

cortical and cortical elements which had determined the sensation of hunger. This picture is in agreement with the result of the destruction of the lateral nucleus of the hypothalamus in the experiments of Andersson and Jewell (1957), of Anand *et al.* (1955), and of Brobeck (1957, 1960), and also with the experiments of Sudakov (1963) in our laboratory, involving anodic polarization of this nucleus (Figs. 2.14, 2.15).

To adequately evaluate these physiological relations, we must recognize the organizing role of the lateral nucleus of the hypothalamus in the integration of the entire organism. In connection with this I would like to direct attention to the theory of "motivated behavior" (Miller, 1958, 1963; Stellar, 1954; and others).

It can hardly be doubted that many behavioral acts are patterned on the basis of internal changes and the gradually increasing excitation of definite structural formations at the subcortical level, rather than in response to an external stimulus of the stimulus-response type. We are familiar with many situations when the internal state, and not an external stimulus, determines the form of behavior in animals and man.

These two forms of behavior can best be compared on the basis of a different need for a stimulus. Behavioral acts developing according to the stimulus-response principle can appear only if there is a specific external stimulus. However, in the case of motivated behavior, there first exists in the animal an internal state, resulting from humoral or nervous factors, which induces it to search for *an appropriate stimulus*. In order to fully understand this specific aspect of motivated behavior, which distinguishes it from be-

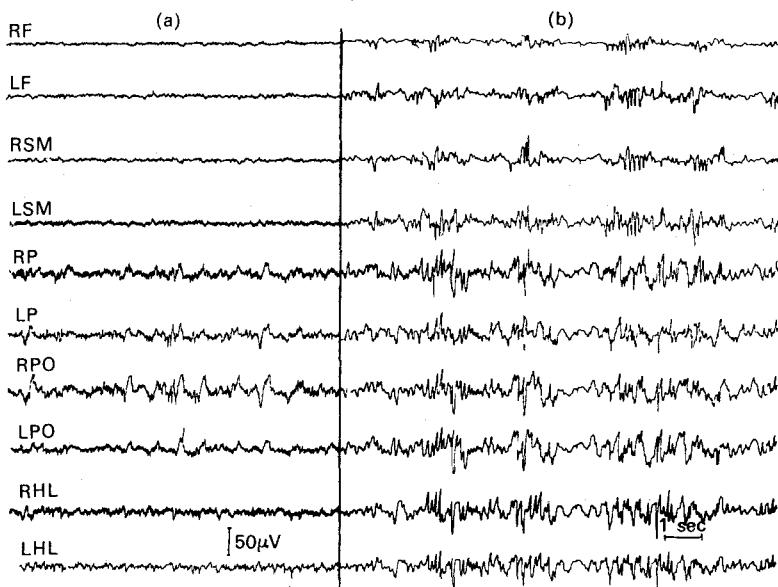


FIG. 2.14. Changes in the activated state in the anterior parts of the brain after anodic polarization of the lateral hypothalamus.

(a) Starvation activation after 2-day fast.

(b) The same recordings of electric activity after polarization of the lateral hypothalamus. RPO, right parieto-occipital, LPO, left parieto-occipital; other abbreviations the same as in Fig. 2.7.

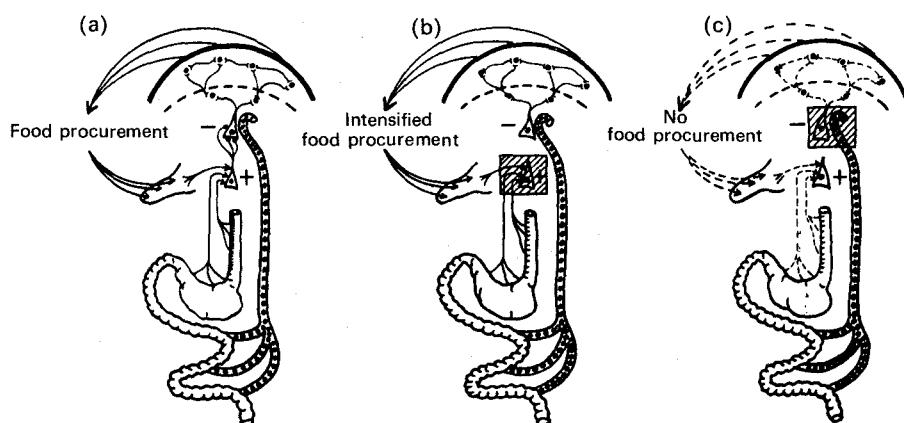


FIG. 2.15. Composite diagram, interpreting the experiments of Brobeck, Andersson, and Anand in the light of our concept of "sensory satiety." It can be seen that the alimentary behavior as a whole constitutes a cyclic self-regulating system with feedback afferentation from the receptor surfaces of the mouth and the digestive tract.

(a) Normal relations between alimentary motivation, food-procuring behavior, and feedback afferentation from the intake of food.

(b) The change in the same system of relations after destruction of the region of the hypothalamus which receives all afferent signalizations from the act of eating.

(c) The change in behavior after destruction of the region of the hypothalamus which receives humoral excitations from "starved blood."

havior in response to a definite external stimulus (e.g., to a previously elaborated conditioned stimulus), it is only necessary to visualize a predator which in a state of hunger prowls for days on end in search of prey.

Both forms of behavior, however, have a common basis—an initial level of general alimentary excitability. Without this initial state, under natural conditions an animal will not search for food, and under experimental conditions an animal will not respond to an applied stimulus with a positive reaction (Fig. 2.16).

Still another essential characteristic is common to both forms of behavior: they terminate in satiety, which sets in, as we have seen, *only on the basis of the sum of afferent impulses received during the process of food intake*. This "afferent satiety" shows that, in spite of the differences in the physiological architecture of alimentary behavioral acts, they have a single reinforcing mechanism, namely, the appearance of positive alimentary states terminating in the elimination of the initial distressing state which results from the stimulation of the lateral hypothalamus by "starved blood" (hunger→excitation during eating→satiety).

In view of the above considerations, the pioneering experiments concerning the alimentary center of the hypothalamus (Andersson, Brobeck, and Anand) also acquire a definite meaning. Indeed, if the lateral nucleus of the hypothalamus is destroyed, this eliminates the controlling center where the generation of neural discharges originates under the influence of "starved blood." Upon reaching a definite threshold value,

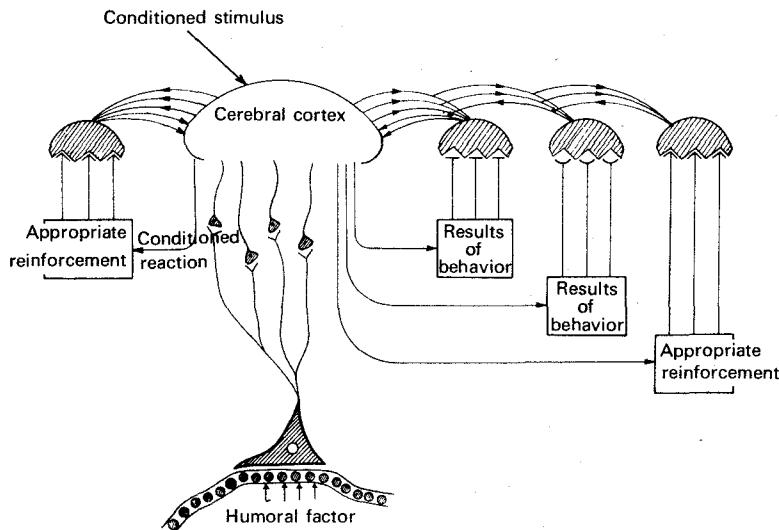


FIG. 2.16. Composite diagram of the relation between motivational and conditioned reflex behavior. It can be seen from the diagram that both forms of behavior are determined by the initial and universal factor of excitation by "starved blood," but the motivational behavior (the search for food) is directed by step-by-step afferentation until an appropriate reinforcing factor is found. On the other hand, the conditioned reflex receives immediate appropriate reinforcement.

these impulses normally proceed toward the cortex, selectively involving all those elements and cortical synaptic organizations which at some previous time were related to food intake and satiety. This ascending propagation of impulses from the lateral nucleus of the hypothalamus is what usually patterns the behavioral acts which in the past had resulted in satiety.

If we consider that all the phenomena in this biological series invariably appear in the same sequence (hunger—food-procuring behavior—feeding emotion—satiety), and also that satiety has a reinforcing value, i.e., one that associates the stages of this sequence, we can well understand motivational behavior according to the concepts of the Pavlovian school.

In fact, the state of hunger appears first in the series of the sequential phenomena indicated above. This means, however, that in a sequential series of phenomena when there is a crucial reinforcing phenomenon such as the state of satiety, i.e., the alleviation of the oppressive sensation of hunger, *all the factors preceding satiety must become conditioned signals of this satiety*. Thus we arrive at the seemingly paradoxical conclusion that hunger is a conditioned signal for satiety and, therefore, causes food-procuring behavior, just as a bell causes the dog to approach the feeder.

These sequences are most common in the natural life of animals and man. For example, the pain associated with a splinter entering the foot evokes a number of motor acts which terminate in the elimination of the painful sensation, i.e., *in a state of general satisfaction*.

Under experimental conditions an intentional combination can also be created in which an unconditioned nociceptive stimulus can become the signal of an unconditioned alimentary stimulus (experiments of Erofeeva, 1912a, 1912b in Pavlov's laboratory). The actual feeding of the experimental animal from the feeder can also be made a signal for the removal of the food a few seconds after feeding has begun, and then the animal, with amazing ingenuity, will remove all the food from the feeder, throwing it on the floor and filling its mouth with it (Strezh, 1937).

Thus, the usual sequence "need→search→satisfaction" is an extremely ingenious acquisition of evolution, which has conferred contrasting emotional states upon this essential cycle.

This constitutes the true physiological meaning of motivation and also the reverse associating effect of the last link of this triad which strengthens all beneficial behavioral acts of searching. This *reverse* reinforcing effect spreads on all pathways and combinations of searching movements with a definite gradient *from satiety to hunger*. The greatest "coupling" force exists between the state of satiety, or the alimentary emotion, and the afferent stimulating and motor acts closest to it.

In accordance with this rule, the reverse reinforcing effect resulting from satiety has a tendency to spread ever more widely over the synaptic organizations of the central nervous system, at the same time obeying the law of the greatest statistical probability of the concurrence of a given series of processes with the final moment, satiety (Fig. 2.17).

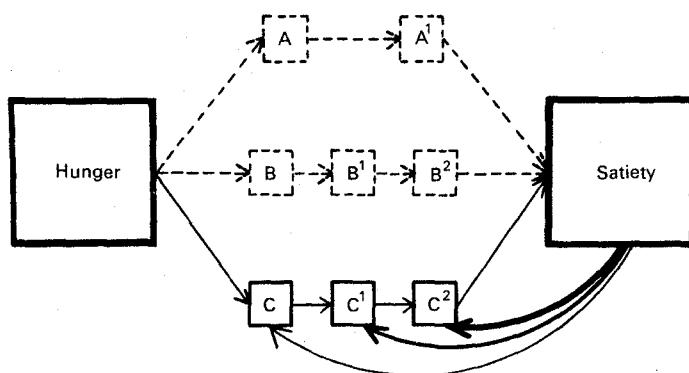


FIG. 2.17. Diagram of the relationship between two states of the organism, hunger and satiety, with emphasis on the reinforcing role of satiety. All preceding phenomena which have not terminated in satiety become inactive (broken-line arrows A, A¹, B, B¹, B²). On the other hand, all phenomena which have terminated in food intake and satiety, receive a feedback and ascending emotional activation which stabilizes the conditioned connection (solid-line arrows C, C¹, C²).

This statement can be supported by the case of a 3-year-old boy with a pathological craving for salt (Wilkins and Richter, 1940). This boy found at a very early age where the salt was kept and always tried to reach it himself. Moreover, the boy's first spoken word was "salt." These observations clearly demonstrate that the dominant motivation, which originates in the hypothalamic region, induces excitation in the cortical synaptic organizations in a very selective manner.

In this section we have established that the functional system of nutrition includes two antipodal states : hunger and satiety. Evolution has strictly limited the alimentary life of animals to these two states. All the other parts of this system are included in the period which contains all forms of food-procuring reactions that terminate in the elimination of the initial motivations. This constitutes the entire architecture of the alimentary functional system.

There remains, however, another great problem which must be solved in order to understand both the actual nature of the process of coupling of new connections and the mechanisms of joining numerous neurons into long chains which facilitate the conduction of anticipatory excitation.

Indeed, why does the excitation which arises from the afferent mechanisms of satiety have this reverse cementing capacity? Why do the excitations with this biological quality, arriving in the cerebral cortex, have the capacity to enter into "chemical coupling" with the traces of excitations that have just subsided? The answer to this problem is beyond the scope of this chapter and will be discussed in Chapter 4, which deals with the theories on the coupling of the conditioned reflex.

In conclusion, we shall now analyze one more important characteristic of afferent satiety which constitutes a universal law of animal life. I have in mind the seemingly paradoxical fact that the series of afferent impulses arising *only from the process of food intake* are capable of inhibiting the strongest excitation of hunger, which sometimes sets in at the highest level of stress involving the entire organism. How can this phenomenon be understood? Why are these afferent impulses that arise only in the exteroceptors of the tongue so strong?

Furthermore, this inhibitory action of the afferent impulses from the tongue can be adapted in a remarkable way to the level of the initial urge, i.e., to the level of excitability of all those conjugated cortical elements which together determine appetite and the state of hunger.

Indeed, it is well known that the sensation of satiety or that of quenching thirst can appear at any moment of eating or drinking. We can stop drinking when half a glass of water is left, or after finishing one glass we can request a second one. In other words, the afferent impulses accompanying the act of drinking are dosed very accurately according to the level of excitability of the basal hypothalamic nuclei, but they invariably inhibit this excitability, however strong it may be.

Let us try to understand the biological and physiological aspects of this phenomenon. If the ingested food or water should *immediately* alter the blood composition, the whole process would simply involve decreasing the strength of the initial stimulus, and satiety would be accomplished by the direct physiological elimination of the initial motivation. In reality, however, the afferent impulses arising during eating act as *substitutes* for true metabolic satiety, and their inhibitory strength, with respect to the humorally evoked excitation, appears to be truly remarkable from the physiological point of view. From the biological point of view this strength can be explained only by the fact that this afferentation is a *maximally reliable* signal of satiety which had been incorporated by evolution into the corresponding inborn morphological connections.

In relation to this we must point out that the specific physiological mechanism of this

inhibitory action of afferent stimuli on humorally excited centers must be based on special types of connections between the axons of the cells of the satiety center and the cells excited by the humoral factors of "starved blood."

Modern neurophysiology provides two possibilities for explaining such an inhibitory contact between centers. First of all we can think of those structural characteristics of the contact between nerve cells which was described by Lorente de Nò (1933b, 1935) as a specific apparatus of multiplication of nerve impulses. If one imagines that every impulse from the satiety center is multiplied into a long chain of discharges by means of internuncial neurons, it is quite possible to conceive that in the presence of a certain number of internuncial neurons the frequency of these discharges reaching the cells of the humorally excited center may be so high that we can obtain the phenomenon of pessimal* inhibition (pessimum of frequency). If such a system of internuncial neurons should act as a permanent mechanism, we could satisfactorily explain the ability of the satiety center to directly inhibit the hunger center.

The other possible explanation of the phenomenon of satiety could be related to the assumption that the synaptic endings of the axons coming from the satiety center always have a hyperpolarizing influence on the cell membranes of the hunger center. In this case any afferent impulses reaching the hunger center during eating would inevitably induce an inhibitory state in this center. This second assumption, like the first, can easily explain the proportional relation between the amount of ingested food and the appearance of satiety. Indeed, the duration of eating, being the cause of prolonged and massive excitation of the taste receptors, may be equivalent to the amount of inhibitory substance secreted at the cells of the hunger center. Consequently, with increasing humoral excitation of the hypothalamic cells that determine the state of hunger, there is needed a greater amount of inhibitory substances for the inhibition of these cells; therefore, eating must be prolonged, and there must be a greater amount of ingested food signaled by all the oral, the esophageal, and especially the gastric receptors.

Thus, both kinds of inhibition could be accepted as an explanation of "afferent satiety." Which one is the most probable could be demonstrated by direct experiments involving the injection of substances which block the hyperpolarization processes at the membranes of the neural elements. As far as I know, however, such experiments have not yet been performed. At this time it is only important to state that these interrelations of the two parts of the alimentary system are stable, inborn, and hereditarily determined.

This leads us to the formulation of the general principle that governs the physiological interrelations of the two neural substrates, one creating a *need* of an organism and the other *eliminating* this need, i.e., creating a state of satiety. It is quite evident that the absolute inhibitory strength of the latter substrate is a necessary condition for the survival of the organism and for the regulation of the rhythmic alternation between the two opposite states : need and satisfaction.

This alternation of strengths is apparently very widespread in the physiological dynamics of the organism and regulates the coordinated relation of animals and man to the environment. The general principle could be formulated as follows: *any condition of physiological need, however strong it may be, must always be weaker than the sum of the afferent*

* Reference to Glossary.

influences which arise from the mechanisms of satisfaction of this need. A physiological analysis shows that this principle applies to many types of behavior in animals and man. It may be stated that any motivated behavior follows this law. Otherwise, all the results of adaptive activity (for example, food-procuring activity) would lose their reinforcing strength, and thus the possibility would be excluded for the formation of long associative chains leading to the elimination of a given need.

If some processes of self-regulation of the organism are examined from this point of view, it will turn out that they, too, are based on the same principle which is firmly established in inborn neural relationships. For example, during the regulation of a constant blood-pressure level, we have, depending on the quantity of afferent impulses, an equilibrium between the pressor tendencies existing at a given moment and the automatic mobilization of the depressor mechanisms of the body.

It is clear that the normal condition of the organism, its well-being, depends on the fact that the sum of the possible depressor impulses from the wall of the aorta and from the region of the carotid sinus must always be greater than the sum of possible pressor influences on the vasoconstrictor center. Only with these inborn conditions is the normal organism potentially capable of reducing any sudden increase in the blood pressure and restoring its optimal state. On the other hand, in those pathological cases in which the pressor tendencies of the organism predominate, we usually have a tragic outcome in the form of hypertension, myocardial infarction, or brain damage. The delicate physiological mechanisms of these relationships have been studied in detail in our laboratory for a number of years. These data have been summarized and published by my students and me, and I refer the reader to these publications that he might become more familiar with the problem (Anokhin and Shumilina, 1947; Alvarez-Buylla, 1948, 1949; Anokhin, 1960a; Anokhin and Schumilina, 1962).

Let me emphasize that the above-mentioned physiological imbalance between a need and its satisfaction *creates conditions for reinforcing actions* and preserves the physiological constants at an optimal level throughout life.

In conclusion, this generalization may be symbolically stated. If we designate the maximally possible deviation of any physiological constant of the organism by the symbol "MD," and the maximal afferentation capable of suppressing these deviating influences by "MA," then the universal formula of life, which determines the appearance of satiety and the quenching of thirst, which lowers blood-pressure levels, etc., may be expressed as follows: $MA > MD$. This inequality can justifiably be called the "golden rule" of normal life.

Pathological conditions of the organism always begin at the moment when this beneficial inequality has a tendency to be transformed into an equality and, what is especially dangerous, into an inversion of the initial relationship.

From the broad biological point of view, the reinforcing strength of the unconditioned stimuli, which always leads to the optimal satisfaction of the organism, remains in force because the hereditarily determined inequality between the above-mentioned factors remains constant throughout life.

More intimate possible synaptic relations at the nerve cells, which correspond to the *reinforcing action* of the unconditioned stimulus, will be discussed in detail in Chapter 4.

CHAPTER 3

Systemogenesis as an Evolutionary Basis for the Development of Unconditioned Reflexes

In Chapter 1 we indicated that the signaling character of all phenomena of life is a universal property inherent in all manifestations of life, especially in the realm of nervous activity. Considering the relation of the conditioned and the unconditioned reflex in the classical sense, we know that the formation of unconditioned reflexes and the appearance of the first signs of conditioned reflex activity constitute a most important problem in the explanation of the behavior of animals and man in general.

At the moment of birth the organism enters the world with definite adaptive functions which we call "inborn" or "unconditioned" reflexes. However, even during the first days after birth all organisms exhibit such an extensive adaptive activity with respect to the environment that it is difficult to deny the existence of some individual, acquired experience. Nevertheless, we have many special investigations which comprehensively discuss the question of exactly when the first conditioned reflexes appear in newborn animals. In other words, *at what instant after birth does the structural and functional readiness of the nervous system of the animal set in for the implementation of coupling activity, i.e., conditioned reflex activity in its classical sense?* The various types of embryonic development of animals indicate that the question concerning the time of appearance of the conditioned reflex "in general" is unsounded.

While some animals are born completely incapable of independent life, for example, the young of the opossum, the newborn of such animals as the guinea pig lead an independent life and are capable of quite extensive adaptive activity even in the first hours after birth. It is clear that the actual moment of birth as a criterion for determining the time of appearance of the conditioned reflex, i.e., acquired adaptive activity, cannot at all be decisive.

The problem of the time of the appearance of the first indications of a conditioned reflex in newborn animals becomes even more indefinite if we consider the existence of a type of inborn activity such that, in spite of its evident inbornness, it develops according to the principle of signaling activity, i.e., on the basis of the universal principle of the formation of temporary connections. It is only necessary to refer to the reaction of the newly hatched rook, which reacts to distant signals by opening its beak (see Chapter 1), in order to see the extensive capacities of nature to solve the cardinal problem of *adapting the newborn animal most successfully to all the features of its ecology.*

Another example is the opossum, which develops in the mother's uterus for only 13

days. At this time the embryo is actually quite immature. Its extremities are so undeveloped that the individual toes are not yet differentiated, and its central nervous system is almost completely immature. However, those neural structures which must ensure the embryo's movement from the uterus into the pouch of the mother, where the fetus continues to mature, *are in exact systemic connection at this time*, and therefore the function of movement is successfully executed. This phenomenon could occur only if some systems of neural connections mature *with extraordinary acceleration and with complete harmony of their parts*. It is important to note that at this time there is here no acceleration of a maturing "organ." All the organs of the opossum fetus are immature at this time. However, under the conditions of accelerated heterochronous growth, some system of relationships proves to be matured exactly at the moment of the passage of the fetus from the uterus into the pouch. This is what we refer to as systemogenesis.

Our systematic investigation performed on living human embryos, removed from the uterus for various medical reasons, have convinced us that systemogenesis is a universal principle by means of which phylogeny and heredity adapt themselves to the characteristics of the postnatal existence of each species of animal.

For the newborn opossum with its completely immature brain, this adaptation involves quite active movements of the still unformed legs, leading to an accurate entry into the mother's pouch; for the rook, it consists of opening the beak and the maintenance of a definite posture; and for the guinea pig, the chewing of vegetable food. It is clear that in all these cases the actual moment of birth cannot serve as a starting point for evaluating the period after which the first conditioned reflex appears.

What, then, can serve as a criterion of the formation of the first conditioned reflex in its classical sense in the developing organism?

The literature shows that this question has largely been answered during systematic studies on the formation of the conditioned reflex in general. Visual and auditory stimuli are ordinarily used as the indifferent stimuli for the elaboration of conditioned reflexes, regardless of what role these stimuli play in the initial adaptive activity of a given organism. Figurin, perhaps the first to investigate this problem, used auditory and visual stimuli (Denisova and Figurin, 1925; Figurin and Denisova, 1925, 1949). In the work of Kasatkin, various combinations of stimuli of the same analyzers were applied (Kasatkin, 1935, 1948, 1951; Kasatkin, ed., 1964). We have seen above how different the ecological factors are which act on different animals, and how specifically different the readiness of the nervous system is for the patterning of external activity. This alone is sufficient to reject the customary point of view described above and to approach this problem primarily on the basis of the ecological characteristics of a given species of animal and the nature of its individual embryogenesis.

This approach was used for the first time in our laboratory by my collaborators Golubeva (1939) and Miliagin (1958). They have shown that the development of the first conditioned reflexes occurs with extreme rapidity for those indifferent stimuli having neural substrate which is the earliest and most completely matured by the moment of birth. This maturation depends on the conditions of the specific ecology of a given species of animal. It has thus been demonstrated that it is impossible to elaborate a conditioned reflex in a newborn animal of a given species without considering which

stimuli are *ecologically* significant for it, since the "unconditioned basis" for every species of animal is different, and the perceiving receptor zones are exactly adapted to its ecological factors.

A natural result of this approach to the evaluation of the first conditioned reflex connections was to focus attention on what the maturation mechanisms are for each vitally important activity of an animal during early embryogenesis. Knowing what these mechanisms are enables us to understand the development of the first conditioned reflex connections in the early postnatal period. It was clear that the development of the first conditioned reflex cannot be independent of the extent, rates, and characteristics of the maturation of neural structures in the particular species being studied. This approach, however, can be fruitful only when based on our knowledge of the true principles of the morphophysiological development of unconditioned reflexes in the prenatal period.

We must proceed from the fact that the vitally important adaptive activities of the newborn animal must be ready *by the moment of its birth*, since only their complete functional adequacy can ensure its survival on the basis of natural selection. We also know that every species must be prepared for its own particular ecology. At birth a squirrel, for example, must already have a complete set of appropriate adaptive acts; a newborn monkey must also have adaptive features but in a different combination; and a nestling must possess mechanisms to allow it to adapt to still different environmental conditions. Further, at the moment of hatching, each kind of bird must have a set of adaptive reactions suitable and characteristic only for this particular species. Chicks, immediately after hatching, begin to peck vigorously at seeds scattered on the ground, while the rook nestling for a long time passively accepts the food from its parents. However unique the adaptive activities of a given species may be, *they must necessarily be ready by the moment of birth*.

From these assumptions we may draw a very important conclusion which was our main guide during more than 30 years' study of the embryogenesis of nervous activity: if the forms of adaptive activity are different, i.e., if each individual newborn animal must be adapted to the particular ecological situation characteristic for it, then the mechanisms of embryogenic development of nervous activity in each individual case must be unique and specific for that particular species. A question naturally arises: what unites these different forms of embryogenic development of nervous mechanisms? That is, are there any common principles of development which govern all forms of adaptive reactions in different species?

Attempts have often been made to adequately formulate these principles. The most important and popular of these is the theory of Coghill (1929) which postulates that the initial form of activity of the organism is the "total" pattern of muscular activity of the entire body, termed "mass action." It is this total pattern, according to Coghill, which is the chief regulator of the whole development of differentiated forms of adaptive reactions. These differentiations of the more specific forms of activity take place *within* the already existing total pattern by the process of "individuation."

Briefly, Coghill's concept can be presented in the following manner. Studying the early development of the axolotl (*Ambystoma tigrinum* and *punctatum*), Coghill concluded

that behavioral acts develop during embryogenesis in such a way that initially an integrated act appears which, in the structural sense, is implemented by a definite "total" complex of neural connections ("total pattern") and from the first moment is therefore indivisible into any components. Any separate local reactions of the animal in the form of a leg lift in response to stimulation subsequently appear in the form of isolated reflexes as a result of increasing "individuation" within the limits of the initial total complex of behavior and under its constant control (dominance of the whole over the part). This theory of the primacy of the "total pattern" or "predominance of the whole" was subsequently extended to the embryogenesis of all species of animals, including man.

Coghill's theory had many adherents among both physiologists and pediatricians (Irwin, 1932a, 1932b; Barcroft, 1938; Barcroft and Barron, 1939; and others). At the same time the theory met objections which were based on contradictory data obtained in the course of such investigations as those involving the motor reactions of a newborn infant. These new data contradicted the principle of proximodistal development, which inevitably follows from Coghill's principle of the primacy of a "total pattern."

It is most important to note that Coghill developed his theory on the basis of his observations on only one genus, *Ambystoma*. Our own investigations of the development of nervous activity in embryogenesis which were performed on various species (fishes, *Ambystoma*, birds, mammals, and living human fetuses), demonstrated that Coghill's concept was incorrect.

Our basic premise, that *there are as many embryogeneses as there are species*, naturally leads to the conclusion that the common principle of embryogenic development of inborn activity can be formulated only by disregarding the enormous diversity of individual embryogeneses and selecting from among them the common features that may constitute a principle for all species. These considerations led us to formulate the concept of systemogenesis, the purpose of which is to compensate for the inadequacy of "morphogenesis," "organogenesis," "reflexogenesis," and, finally, the primacy of a "total pattern."

Even briefly I cannot present here all the experiments performed and published during the past 30 years by my colleagues and myself. I wish, therefore, only to state the fundamental premises and to present some results of our investigations.

THE THEORY OF THE FUNCTIONAL SYSTEM

Our work in the field of the embryogenesis of nervous activity is founded on the universal physiological *theory of the functional system* which was developed on the basis of our investigations concerning compensatory adaptations of disturbed functions of an organism (Anokhin, 1935). This concept will be discussed in greater detail in Chapter 6. Now we shall formulate certain properties of the functional system in its capacity as an integrative formation, only so far as this is essential to an understanding of the historic development of inborn activity in general.

Investigations have shown that any compensation of a disturbed function, i.e., the restoration of the beneficial and effect, can occur only with the mobilization of a consi-

derable number of its physiological components, which are often located in different parts of the central nervous system and the operative periphery but which are always functionally united for the purpose of attaining the adaptive effect. This type of extensive functional unification of differently localized structures and processes based on the achievement of the end effect we have designated the "functional system." We distinguish several types of functional systems characterized by different degrees of variability, i.e., by different capacities to change their structural bases and to plastically use different parts of the central nervous system. The functional system of respiration, for example, which is largely composed of inborn and stable interactions, has a very low degree of plasticity with respect to the choice of participating central and peripheral components (Anokhin, 1937, 1947). On the other hand, the functional system which provides for the locomotion of a body can show extreme diversity in the nature of its central and peripheral (muscular) components. We can, in fact, approach the same point by different means: by jumping, walking, moving on all fours, or somersaulting (like the rats which approached the feeder by barrel-like movements in the experiments of K. S. Lashley).

We consider that one of the important conditions for the unity of the functional system as an integrative formation, including both the central and peripheral structures, is the presence of *reverse afferentations* signaling the achievement of the beneficial end effect. This allowed us to regard the functional system as a closed physiological formation which has continuous reverse information concerning the success of a given adaptive action (Anokhin, 1935). In this theory, in fact, all the main features of the cybernetic closed circuit with a feedback were already anticipated. At that time we were mainly interested in the basic mechanisms of the integrative activity of the nervous system. For this reason we used the principle of the functional system as the unit of self-regulatory adaptations in the manifold activities of an organism.

We formulated the following basic characteristics of a functional system as an integrative formation:

1. A functional system is, as a rule, a central-peripheral formation. It maintains its unity on the basis of a circulation of information from the center to the periphery and back again.

2. The existence of any functional system invariably depends on the achievement of some clearly defined adaptive effect. This end effect determines the distribution of the impulses and activities over the entire functional system.

3. Another undeniable indication of a functional system is the presence of receptor mechanisms which evaluate the results of its action. These receptor mechanisms may be inborn, such as the chemoreceptors of the respiratory system or the osmoreceptors of the extensive functional system which regulates the osmotic pressure of the blood. In other cases they may be extensive afferent formations of the central nervous system which receive afferent signalization from the periphery concerning the results of the action. These central combinations, which act as the receptor of the results of an action (action acceptor), are dynamically created extempore during patterning of the functional system which adapts the organism to an unexpected situation. A characteristic feature of this afferent mechanism is that it is forming before the actual achievement of the results of the action.

4. Every adaptive effect of a functional system, i.e., the result of an action, forms series of *reverse afferentation* which report all the important indices of the achieved results. During the selection of the most effective result, if this reverse afferentation fixes ("sanctions") this action, then it is called "sanctioning afferentation" (Anokhin, 1935).

5. The functional systems, on the basis of which a newborn animal's adaptive response to characteristic ecological factors develops, possess all the above-mentioned features and prove to be mature just at the moment of birth. It follows that the consolidation of the components of the functional system must have been fully completed at some definite point of *prenatal* development.

Considering all the characteristics of the functional system described above and realizing that they are perfected by the moment of birth, we inevitably had to ask this question : *by means of what mechanisms and on the basis of what kind of processes can the innumerable components of the functional system, which differ in complexity and which often are situated far apart, successfully consolidate at the moment of birth?*

In the subsequent parts of this chapter we will analyze and characterize these specific embryogenic mechanisms.

HETEROCHRONIA OF GROWTH, THE FUNCTIONAL SYSTEM, AND SYSTEMOGENESIS

As we have said, an absolute factor of evolution which ensures the survival of the newborn is the perfection of its functional systems by the moment of birth. Each of these must necessarily include the following components which are already matured at birth :

- (a) the specific receptor apparatuses which receive the influences of ecological factors;
- (b) the conductive apparatuses which convey peripheral information to the central nervous system;
- (c) the central interneuronal (synaptic) interrelations which determine the most significant part of the integration of the complete effect;
- (d) the sum total of the peripheral operative mechanisms with their nerve endings (organ synapses), which make it possible to achieve the functional effect of the system;
- (e) the sum total of afferent apparatuses which together provide *reverse afferentation* concerning the degree of success of a given vitally important adaptive action of the newborn, i.e., information about all parameters of the obtained result, since only on this basis is a correction of inappropriate behavioral acts possible.

The biological specificity of embryogenesis lies in the fact that the slightest defect in the maturation of the functional system, in any one of these numerous and differently localized components, immediately leads to defects in adaptation. The law of natural selection then eliminates the defective individual.

A powerful agent of evolution, by means of which harmonious interrelations between all the numerous components of the functional system of a newborn animal are established, is *heterochronia* in the anlagen and rates of development of the different structural formations of the embryo. Heterochronia is a special, hereditarily fixed principle of

development by means of which the basic requirement for the survival of the newborn is implemented: *the harmonious interrelation of the structure and function of a given organism with the sudden influence of its characteristic ecological factors.* Thus, heterochronia in the development of fetal structures is one of the powerful means of implementing the "common principle of ectogenic development" as understood by the great naturalist Severtsev and his school (Matveev, 1939; and others). Heterochronia in the development of individual fetal structures serves the basic purpose of evolution: *to provide the newborn with fully matured, vitally important functional systems.*

This selective and heterochronous growth of fetal structures is not related to the uniform maturation of an organ as a whole (e.g., the brain), since it may involve only a few of its cellular elements and conducting structures which participate in extensive functional combinations outside the given organ. Thus the concept of "organogenesis," which still has a basic place in the theories of evolutionary morphology, does not explain the systemic character of the morphogenic process of fetal development. Neither does the concept of "organogenesis" encompass all the diversity of selective connections which develop between different organs and tissues during maturation of the functional system (Emel'ianov, 1963; Gauze, 1941; Vasnetsov, 1938).

All these considerations compelled us in 1937 to introduce the new concept of *systemogenesis*, which more fully explains and characterizes the above-described principles of the embryonic maturation of functions (Anokhin, 1937, 1947, 1948b, 1949a, 1949b, 1949c, 1949e, 1955a, 1956a, 1961a, 1961b). Thus, systemogenesis is the selective and accelerated embryogenic development of qualitatively and spatially diverse structural formations which provide a fully developed functional system to ensure the survival of the newborn. This selective consolidation of diverse structures of the organism into a functional system becomes possible only on the basis of heterochronia in the anlagen, in the rates of development, and in the points of consolidation of these structures throughout embryonic development.

One of the basic principles of life is the continuous development and progressive incorporation and substitution of its functional systems which ensure appropriate adaptation of an organism at different stages of its postnatal life. In regard to this we divide the heterochronous processes of structural development into two main categories: (a) *intrasytemic heterochronia* and (b) *intersystemic heterochronia*.

Intrasytemic heterochronous development represents the nonsimultaneous anlage and differing rates of maturation of the different components of the same functional system. This heterochronia is chiefly determined by the differing degrees of structural complexity of the functional system.

Intersystemic heterochronia pertains to the anlage and rates of development of those structural organizations which the organism will need at *different periods* of its postnatal development.

There is, of course, interaction and overlapping between the two types of heterochronous development, but this division into *separate* types ensures a correct perspective in the investigation of the heterochronous growth of the various structures of the organism.

As a general principle of development, systemogenesis is especially evident during

embryonic development since, during this stage, there occurs a condensed heterochronous maturation of many vitally important functions of the organism over a short period of time.

Systemogenesis, being the result of prolonged phylogenetic development and hereditary fixation of the most progressive forms of adaptation, enables us to understand the principles of transformation of organs and structures of the organism throughout the process of evolution (Golubeva, 1939). This concept is the common basis for the research interests of biologists, morphologists, and physiologists.

CHEMICAL PREREQUISITES FOR THE MATURATION OF THE FUNCTIONAL SYSTEM OF THE BRAIN

As a physiological structure, the functional system comprises, as we have seen, a great diversity of individual components which differ from each other in complexity of structure, type of tissue, and chemical specificity. The distinctiveness and the difference in importance of the components of the functional system are the basis for its heterochronous maturation during embryogenesis. The differing complexities of the components along with the *simultaneous* onset of their activity at the moment of birth as a mature functional system constitute the impetus which, during the process of evolution, has led to the selective initiation of anlagen and accelerated growth of individual structures; these characteristics determine intra- and intersystemic heterochronia.

Experiments have shown, however, that *structural* heterochronia, which prepares the establishment of the functional systems of an organism, is not actually the beginning of the heterochronous development of the components of the functional system. As a rule it is preceded by the biochemical acceleration and biochemical establishment of various prestructural formations. This can be clearly demonstrated in the maturation of synaptic formations with well-known physiological properties.

In individual cases we can note a marked temporal dissociation of those characteristics of synaptic conduction which are inseparable in the adult. For example, from experiments on adult animals it was concluded that the conduction of impulses through the neuromuscular synapse of the striated muscle and the sensitivity of that synapse to curare are inseparable.

In our laboratory, experiments performed during the early stages of ontogenesis show, however, that there is a phase in the maturation of the neuromuscular synapse during which impulses freely pass through it, and the animal easily performs locomotor acts. At this stage (the 32nd, according to Harrison) of ontogenetic development of the axolotl, curare does not produce its paralyzing effect; the axolotl can swim freely in a 1 per cent solution of curare. The same axolotl, however, immediately becomes completely paralyzed only 5 days later in the same solution of curare (Alekseeva, 1943).

The action of sedatives on the central nervous system shows this principle even more clearly. For example, during the postnatal ontogenesis of the rabbit one can observe a stage in the maturation of the cortico-subcortical interrelations during which pain-induced desynchronization of cortical electrical activity appears in response to stimulation of the sciatic nerve. This occurs on approximately the 10–11th day of postnatal

life. However, the injection of chlorpromazine, which usually blocks the pain-induced activation of the cerebral cortex in the adult organism, does not produce such blocking at this stage of development: after the injection of chlorpromazine, painful stimulation evokes, just as before, a desynchronization of the electrical activity of the cerebral cortex. After an additional 5–6 days, though, the injection of the same dose of chlorpromazine completely blocks the pain-induced activation of the cortex (Ata-Muradova, 1960b) (Fig. 3.1).

From these examples it can be seen that during ontogenesis there is, even at the molecular level, a heterochronous maturation of those chemical characteristics which are the action acceptors of various pharmacological blocking agents.

It is noteworthy that the usual conduction of impulses always matures earlier than do the chemical complexes of the synaptic protoplasm which are capable of accepting the action of *extraneous* drugs. This peculiar molecular dissociation is evidence that during the development of the conducting properties of the synaptic formations, the heterochronia of the structures is anticipated by an even more delicate heterochronia in the molecular groupings.

EXAMPLES OF HETEROCHRONOUS MATURATION OF THE COMPONENTS OF DIFFERENT FUNCTIONAL SYSTEMS

In our laboratory a detailed study was made of the maturation of various systems which ensure the basic, vitally important functions of newborn animals. By means of morphophysiological correlations the functional systems were studied which provide for sucking, respiration, grasping, food intake by birds, the relation between swimming and walking in the axolotl, etc. For all these investigations we used newborn animals of several species, including live human fetuses. The results showed that in all cases in which the appropriate systems ensure vitally important functions, the heterochronous maturation of different neural structures is always involved. All structures which by the moment of birth must constitute a functional system that fulfills a vitally important purpose originate and mature selectively and with acceleration. All these individual structures establish synaptic contacts with each other and eventually form a completely defined functional system which can provide the animal with the minimal useful adaptive effect, characteristic of that system and essential in the ecological situation of a given species.

Thus, the heterochronous maturation of structures during embryogenesis is a powerful agent by means of which evolution brings into simultaneous operation variously complex components of a system as a harmoniously consolidated functional system. It is due to this principle that the anlagen of the central interrelations of the nuclei of n. trigeminus and n. facialis, which are most delicate and important in the functional system of sucking, are already established at the stage of the unclosed neural tube (Tilney and Riley, 1938).

However, this heterochronia of development is not limited to the anlage of complete nuclei of the cranial nerves. If this process is examined in more detail, one can detect an almost infinite variety of stages of maturation in the different elements of these nerves.

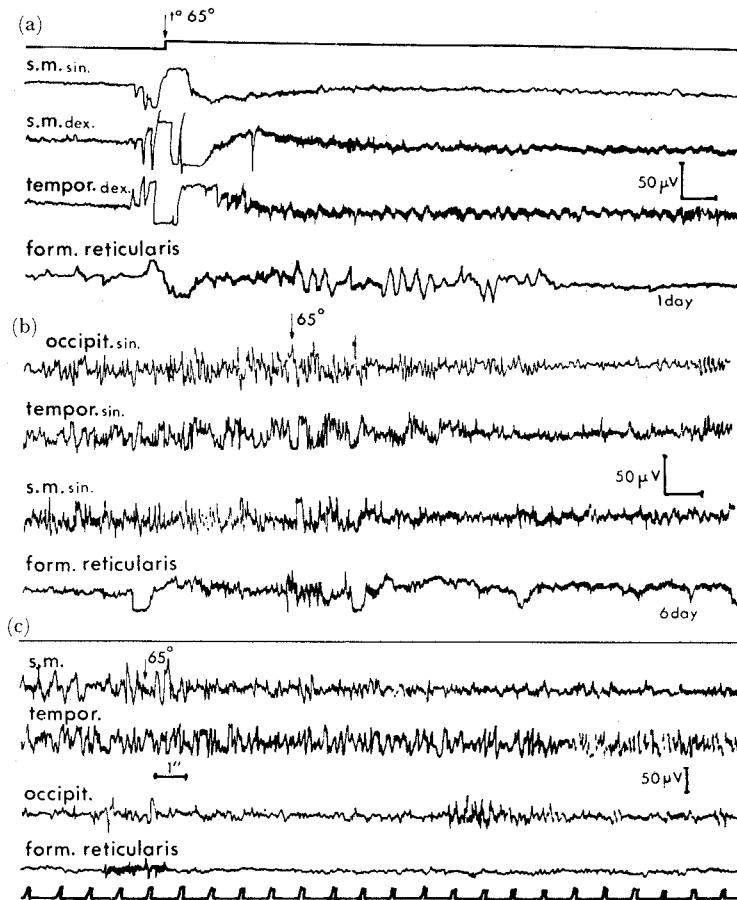


FIG. 3.1. Gradual changes in the electrical activity of the newborn rabbit and the appearance of subcortical sensitivity to chlorpromazine.

(a) Electrical reaction in the form of hypersynchronization to painful stimulation in the first days after birth.

(b) Reaction in the form of desynchronization at a later period when chlorpromazine has no blocking action.

(c) The appearance of the blocking action of chlorpromazine: pain-induced desynchronization is absent in the temporal area, but is still present in the sensorimotor and occipital areas. s.m. sin., left sensorimotor area; s.m. dex., right sensorimotor area; tempor. dex., right temporal area; form. reticularis, reticular formation; occipit. sin., left occipital area; tempor. sin., left temporal area; s.m., sensorimotor area; tempor., temporal area; occipit., occipital area.

This diversity is subject to one universal requirement of evolution: *vitally important functional systems must be established by the moment of birth, thus ensuring the newborn's survival.*

For example, n. facialis is a separate structure, but at a certain stage of embryogenesis extreme nonuniformity may be seen in the degree of maturation of the individual fibers that constitute this trunk (Fig. 3.2). The fibers going to m. orbicularis oris, which

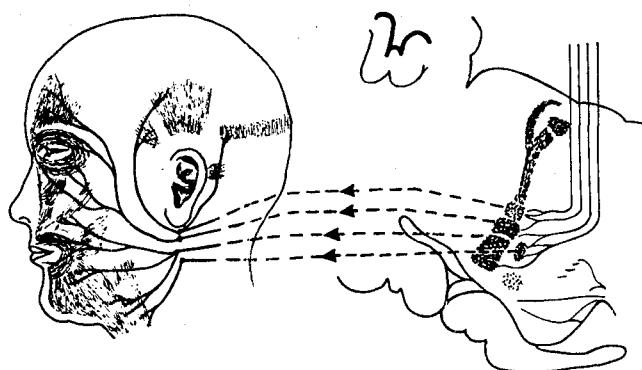


FIG. 3.2. Composite diagram of the accelerated growth and differentiation within the nucleus of the facial nerve, the facial nerve itself, and its neuromuscular connections with the facial muscles. After Pearson (1946, pp. 468 and 473).

provides the most important factor of sucking, a vacuum, prove to be already myelinized and to have formed a synaptic connection with the fibers of *m. orbicularis oris*. At the same time, no other facial muscles, especially not the frontal muscles, have such well-developed fibers and synaptic formations (Golubeva, 1961b).

Turning now to the nucleus of *n. facialis* in the medulla oblongata, we can see that here also the different cell groups mature and differentiate at different rates. While the parts of the nucleus which concern the functional system of sucking have already become fully differentiated, those parts which give rise to the frontal branches of *n. facialis* are only beginning to be differentiated (Golubeva, 1961a, 1961b, 1961c, 1962).

Thus, we see that, even within the limits of a single nerve and its center, there is a markedly accelerated maturation of the components participating in the vitally important functional system of sucking. Undoubtedly the same kind of differentiation occurs in all the other parts of the functional system of sucking, with a selective and accelerated maturation of its components.

The same principle also applies to the maturation of the reaction of suspension by the hands, which already appears during the 5th month of embryonic development and is closely related to the development of the grasping reflex (Fig. 3.3). The morphological basis of this reflex was studied in detail in our laboratory by Shuleikina (1958). She showed that of the nerves innervating the hand, those providing for the contraction of *m. flexor digitorum* mature first. At the stage when the *n. flexor* has already become differentiated, the other nerves, for example, *n. interosseus*, do not yet have this degree of differentiation (Fig. 3.4).

The various components of the grasping reflex were studied in detail in our laboratory with respect to both their functional and morphological aspects. The anterior horn cells of the 8th segment of the cervical region of the spinal cord, which control the flexion of the fingers, are completely differentiated as early as the 6th month of pregnancy, while the cells of the 5th segment of the cervical region of the spinal cord are still completely

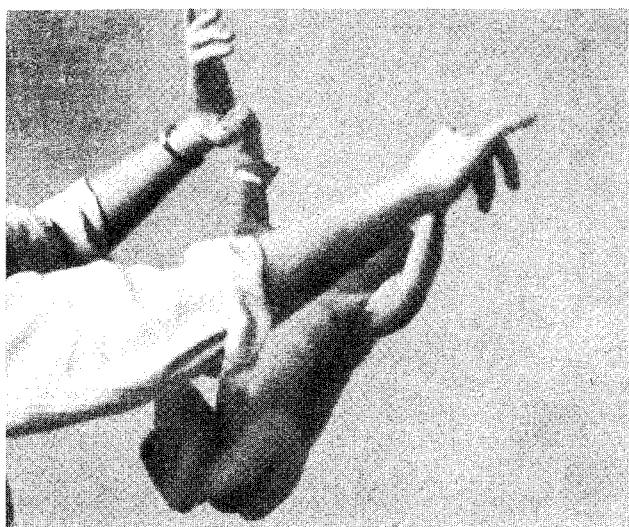


FIG. 3.3. Selective manifestation of the grasping reflex in the newborn.

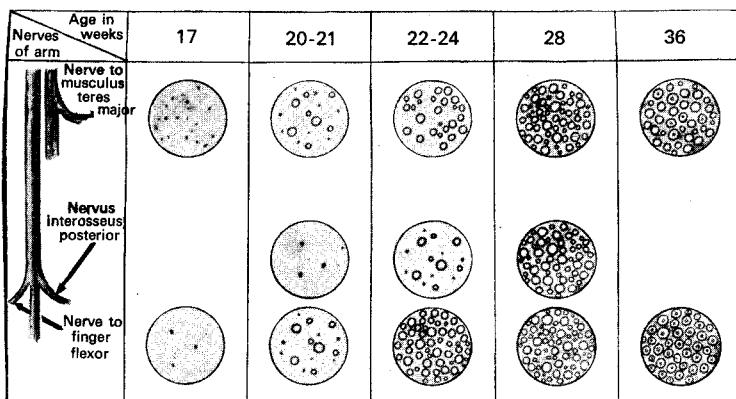


FIG. 3.4. Earlier maturation during embryogenesis of the nerve fibers ensuring the grasping reaction. For explanation see text.

undifferentiated. Here there is a manifest selective and accelerated growth of the motor cells which are directly related to *m. flexor digitorum profundus*, i.e., to the grasping reflex. If these morphological investigations were performed in more detail to include the descending control of the motoneurons of the 8th segment, it would be found that descending from the mesencephalon there is a conducting fasciculus whose fibers are distributed only over the 8th segment, i.e., where the motor cells which innervate *m. flexor digitorum profundus* are located. Since this fasciculus is the only one on the segments of the spinal cord at this stage, we have termed it the "primary fasciculus" (Fig. 3.5) (Shuleikina, 1959b). Its accelerated growth is direct evidence of the selective maturation of the

functional system which must be ready immediately at birth as it was in our remote ancestors, as well as in present-day monkeys, for the performance of a very essential function : *to hold the newborn on the mother's back.*

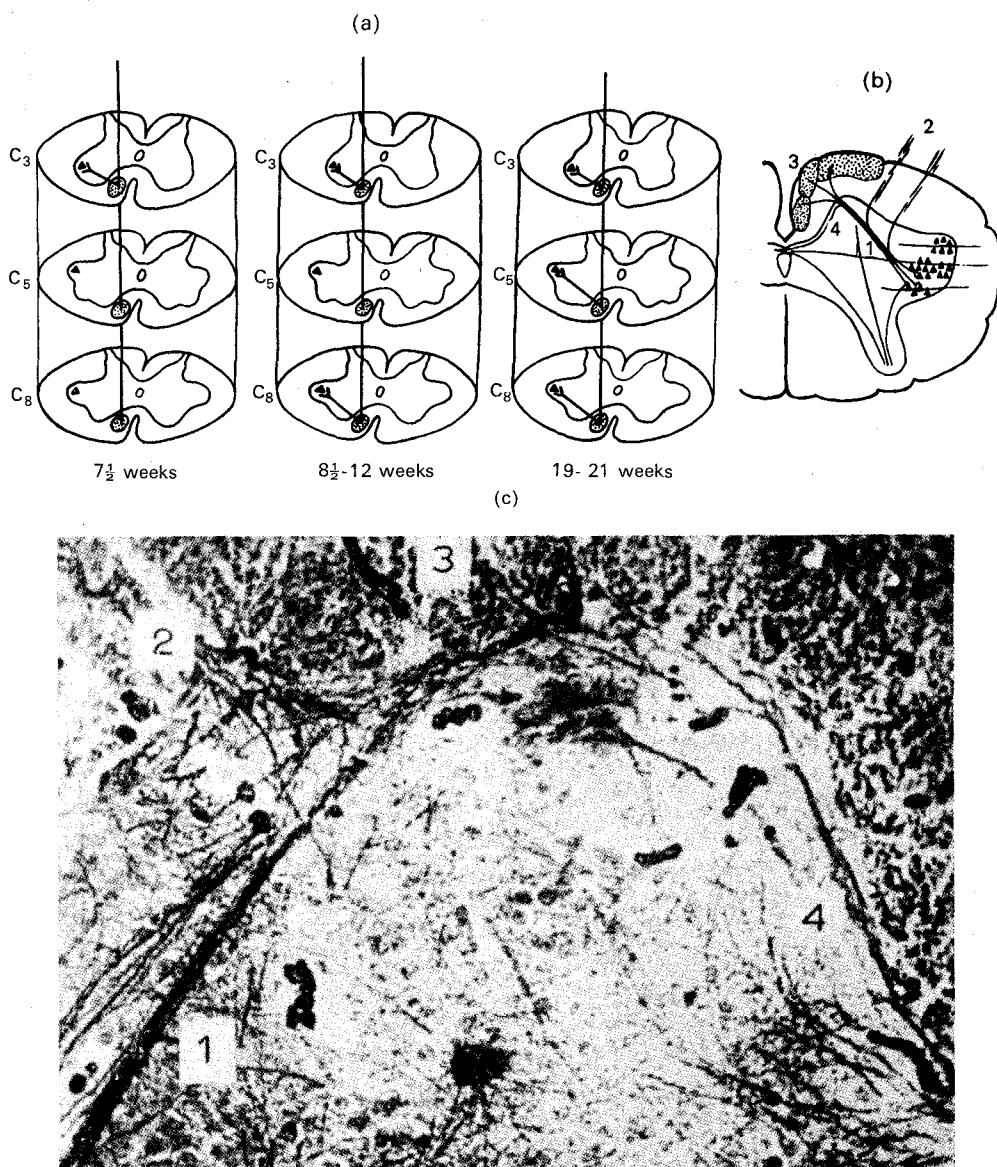


FIG. 3.5—(a) Heterochronic growth of the fasciculus descendens. The control over the motor neurons of C₃ begins to act much earlier than the connection at the C₅ and C₈ levels. (b) and (c) Cross-section of the spinal cord at the C₈ level. The "primary fasciculus," which goes from the anterior horns of the spinal cord to the motor cells of the flexor muscles, can easily be seen.

Perhaps the selective and accelerated maturation of the structures of the functional systems essential for the survival of the newborn is best exemplified by the embryonic and postnatal maturation of birds. For 12 years we studied the behavior of the embryos and nestlings of rooks (Miliagin, 1951, 1954, 1957, 1958). These birds illustrate exceptionally well the selective and accelerated maturation of the neural structures which must ensure the immediate adaptive reactions of a nestling to the specific factors of its ecology.

The investigations on the rook embryos were carried out from the first days of incubation until adulthood was attained, i.e., when the birds were able to eat independently. Rook eggs were taken from nests and incubated in the laboratory at a temperature of 38–39°C. Then observations were carried out on the embryos at different periods of development with subsequent morphological analysis of a given stage of structural maturation. This approach enabled us to diagram the sequence of maturation of different behavioral forms of the rook in relation to environmental conditions.

At present we shall discuss only the most characteristic reaction of the rook, on the basis of which we shall try to demonstrate the decisive role of ecological factors in the selective and heterochronous maturation of individual neural structures and behavioral acts.

The primary alimentary reaction of the rook is very distinct and constitutes a typical functional system with diverse components: opening the beak, thrusting up the head, and placing the entire trunk and neck in a vertical position (Fig. 3.6). As a whole, this functional system brings about the nestling's posture of readiness for food intake. The reaction of the nestling which we chose for analysis is an example of a widely ramified reaction which is accomplished with the participation of the entire central nervous system and the various organs. Since it appears in the rook nestling immediately after hatching, it is a good example of an *inborn reaction*, i.e., a reaction which has been completely patterned during the period of embryonic development.

Under laboratory conditions it has been demonstrated by our collaborators that the reaction of readiness for food intake appears immediately if the nestling, just hatched in the incubator and lying quietly in the "nest," is exposed to one of the following three stimuli: the sound "kar-r-r," which imitates the mother's call; moving air; and jarring of the nest. Investigations revealed an extraordinary degree of differentiation of this reaction with respect to the quality of the stimuli and the localization of their action, which we shall now discuss.

We first made a thorough study of the reaction of readiness for food intake in response to the sound "kar-r-r." The investigation was carried out in the following order: the acoustic spectrum of the mother's call was studied in a physics laboratory with regard to the frequencies of its component sound vibrations; then the readiness of the auditory apparatus (organ of Corti) of the nestling for the perception of pure sounds of different frequency was checked. A comparison of both factors enabled us to evaluate the sequential order of maturation of the nestling's auditory organ with respect to the natural sound constituting the specific ecological stimulus for the alimentary reaction.

These investigations produced an exceptionally interesting result. From the moment the nestling is hatched its organ of Corti is capable of converting quite definite frequen-



FIG. 3.6. General appearance of the result of the highly complex functional system which provides for the intake of food by the newly hatched rook. One can readily see the points of support and the strained contraction of the neck muscles which combine to ensure the orientation of the open beak towards the food. For the successful achievement of food intake, it is essential to have a precise coordination of numerous components which mature at the moment of hatching. Reactions in response to blowing air at the neck of the quietly reposing nestling are shown.

cies of sound vibrations (between 300 and 1600 cycles/sec) into nerve impulses (Fig. 3.7). Pure tones having frequencies outside this range do not evoke a reaction of the auditory apparatus during this period. The interesting point is that the natural sound "kar-r-r," which is the natural stimulus for the alimentary reaction of the nestling, *lies exactly within the range of those frequencies of which the ear of the newly hatched nestling is capable of reacting*.

This coincidence of two series of phenomena is a striking example of the exact correspondence between the *rate* of maturation of the individual receptor cells of the organ of Corti in the rook embryo and the acoustic characteristics of the natural ecological stimuli. These data provide the best example of the fact that the embryonic development of neural elements, i.e., the morphogenesis of neural connections, proceeds selectively and accurately "toward" those ecological factors which will act upon the nestling immediately after hatching.

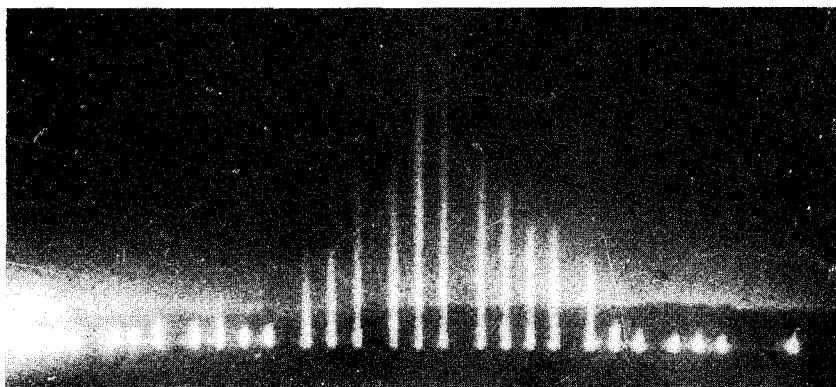


FIG. 3.7. Acoustic spectrum, recorded by means of a Siemens-Halske spectrograph, from the cochlear system of a newly hatched rook. Bands can be seen which exactly correspond to the frequency range represented in the sound "kar-r-r." Other vibration frequencies remain inactive, i.e., they do not produce an effect in the organ of Corti.

This is another example that the heterochronous and selective development of the different neural structures at different stages of embryogenesis is a reliable instrument for the adaptation of the newborn to the conditions of existence specific for it.

The action of moving air proved to be equally illustrative as a stimulus for the above-described alimentary reaction of the nestling. For a more accurate and localized stimulation of the nestling by moving air under laboratory conditions, we used tubes of different diameters which were connected to a blower. By means of this device we were able to stimulate extremely small body surfaces of the nestling with moving air.

First of all, the exact dependence of the appearance of the alimentary reaction on the location of the stimulation was demonstrated. The result was that *only blowing on the dorsal surface, especially on the occipital area, of the skin invariably evokes the alimentary reaction of the nestling, whereas similar blowing on the ventral surface does not evoke this reaction.* Considering that the nestlings lie in the nest with their heads down, there is again complete correspondence of the stimulating action of the air with the developmental characteristics of the nervous system and with the conditions of existence of the nestling after hatching.

This correspondence was equally striking upon testing different temperatures of moving air. Air, preheated to 42°C, *does not evoke the alimentary reaction* of the nestling when blown on the occipital area. Similarly, neither does placing the nestling in *calm* air at a low temperature (about 5°C) evoke the characteristic reaction. Thus, neither of these stimulating agents, movement of air or low external temperature, is capable per se of evoking the alimentary reaction. It arises as a result of the stimulation of definite zones of the skin only by a complex of simultaneous thermal and mechanical stimuli.

All these data were even more startling when we realized that these stimulating agents imitated exactly the identical aggregate of natural ecological factors acting on nestlings in a natural nest.

The same can also be said for jarring the nest as a stimulus of the alimentary reaction of the nestling. Only *sudden* and *sharp* jarring evokes the alimentary reaction, whereas a *slow* turning of the nest, through an even wider angle to the horizontal plane, does not evoke this reaction. The true meaning of this delicate differentiation of the alimentary reaction of the nestling to all the above-described stimuli became clear to us when we undertook a study of the behavior of rook nestlings in a natural nest and under natural conditions.

Placing a motion picture camera with a telescopic lens and microphone in a convenient position near the nest enabled us to observe the entire process of the feeding of the nestlings by their parents. The mother sits in the nest on the nestlings, and at the moment the father rook approaches with food, she gets off the nest and *begins to fan the nestlings strenuously with her wings, continuously emitting the sound "kar-r-r."* In response to these two stimuli the nestlings quickly assume the position for taking food, opening their beaks widely (see Fig. 3.6). The father alights on the rim of the nest, *jarring* it sharply, and places the food he has brought into the already open beaks of the nestlings.

We see, therefore, that all three kinds of stimulating agents which we studied in the laboratory (the sound "kar-r-r," the movement of air, and the jarring of the nest) are *natural stimuli* of the alimentary reaction in the nestlings, accurately reflecting all the conditions of feeding in the nest. It is in complete conformity with this ecological complex of stimuli that the selective and accelerated maturation of the receptor apparatuses and intracentral connections proceeds.

It is interesting to note that the simultaneous action of sound, movement of air, and jarring of the nest considerably prolong and stabilize the alimentary reaction of the nestling. This circumstance occurs under natural conditions, since at the moment the father rook alights on the edge of the nest, both of the other stimuli (the sound "kar-r-r" and blowing air) also continue to act on the nestlings.

We compared the behavior of the newly hatched rooks with that of the nestlings of other birds, for example, those which live in hollows (pied flycatcher, *Muscicapa hypoleuca*), under entirely different ecological conditions from those of the rook. The question naturally arose as to what constitutes the stimulus for feeding in this species of bird, i.e., the *stimulus for opening the beak*, without which food intake is impossible.

It is interesting that under these conditions the active stimulus proved to be the *darkening* of the hollow when the mother, as she enters with food, covers the only opening that admits light (Khaitin, 1963a, 1963b). It is evident that by the moment of hatching there has been a selective maturation of those synaptic formations which ensure the perception of a change in the amount of light in the hollow and direct the arising impulses onto the effector pathways, thus leading to the opening of the beak (Fig. 3.8).

Upon comparing all the above observations, we can formulate a universal principle according to which all the vitally important functional systems of the newborn animal are prepared during embryogenesis. This principle is as follows: *among the different structures of the organism which mature during embryonic development, those structures which ensure the primary functions essential to a given species of animal are distinguished by their accelerated growth and differentiation.* This acceleration may be so pronounced (as in the case of the grasping reflex) that only those structures which pertain to the primary functional

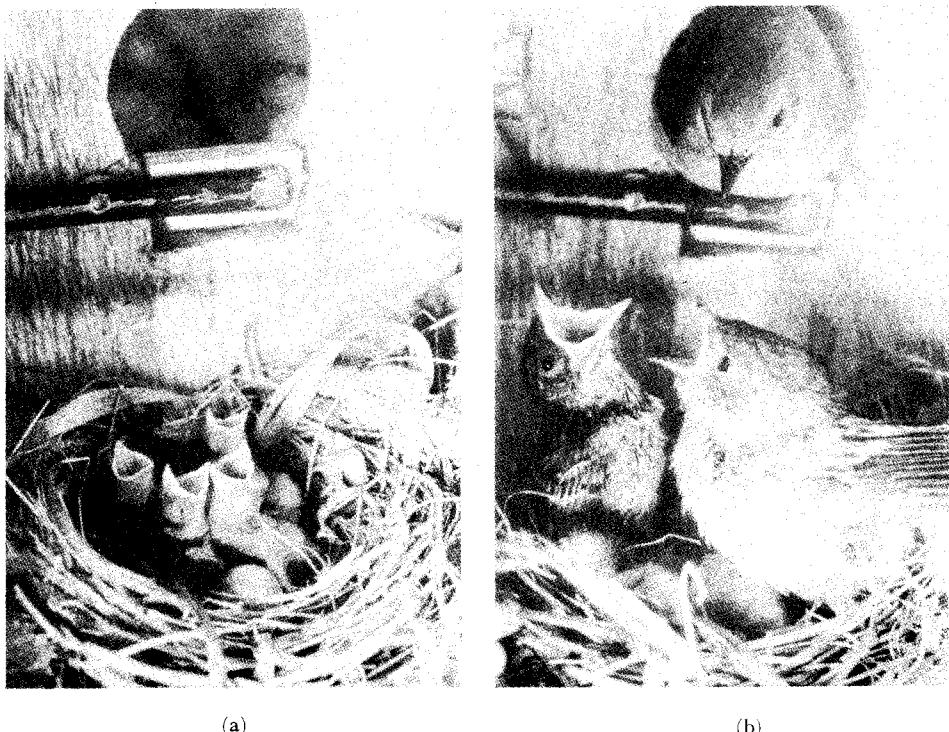


FIG. 3.8. Alimentary reaction of nestlings of the pied flycatcher (*Muscicapa hypoleuca*) in a hollow. The nestlings react to the faint sound emitted by the mother and to the closing of the opening (a). When older, the nestlings react to darkening as the main stimulus of the alimentary reaction (b). The pictures were taken by using a photoflash in the hollow itself.

system prove to be mature, while adjoining structures are still undifferentiated. Thus during embryogenesis all the functional components of an organ, such as an extremity or the spinal cord, do not mature simultaneously. Only those parts and structures of these organs which are essential for the implementation of a vitally important function *immediately after birth* mature selectively and more rapidly.

It is very important to note that while these components of various organs which are often anatomically very far apart originate and develop in some degree of isolation at first, subsequently they become consolidated and form an operative, synaptically connected functional system. As can be seen, the selective growth and maturation of structures is subject to the law of formation of the functional system essential to the newborn. Therefore, we have a development of embryonic structures which differs from that expressed in the concept of organogenesis, which assumes a more or less uniform maturation of organs as a whole. In contrast to a uniform maturation, there is rather an accelerated and selective maturation of those parts and structures of organs which must subsequently form a functional system independent of the maturation of the entire organs. This, then, is the new law of development which we have called *systemogenesis*.

SYSTEMOGENESIS AS THE REGULATOR OF THE DEVELOPMENT OF INBORN NERVOUS ACTIVITY

From the preceding sections it is obvious that within the embryo, there occur processes of accelerated and selective formation of the substrates which, upon subsequent unification, must provide an effective functional system with a positive adaptive effect for the newborn. The numerous investigations performed in the course of 30 years have completely convinced us that this growth of structures and this unification of selectively matured components are clearly of a systemic nature, since at the end of this whole process an effective functional system is established. For this reason we have called this law of development "systemogenesis." This term, it seems to us, is fully applicable to a process which leads to the formation of functions rather than of organs. In fact, while the arm as an organ has not yet fully developed due to the incomplete innervation of many muscles of the forearm in particular, the innervation of the flexors which provide for the grasping function has already been completed. The above examples furnish many illustrations of this law of the development of functions. In connection with the unequivocal law shown in all the examples taken from various classes of animals, the specific principles of systemogenesis were gradually formed; they have since guided our investigations.

It seems to me that in the solution of general problems of cerebral development, these principles can be equally applied to the investigation of both the embryonic and the postnatal development of functions. On the basis of these considerations, I can present the most important of these principles which guide the whole ontogenetic development of animals from the moment of anlage of a component in a system to the appearance of an effective adaptive function in the newborn animal:

The Principle of the Heterochronous Anlage of the Components of a Functional System

We discussed the essence of this principle in a previous section. Its meaning lies in the fact that the structural components of the functional system, regardless of their complexity or simplicity, must by the moment of birth constitute a functional unit, i.e., a functional system. Upon analysis of the interrelation of certain components of the functions, for example, locomotion, sucking, or respiration, we can say that any effective distribution of muscular exertion at the periphery in all these three functional systems requires a very delicate integration in the central nervous system. The central nervous system, which forms part of any of these functional systems, must bring about the complex process of integrating the act as a whole by regulating the spatial and temporal interrelations in the action of its components. Thus, in the sucking act, for example, if the facial muscles which create a vacuum in the oral cavity begin to contract before it has been sealed by the contraction of *m. orbicularis oris*, this functional system will naturally have no positive effect. Therefore, the central excitation must be accurately coordinated by means of very delicate synaptic formations at the cells of the corresponding center.

In view of all these considerations we must admit that the most delicate component

of the functional systems of sucking or respiration is its central component. One must therefore admit it to be phylogenetically purposeful that in most cases the neural centers are formed and start to mature before the substrate they innervate (Fig. 3.9). In this sense the development of muscular tissue, for example, is incomparably simpler and more rapid than that of the central apparatus which will subsequently integrate these muscles. Our observations show that the formation of synapses with delicately selective interrelations of cells is especially important. A slight discrepancy in these interrelations is sufficient to disrupt the function of the entire complex of organs and structures which unite in its execution.

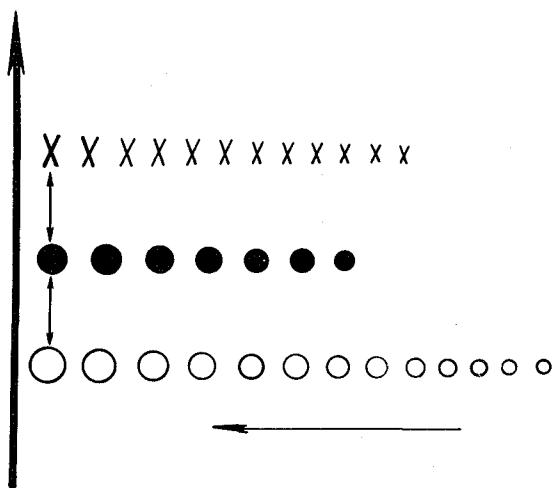


FIG. 3.9. Diagram demonstrating the different moments of initiation and the different rates of maturation of various components of the functional system of sucking. The individual components of the functional system are designated by different symbols: Circles—central integration; solid circles—muscular elements; crosses—nerve trunks. The heavy vertical arrow indicates the moment of birth. The larger symbols before the moment of birth show the readiness of the components and their consolidation into an integrated functional system.

To my knowledge, no systematic investigation of the rates of appearance of the various functional systems of a given species of animal has yet been performed. Thus, it seems necessary to call attention to this important principle by which the functional systems of the organism reach full development precisely by the moment of birth. It is possible that many cases of perinatal inadequacy of functions may be related to insufficiently accurate timing of the anlage and development of the individual components of the functional system.

The Principle of Fragmentation of an Organ in the Process of Embryonic Development

As stated above, systemogenic development necessarily assumes a nonuniform structure of an organ at each particular moment of its development. Those components

necessary for the organization of a vitally important functional system by the moment of birth will develop first. This is clearly apparent in the selective innervation of the facial muscles. Similarly, in accordance with this principle, any peripheral nerve will mature with respect to the composition of its fibers. Thus, throughout ontogenesis an organ has heterochronous anlagen and different rates of development of its individual components (Fig. 3.10).

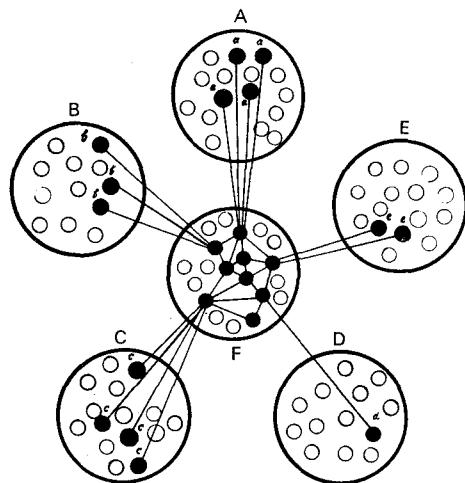


FIG. 3.10. Diagram illustrating the process of fragmentation of organs during the development of a particular functional system. A, B, C, D, E: individual organs in which there is a singling out of the structural elements a, b, c, d, e, which undergo accelerated growth and consolidation on a background of overall maturation.

Another illustration is the previously discussed case of the maturation of the parts of the organ of Corti which interpret the sounds in the mother's call "kar-r-r." In the later life of the rook, all parts of the organ of Corti will, of course, be fully developed. However, at this moment it is fragmented in accordance with the immediate requirements of postnatal adaptation.

One further example may be cited. A comparison of the developmental rates of the cellular elements of the spinal cord in the chick and rook embryos shows that the differentiation of these elements in the cervical and lumbar segments proceeds very differently in these two species. While in the chick the cellular elements and interneuronal connections are differentiated more rapidly in the lumbar segments, in the rook the differentiation is more pronounced in the area of the cervical segments. Here there is an obvious fragmentation of the spinal cord as an organ, but this fragmentation is clearly related to the ecological characteristics of each species of bird.

It seemed to us that it would be important for more direct investigations in this field to emphasize this characteristic of nonuniform development of the organs of the body, especially since this nonuniformity both in time of anlage and rate of maturation can be so great as to lead to "local reflex activity." It follows that the "local reflexes" are only parts of extensive functional systems which have matured selectively and at an accelerated rate.

The Principle of Consolidation of the Components of the Functional System

The moment of consolidation of the functional system is a critical point in its development. To illustrate the processes which the functional system undergoes at this time, I shall describe one functional system studied in great detail in our laboratory. I refer to the functional system of jumping in the guinea pig. The biomechanical architecture of this act is such that the load on the different extremities is quite unequal. Since the body moves forward by means of pushing off with the hind legs, these naturally exert the greater effort. Observations on fetuses of the guinea pig at the age of 23–25 days show that at this stage, touching the face of the fetus with a bristle immediately evokes the coordinated act of pushing off with the hind legs, but with very limited participation of the trunk. We made detailed morphophysiological investigations of all the stages of development of this functional system, particularly the moment of its consolidation, since its components (the front and hind legs), actually being at opposite ends of the body, provide the investigator with great advantages.

The descending pathway, having its cells in the brain stem, gradually grows toward the lumbar segments and establishes synaptic connections with those motor elements of the lumbar segments which have become previously differentiated and connected with the periphery. Thus, the brain stem, having established highly delicate synaptic connections in which the architecture of the future function of jumping is reflected, gradually takes control of the lower segments of the spinal cord. The descending pathways establish selective synaptic connections for the individual motoneurons of the lumbar segments. These new conditions radically change the previously established relations at the segment. Controlled by the descending pathway, the components of the segmental neuronal units acquire a quite definite role in the functional system, which is integrated at the level of the brain stem.

There are several indications that a descending neuron of the brain stem, which has reached the lumbar segments, radically alters the relative importance of the components of the system. For example, during the development of the spinal segments of the guinea pig, the principle of the axial gradient holds to a certain extent, i.e., the anlage and differentiation of the brachial segments occur somewhat earlier than those of the lumbar segments, even though both are heterochronically accelerated in their development in comparison with the other structural formations of the spinal cord. However, as soon as the descending pathways originating in the centers of the brain stem reach the brachial and lumbar segments, the relative importance of the latter suddenly changes. The lumbar segments acquire special strength and assume the leading role in the functional system of jumping.

This sudden reevaluation of the individual components of the functional system at the moment of their consolidation is a direct result of the structural characteristics of this functional system. We have seen many examples of such a reevaluation of the proximodistal principles of development at the moment of consolidation of the functional system. For example, the initial stage of the development of the human embryo (8 weeks) is characterized by the fact that all the neurons growing through the plexus brachialis to the upper extremity reach the muscles in exact accordance with the law of proximodistal development, with the acceleration in the development of the flexor

nerves which we mentioned above. However, *the predominance of flexion as a component of the functional system begins only when the descending pathways from the brain stem (the primary fasciculus) reach the motor elements of the 8th segment.* From this moment on, the relative importance of the distal and proximal parts of the arm in the system changes radically. Grasping with the fingers and clenching the fingers, although occurring in the distal part of the extremity, nevertheless assume the leading role in the whole functional system of grasping and maintaining the body in a suspended position.

Thus, we see that the moment of consolidation of the separately maturing components of the functional system is an exceptionally important and critical one: the central component of the system, which gives this system its final physiological architecture, immediately assumes the leading role. Due to this importance of the moment of consolidation, we believe that it must be thoroughly investigated in order to reveal the individual characteristics of the various functional systems and the activating order of their individual components. Here the question arises as to which parts of the functional system are already prepared for consolidation, and which parts cannot yet be consolidated. In the following section we shall try to answer these questions.

The Principle of the Minimal Ensurance of the Functional System

This principle, exemplified in the development of functional systems, is a tremendous achievement of evolution and probably expresses one of the most perfect forms of achieving success in the struggle for the "norm of survival." The essence of this principle is that the functional system as seen in the adult animal does not immediately appear in this complete form. The first to unite are those structural parts of the individual components of the system which have already matured by the moment of consolidation. For this reason the functional system, after entering the period of consolidation of its components, becomes effective *long before all its components are structurally developed.* As a result, the functional system assumes an adaptive role in the life of the newborn before having completely and finally matured.

We may recall here the action of curare on the axolotl. The conduction of nerve impulses through the synapse had begun long before the molecular structure of the synaptic formation had completely matured. It is interesting that it is possible to observe a moment when curare has already begun to paralyze the gills and the anterior part of the trunk, and yet the axolotl still swims by means of peculiar movements of the caudal part of the trunk. It is clear that by means of the accelerated consolidation of individual, probably very minute fragments of the functional system, the organism avoids the risk of being unprepared in case of a sudden interruption of embryonic development.

We had the opportunity to observe for some time a premature human infant which was born alive weighing 560 g. This infant, although immature in all respects, nevertheless performed coordinated sucking movements and sucked up approximately 10 ml of milk. The infant lived for 42 days, and during this time we could observe a definite improvement in its functional system of sucking. It is clear that in this case a consolidation of the individual components of the functional system had occurred. Some

fraction of the central cells became integrated, and some portion of the peripheral nerves related to sucking had established functional connections with individual muscle fibers. We know, however, that in the normal full-term infant this act is accomplished much more vigorously and with a greater adaptive effect. Therefore, in the premature infant which we observed, only some of the possible connections had been established at the time of its premature delivery.

Upon comparison of all our data we can note one especially interesting fact which is conspicuous in evaluating the principle of the minimal ensurance of the functional system: the consolidation of the functional system begins in a far from disorderly manner and in such a way that all its components do not mature or consolidate simultaneously. On the contrary, only some structural units mature so that *they are ready to unite into a primitive, very imperfect, but nevertheless structurally complete functional system* (see Fig. 3.10).

Of all the principles we have studied, it seems that the principle of the minimal ensurance of the functional system has a profound biological significance, since all further development of the functional system proceeds from this already functioning nucleus. Because of this principle the animal can survive even under conditions in which for any reason it must start an independent life. In spite of the great importance of this mechanism, its study has only begun.

THE ONTOGENETIC DEVELOPMENT OF ASCENDING INFLUENCES ON THE CEREBRAL CORTEX

Until now we have considered the principles of development of entire functional systems which constitute the basis for the successful adaptive activity of newborn animals and consequently for their survival.

Among the components of vitally important functional systems, the central integrating component is usually located in the central nervous system and has decisive importance for the structural features of the functional system and for the spatial and temporal distribution of the activities of all its components. This distribution of activities must always be such that the activity of a functional system as a whole inevitably terminates in a positive effect which is specific for this functional system. The slightest discrepancy in the times of activation of the various components can lead to a complete disintegration of the processes of the entire functional system and to a loss of the final adaptive effect.

It follows that the heterochronous processes of growth and maturation *within the central nervous system* simultaneously indicate both *intra-* and *intersystemic* heterochronia. Thousands of functional systems of different adaptive significance interweave in the brain, particularly in the cerebral cortex. In view of this it is quite difficult to sort out the structures pertaining to each of these functional systems. This can be done rather easily for the functional system of sucking, considering its early maturation and relatively simple structure. It is far more difficult, however, for functional systems which form later, such as the integrated behavioral acts during the transitional postnatal period (upright posture, speech, etc.). For exactly this reason, it is more important in the case

of functional systems of a behavioral nature to select those crucial forms of growth and maturation which combine all the acts and parameters of the integrative activity of the entire brain, both local and generalized. The maturation of the subcortico-cortical ascending connections and of their dynamic interactions exhibits this crucial feature. These areas of the brain are very clearly distinguished according to their functional properties and to their phylogenetic age. This has been clearly demonstrated in the investigations of Herrick, Bishop, and others, who have shown the structural transformation of the cortical areas during the development and increasing complexity of the sensory analysis and synthesis of the environmental phenomena under the influence of the increasing needs of adaptive behavior (Herrick, 1933a, 1933b, 1933c, 1948; Herrick and Bishop, 1958; Bishop, 1958) (Fig. 3.11).

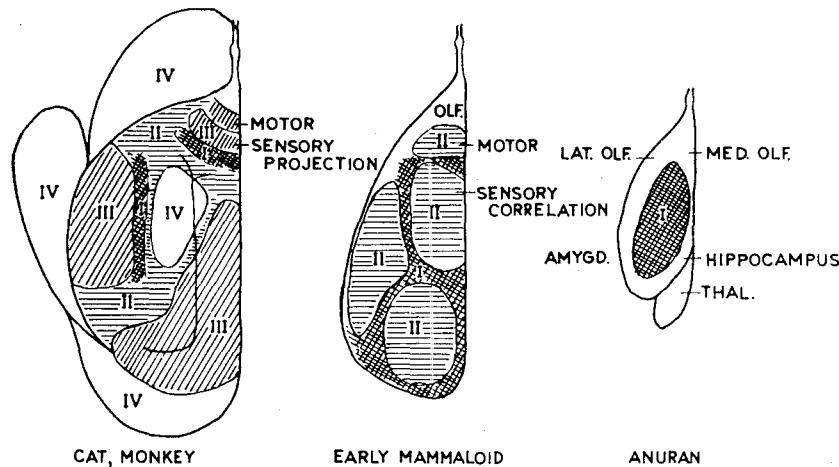


FIG. 3.11. Diagram of the specialization of the sensory areas of the cerebral cortex during phylogeny (after Bishop, 1958, p. 420). All diagrams are made arbitrarily in the general form of the familiar cat cortex. Right: earliest somatic cortex (I) developed by segregation of a central region of pallium from olfactory cortex; it becomes a facilitator of the sensory thalamus. Middle: hypothetical premammalian, at a stage anticipated in the snake, where cortex becomes differentiated into fields associated with the main sensory systems (II), but without specific projection to cortex. Left: III, specific projection areas of cat, segregated from old association cortex (II); IV, new association cortical lobes of primates presumably acting as facilitators or modulators of older association thalamocortical complex (II).

This premise naturally leads to several questions. How does heterochronia affect the maturation of ascending pathways and influences which have a different phylogenetic history? How does the differentiation of "specific" and "nonspecific" ascending influences on the cerebral cortex occur during ontogenesis? This problem becomes understandable if one considers that this interlocking must be heterochronous for the simple reason that, due to the participation of the cortico-subcortical components in the great variety of functional systems, these components must begin to function in a certain sequence. The difference in phylogenetic age of the ascending influences on the cerebral cortex, ranging from the neuropilar integrating substrate to the special sensory fields

which implement the specific sensory activites of the cortical cells, supports this conclusion.

An investigation of the ontogenesis of the ascending influences on the cerebral cortex is essential for still further reasons. Studying the ascending influences on the cerebral cortex in adult animals, the investigator finds already completed synaptic formations both in the subcortical nuclei and at the level of different layers of the cerebral cortex. The synaptic delays for *qualitatively different* ascending influences in the adult animal have already equalized; therefore, we often observe on the cortical surface an electrical manifestation of complete and summated synaptic connections.

During early postnatal development, due to the heterochronous growth of structures at all levels of the cortex and of subcortical structures, there is something resembling a filtration of ascending impulses. We can, therefore, conceptualize the *diversity* of the actual influences on the cerebral cortex which are uniformly reflected in its overall electrical activity. Our recent investigations have shown that the study of systemogenesis will be incomplete if the principles of maturation of cortico-subcortical interrelations are not regarded from the point of view of this diversity. This problem will be discussed below.

Three electrical indices with different degrees of precision are generally used for the physiological evaluation of ascending influences on the cerebral cortex:

- (a) the *electroencephalographic index*, i.e., the so-called slow electrical activity which, in spite of its extensive utilization in the solution of neurophysiological problems, still remains *terra incognita*;
- (b) the *evoked potential*, which arises upon stimulation of some receptor surface by a single stimulus or upon stimulation of the corresponding nerve by an electric current;
- (c) *discharges of single cells* due to an interference in the activity of the nervous system.

By means of the third method of study, the microelectrode technique, we were able to elucidate the nature of the influence of the subcortical nuclei on the cerebral cortex and to understand the selective mobilization of cortical elements in accordance with their biological or sensory modality.

In the section on the heterochronia of development at the molecular level, we stated that the chemical groups of the central synaptic formations which are responsible for the perception of the action of various drugs mature in the last stage of development of the nerve cells. They appear as a result of adequately developed protoplasmic characteristics of a synapse which is capable of conducting excitation.

At this point I would like to stress the importance of sequential order in the maturation of the various types of ascending influences on the cerebral cortex. For example, an analysis of cortical activity with regard to evoked potentials shows that in the guinea pig fetus (Fig. 3.12), only a secondary Forbes discharge takes place, whereas after artificial birth there appears a high-amplitude negative component with even some indications of a positive component (Nadirashvili and Kiselev, 1965a, 1965b). Moreover, during the first postnatal days, electrical stimulation of the sciatic nerve evokes a marked reaction in the sensorimotor area of the cerebral cortex in the form of regular high-amplitude waves. This type of reaction is unusual in an adult, since in this area a

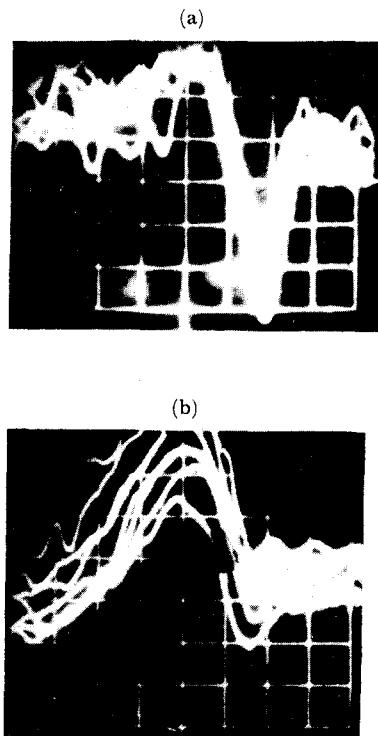


FIG. 3.12. Changes in the character of the evoked potential arising in the guinea pig in response to stimulation of the sciatic nerve before (a) and after (b) birth.

reaction to nociceptive stimulation appears as a marked desynchronization. However, a stimulus of equal frequency and strength applied to the same nerve on the 7th or 8th postnatal day evokes perceptible indications of desynchronization, and by the 11th day this desynchronization is fully manifested.

Let us try to visualize exactly what occurs in the cells of the cerebral cortex during these 10 days. The most adequate explanation involves the formation of a new ascending control on the dendrites of the cortical cells. In fact, the high-amplitude rhythm cannot be the basis for its own transformation into desynchronization. Undoubtedly, this is the result of a special ascending influence on the cortical cells, possibly of the type recently discovered and analyzed in detail by the Pisan school (Moruzzi, 1960).

On the other hand, desynchronization is also a specific form of activation of the cerebral cortex and is undoubtedly connected with a qualitatively specific ascending series of impulses which terminates on the dendrites of the cortical cells. Thus, we have a quite evident heterochronous growth of two ascending influences on the cerebral cortex which differ markedly in their phylogenetic origin.

In our laboratory the evoked potential was most thoroughly studied from both the morphological and electrophysiological standpoints. It had been previously shown that

in the newborn rabbit and kitten, ordinary stimulation by light or sound leads to the appearance of only one weak negative oscillation (Scherrer and Oeconomos, 1954). Here we do not have the typical form of primary evoked potential with positive and negative components. Although the investigators described this phenomenon of isolated existence of the primary evoked potential during the first postnatal days, they did not relate its paradoxical nature to the generally accepted theory of the origin and formation of the primary evoked cortical potential. This phenomenon was obviously in contradiction to these accepted views; therefore a resolution was necessary.

Purpura (1959), in his morphological and physiological investigations, also encountered this manifestation of only the negative component during the first postnatal days. Thus, the initial appearance of the negative, and not the positive, component was evident. In the experiments of our collaborator Ata-Muradova (1960a, 1960b), we also obtained an isolated manifestation of the evoked potential in the newborn rabbit upon stimulation of the sciatic nerve. These experiments were also reported several times in American publications.

As with other investigators, we would probably not have dared to doubt the validity of the classical concepts concerning the evoked cortical potential, specifically *its origin from a single and homogeneous ascending impulse which reaches the cortex over the same neural conductors*. However, both the concept of systemogenesis, which was developed in our laboratory many years before the complex nature of the evoked potential was discovered, and the necessarily related concept of the heterochronous growth of neural structures compelled us to suspect that the paradoxical appearance of only the negative potential may be the reason for the heterogeneous nature of the evoked potential. We set up a great variety of checking experiments and concluded that our suspicions were fully justified.

It was shown, for example, that the negative component of the evoked potential has certain characteristics which are completely inconsistent with its supposed derivation from preexisting processes forming the positive component of the evoked response in the adult animal. Testing various general anesthetics, applying stimuli of different strengths, heating the cortical surface, and other procedures showed that the negative component undoubtedly has an independent origin. It has a characteristic increase in amplitude and an expansion of the focal zone of maximum activity in the sensorimotor area of the cortex even before the appearance of the positive potential. These observations indicated that the isolated negative potential during the first postnatal days forms in the cerebral cortex on the basis of independent impulses passing over independent neural conductors.

The direct morphological investigations of Ata-Muradova and Chernyshevskaya (1961) convinced us that this isolated negative component is patterned in the plexiform layer due to discharges of the axodendritic synapses, since at that stage we found fibers arising from the substantia alba and ascending directly to the plexiform layer. These ascending fibers proceed with striking accuracy directly to the focus of maximum activity in the cerebral cortex. Only here can the isolated negative component be detected during the first postnatal day. On the other hand, at this time the "classical" pathway from the specific nuclei of the thalamus has not yet formed any synaptic contacts on the

body of the cortical cells. By this heterochronous maturation of the cortical synaptic formations we may explain the paradoxical fact of the early appearance of only the negative component of the evoked potential (Ata-Muradova, 1960b) (Fig. 3.13).

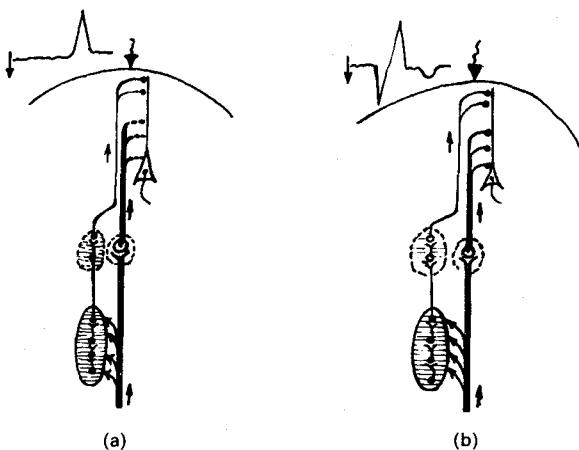


FIG. 3.13. Diagram of the heterogeneous mechanisms of formation of the different phases of the evoked potential. It can be seen that, owing to the numerous ascending volleys, the different phases of the primary response are determined by the excitation of various subcortical and cortical synaptic formations.

- (a) The negative phase of the primary response is determined by excitations entering the cortex over non-specific pathways to the axodendritic synapses.
- (b) The positive phase of the primary response is formed by axosomatic synapses by means of excitations entering over specific pathways.

All the above data, along with those in the literature, especially the excellent data of Purpura (1959) concerning the heterochronous maturation of the synaptic mechanisms in the cerebral cortex, have led us to conclude that the two components of the primary evoked cortical potential have separate anatomical origins and belong to two different systems of ascending influences on the cerebral cortex. We present below a general diagram of the maturation of both components in relation to the maturation of synapses of an axodendritic and axosomatic character (Fig. 3.14).

Deciphering the nature of the individual components of the primary evoked potential brought about the problem that all evoked potentials are of a multiple origin, and that only in relation to strength, frequency, and interval between stimuli can they acquire the most diverse types of electrical oscillation.

Control experiments were set up in order to characterize the physiological properties of the positive and negative components of the primary evoked potential. We reasoned as follows: the positive and negative components differ in their response to high-frequency stimulation and in their rate of propagation. While the positive component is rapid, the negative component is slow and considerably more sensitive to high-frequency stimulation. This is an extremely interesting paradoxical case in which two

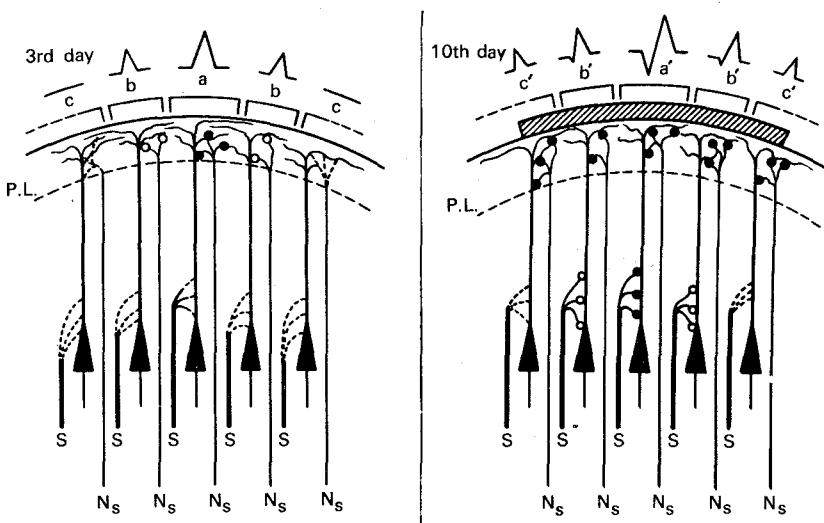


FIG. 3.14. Composite diagram showing the order of heterochronous growth of axodendritic and axosomatic synapses in the newborn rabbit. Also shown is the interrelation between the developing synaptic connections and the transformation of the evoked potential of the sensorimotor area during the first postnatal days. Black circles designate mature synapses; white circles designate maturing synapses which require a stronger stimulation of the sciatic nerve for the conduction of excitation. Dotted lines designate immature synaptic formations which do not give discharges in response to stimuli of any strength. S, ascending pathways from the specific thalamus; N_s, ascending fibers from the nonspecific part of the thalamus; P.L., plexiform layer; a, b, and c indicate the placement of the recording electrodes. The electrode at (a) is just above the stimulation point; at (b) and (c) it is at equal distances from the point of maximum stimulation.

components appear after birth in inverse relation to their physiological characteristics: the slow component appears earlier, and the rapid one later.

It is quite evident that with these paradoxical relationships between the maturation of these two components, there will be a point of intersection of their maturation if we construct curves based on their rates of development and physiological lability (Fig. 3.15).

Special experiments were performed in our laboratory by Sun Ven-in (see Anokhin, 1964c). She used the well-known procedure of paired stimuli with a gradual change of intervals between stimuli. Based on the above curves, we thought that the most interesting moments for examining the paired stimuli were those designated as I, II, and III (see Fig. 3.15).

Let us try to understand what we would obtain upon changing the interval at these different stages of development. Upon stimulation during the 4th postnatal day, i.e., at a time when only the negative component exists, shortening or lengthening the time interval between the paired stimuli will give the first appearance of the negative component when a certain interval is reached, and this component will increase in amplitude. It is apparent that with the use of this method of stimulation during the first postnatal days, there is both a high threshold and a long optimal interval for the second

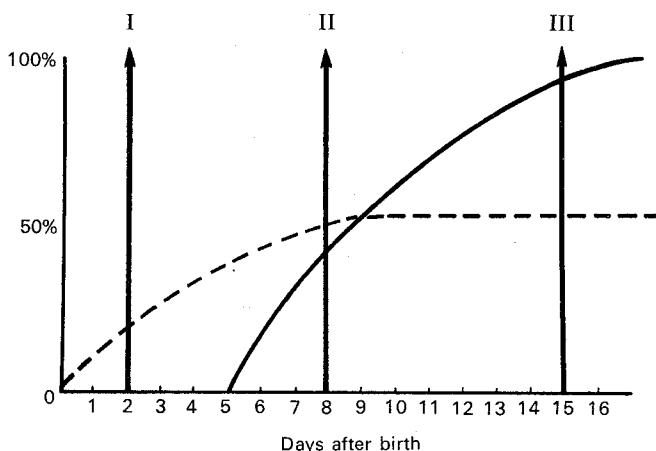


FIG. 3.15. Overall diagram of the temporal interrelations of the excitabilities of the negative and positive components which appear during the second stimulation. Solid line—maturation of structures for the positive component; broken line—maturation of structures for the negative component of evoked potential. The vertical arrows I, II, and III indicate the moments of stimulation of the sciatic nerve by paired stimuli in accordance with a, b, and c in Fig. 3.16.

stimulus, clearly characterizing the low lability or slowness of this component. The most interesting was the second zone of application of the paired stimuli. As is shown by arrow II, this is the zone in which the negative component has already almost attained complete maturity, while the positive component has just begun to form. It is quite evident that during this period of maturation the two components are under very dissimilar conditions. While the positive component which is just appearing must have an extremely low lability, as any maturing substrate must, the negative component already has almost reached its maximum possible lability. With paired stimulation under these conditions we should reach a point at which only the negative component would appear after the second stimulus, and there would be no positive component. The experiments fully confirmed this assumption, as is evident from Fig. 3.16. Since this period is especially brief, it must be detected by special means.

In the third period exactly inverse relations exist. The positive component has acquired its definitive properties of rapid propagation and short duration and consequently depends less on refractoriness from the first stimulation. On the other hand, although it has also completely matured, the negative component depends more on the refractoriness of the first stimulation because of its slowness; consequently, we have an inverse relation upon changing the interval between the paired stimuli. The positive component will be more stable than the negative, i.e., the relationships are those characteristic of an adult animal. Experiments have fully confirmed these interrelations, and as can be seen in Fig. 3.16c, the positive component occurs even with a very short interval between the two paired stimuli.

The above results can be readily interpreted if we proceed from our concepts of the dual nature of the evoked potential and its two components. Let us assume that the

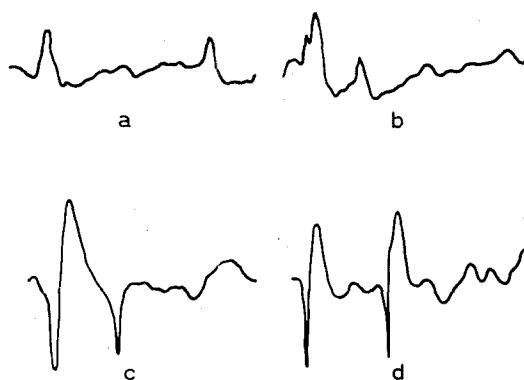


Fig. 3.16. Results of experiments with paired stimulations of the sciatic nerve in newborn rabbits. (a) Two stimulations of the sciatic nerve on the 2nd postnatal day when only the negative component of the evoked potential is present. (b) Stimulation on the 8th postnatal day. One can see the predominance of the negative component of the evoked potential, which has already matured by this time. The positive component is completely suppressed. (c) Stimulation of the sciatic nerve on the 20th postnatal day. The predominance of the positive component of the evoked potential can be seen. (d) The adult animal (control). Explanations in text.

impulse for the positive component comes from the specific thalamus which possesses certain "rapid" parameters of onset and conduction. Let us also assume that the negative component is generated by other cells: either nonspecific cells of the specific thalamus (Whitlock and Nauta, 1954), or nonspecific nuclei of the thalamic system. Then, upon stimulation of the sciatic nerve, the conduction of impulses to the cerebral cortex will depend directly on the rate of development of the processes in the synapses of each of these pathways (see Fig. 3.14). If, however, the stimuli follow each other, it is quite natural that the two series of impulses will also be conducted with respect to the residual refractoriness of each of these conducting systems. It can readily be seen that all variants of the above results can easily be derived from the interrelation of the physiological characteristics of these two conducting pathways. For example, the elimination of the negative component of the evoked potential under the influence of urethane anesthesia becomes apparent. While urethane can act on the subcortical structure which is selectively sensitive to it and which forms the negative potential, it can leave unaffected the structures of the positive potential which are more resistant to its action. This is actually the case (Anokhin, 1961a).

A more profound and detailed analysis of the negative potential shows that it is a rather complex phenomenon and is by no means formed as the result of an ascending impulse alone. At a certain stage of development this isolated negative potential can be tested by stimuli of different strengths, thus revealing its multiple origin (Fig. 3.17). As can be seen from the above material, it is only necessary to decrease the strength of stimulation in order for the evoked potential, at first sight homogeneous, to break into several potentials, thereby revealing its composite nature. It can be seen in the same figure that the secondary negativity does not immediately disappear with an increase in the strength of stimulation. Rather it is absorbed gradually as the intensity of the

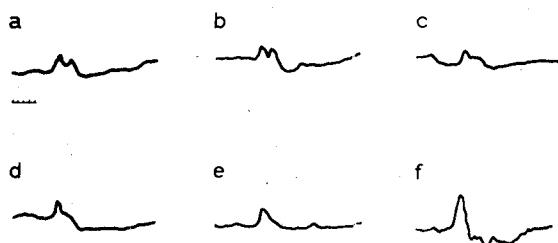


FIG. 3.17. Oscillograms showing the relation of the configuration of the evoked potential to the strength of the applied stimulation during the first postnatal days. The double negative potential changes to a single high-amplitude negative wave as the strength of the stimulus increases from 5 to 10 V in l-V steps (a-f).

stimulation of the sciatic nerve increases. This remarkable fact explains the variety of evoked potentials which we often observed in our experiments.

In accordance with the diagram explaining the separate origins of the positive and negative potentials, we can similarly diagram the above-described phenomenon of the fusion of two negative potentials into a single spiked potential of high amplitude (Fig. 3.18). Let us assume that fibers from a certain nonspecific thalamic formation go to the same cortical site but to different apical dendrites. In the thalamic formation, however, they have different cell bodies with different functional significance and different interaction with the surrounding neural formations (Fig. 3.18, A and B).

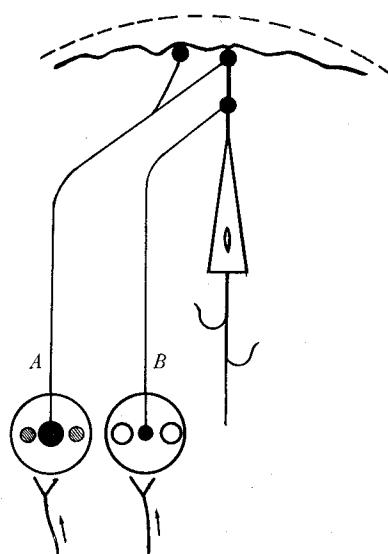


FIG. 3.18. Diagram showing the mechanism for the dissociation and combination of two streams of excitations. A, subcortical structure with almost mature synaptic connections; B, subcortical structure with heterochronically delayed maturation.

Let us now assume that complex *A*, due to systemogenic laws, matures earlier than does cell complex *B*, although this lag is negligible. Now let us visualize what will result if we apply a weak stimulation to the sciatic nerve. After passing through a number of synapses, impulses reach both complex *A* and *B*. In view of the unequal maturity of the synapses, the impulses reaching the incompletely matured synapses of *B* are delayed longer than the impulses reaching the synapses of cell complex *A*. As a result, the two series of impulses which have reached the same cortical site but different apical synapses, create the evoked potential as shown in Fig. 3.17a. However, if we quickly change the strength of the stimulation, say from 5 to 10V, the rate of conduction through both complexes *A* and *B* will be somewhat equalized, both series of impulses will reach the plexiform layer almost simultaneously, and hence there will be one homogeneous negative evoked potential (see Fig. 3.17f).

If the amplitude and time constant of the evoked cortical potential are regarded as results of the limitation of the positive component by a closely following negative discharge from the second impulse, we can derive all the configurations of evoked responses from these interrelations. If, then, the negative component of the evoked potential is eliminated by some means (urethane, GABA), *the time constant of the positive component immediately increases* (Ata-Muradova, 1960a). This occurs because under ordinary conditions we actually never see a *fully manifested* positive phase, since shortly after it starts, a negative discharge occurs in the plexiform layer and is "close on its tail." Thus the positive discharge manifests itself in accordance with the interval between the two ascending series of impulses (Anokhin, 1961a, 1961b).

The negative component can be eliminated by other means, for example, by the application of novocaine to a sciatic nerve to be stimulated. As we know, novocaine first blocks the fine unmyelinated fibers. If at this stage of novocaine anesthesia a single stimulus is applied, then instead of a biphasic potential, only a positive potential can be obtained in the cerebral cortex. This positive potential manifests itself fully and therefore seems to have a greater amplitude and time constant.

As a result of the study of the systemic and heterochronous maturation of neural structures, we can attribute the whole diversity of evoked potentials in the cerebral cortex to the different arrangements of the many ascending influences with respect to their rate of propagation, the intervals between them, and the spatial relations between individual electrical phenomena.

Up to this point we have been discussing the heterochronous growth of cortical structures in connection with the origin of electrical phenomena and their interrelations. Experiments have shown, however, that during early postnatal ontogenesis there is a further possibility of obtaining a breakdown of the electrical phenomena into their component parts. We have already shown that merely a change in the strength of the stimulation is sufficient to immediately reveal the multiple origin of a seemingly homogeneous electrical phenomenon. An even more demonstrative procedure for accomplishing this breakdown is local chemical action on the cortical surface at the focus of maximum activity of the evoked potential.

If a piece of paper moistened with a GABA solution is applied to the cortical surface at the stage of the newly formed biphasic evoked potential (15th day), a remarkable

evolution of the phases of the evoked potential results (Fig. 3.19). Simultaneously with the gradual disappearance of the negative component, which usually occurs in response to the application of GABA in an adult animal, a *secondary negativity* gradually begins to develop. It is quite evident that this negativity appears and increases only as a result of the action of GABA. As can be seen in the figure, the primary and secondary negativities reciprocally change their amplitudes in exact accordance with the duration of the action of GABA (Ata-Muradova, 1963). The marked amplitude of the secondary negativity during the second minute is especially noticeable (Fig. 3.19).

It is possible that this second negativity is not exclusively a phenomenon of early

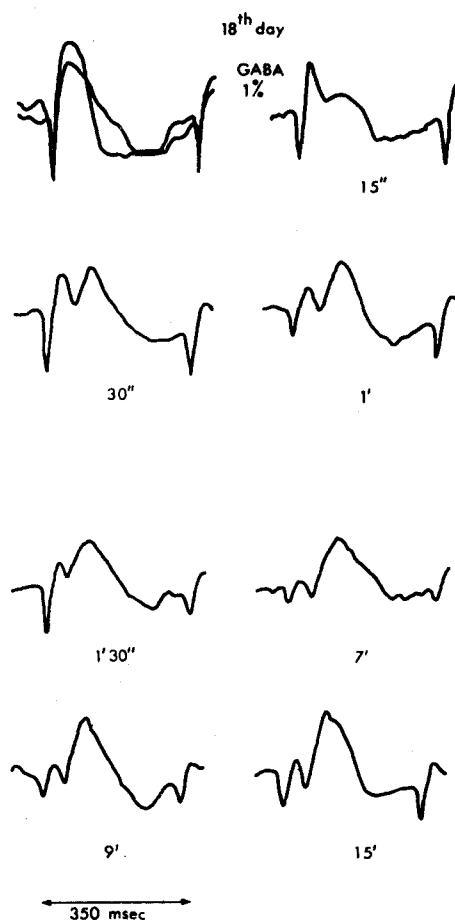


FIG. 3.19. Oscillograms demonstrating the presence of a negative component ("secondary negativity"), on which GABA has a positive effect and not a blocking effect as on the primary negativity. The blocking of the primary negativity and the gradual increase of the secondary negativity are shown in correlation on successively recorded oscillograms demonstrating the gradual course of the action of GABA on the evoked potentials.

postnatal ontogenesis, since in individual cases secondary negativity, as it was designated in our laboratory, can be detected upon the application of GABA even in adult animals (Sergeev, 1964). Without doubt, during the early stages of postnatal ontogenesis (15–20 days), it may appear in a particularly distinct form, which again is the unquestionable result of the heterochronous multiplication of the synaptic formations on the cells of the cerebral cortex.

However, another matter attracted our chief attention: how can this dual action of GABA be conceived? Why is one negative potential blocked by the application of this substance, while the other is activated? From the point of view of the present concept of two types of synapses, depolarizing and hyperpolarizing, we should obtain only a blocking, and never an activation, of the depolarizing, i.e., negative, process. We did not find suitable data in the available literature and therefore attempted to visualize the intimate nature of this phenomenon.

Our usual classification of the synaptic formations of the cerebral cortex is based on the *parameter of polarization* of the cell membranes. However, the polarization and depolarization of the neural elements, particularly of the synaptic formations, depends entirely on the metabolic process which develops both in the membrane itself and in the axoplasm. The question naturally arises: is there always an identical chemical structure in the metabolic processes which maintain polarization (possessing the same electrical signs) in the different nerve cells and synapses? Our study of these phenomena usually does not extend beyond the determination of their electrical signs. And yet, is this enough?

Data from comparative physiology convince us that *in spite of equal electrical phenomena, the chemical specificity of synaptic activity can be entirely different* (Koshtoiantz, 1941). Thus, we have indisputable data showing that the same electrical phenomenon may be based on wholly different metabolic processes with individual and specific chemical sensitivities. In our opinion, the paradox of different relationships of two negative electrical phenomena to one chemical agent, GABA, can be easily explained from this broad metabolic point of view.

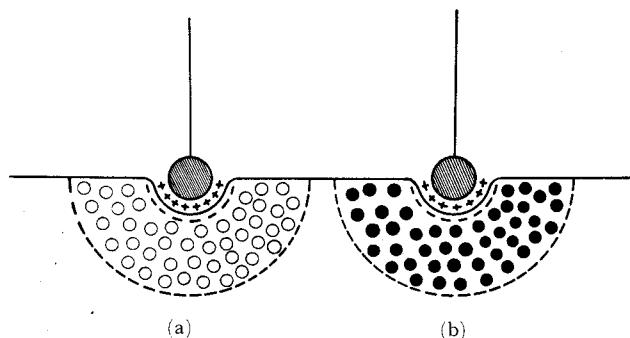


FIG. 3.20. Diagram of the possible metabolic development of the subsynaptic processes in two synapses which produce the same negative electric effect at the cortical surface. a and b represent two synapses with different specificities of cortical processes. The + and - signs indicate membrane polarization; the white and black circles indicate different transmitter substances.

These relationships can be schematically conceived as follows: two synaptic formations with different specificities of chemical processes may exist on the bodies of different cells or even on the membrane of the same cell. This assumption is not improbable if one takes into consideration the extreme heterogeneity of the membrane of the nerve cell (Bullock, 1959) and its different synaptic formations (Fig. 3.20).

It is also important to emphasize that these findings give us the opportunity to study the protoplasmic diversity of postsynaptic membranes, the chemistry of the presynaptic structures being relatively uniform. One can also assume that the highly diverse sensitivity of the nervous system to drugs is based on precisely this metabolic diversity of the different synaptic formations. All these problems, however, must still be solved through careful cooperative investigations by neurophysiologists, neurochemists, and neurohistologists.

THE FUNCTIONAL SYSTEM AS A BASIS FOR THE FORMATION OF THE FIRST CONDITIONED REFLEX CONNECTIONS

The above analysis of the basic embryogenic laws of the development of inborn activity shows that the survival of an organism during the first postnatal days depends directly on the degree to which the systemic growth and the unification of the appropriate cerebral structures are adequate for the implementation of effective functional systems at the moment of birth. In this case, of course, we are dealing not only with the maturation of the brain, as we have seen that even the development of the peripheral synapses proceeds according to the laws of systemogenesis. When we speak of the maturation of the brain, we have in mind that the maturation and consolidation of its synaptic formations is the most decisive factor for the appearance of an effective functional system. This is what explains the early anlage of the central components of the functional system.

We must, however, remember that if the functional systems became consolidated exactly at the moment of birth, actually no survival of premature human or animal fetuses would be possible. Yet we know that infants two months premature are able to live. Special methods of caring for these premature infants bring them to normal life.

We already know that this survival is possible only because the selective development of the functional systems, and especially the consolidation of these systems, do not occur chaotically but in a definite and strict sequential order. The consolidation proceeds in such a way that even with the very first unification of its parts, this still imperfect systemic formation can, although minimally, already function (see the principle of minimal ensurance of the functional system, above).

What does "functioning" mean from the point of view of the *integrative physiology* of the organism? First, even at the initial stage of consolidation, a given functional system can produce a final adaptive effect characteristic of it. Moreover, owing to the action of its parameters on the corresponding receptor formations and the appearance of reverse afferentations, this end effect of the functional system can already be evaluated in the central nervous system as to whether it is beneficial to the preservation of life.

These essential requirements of physiological beneficability are met by the minimal

consolidation of the functional system. Here one must again emphasize this amazing characteristic which has been developed by the organism throughout millions of years of evolution in the struggle for survival.

Even the first maturation of the components of a functional system does not proceed in an uncoordinated or disorderly manner, but in such a way that the *first elementary structures of the system form a whole integrative unit possessing all the features of self-regulation*. If this formulation is somewhat changed and adapted to conditioned reflex terminology, we can say that even *when its beneficial end effect is minimal, the functional system is capable of reinforcing action, i.e., it contains within itself everything necessary for unconditioned reinforcement*. This fact is of fundamental importance in the systemogenic approach to the formation of the first conditioned reflex during the postnatal period.

As mentioned in an earlier part of this chapter, we had the opportunity to study a premature infant weighing only 560 g and surviving only 42 days. We observed an extremely interesting phenomenon : the infant already had a sucking reaction, but it was very ineffective since it took in only 8–10 ml of milk. In view of what has been said about the minimal insurance of the functional system, we can confidently say that this negligible quantity of milk represented a minimal beneficial end effect of the functional system and consequently had a *quite definite reinforcing action*.

Observations have shown that even this reinforcement may become the basis for the elaboration of conditioned reactions. We carried out the following experiment : in order to utilize the most completely matured receptor (the skin surface) for the application of an indifferent stimulus, we uncovered the infant *before every feeding* and thus subjected its skin to a temperature change. After several days of this pairing of uncovering and feeding, *the infant began quite evident sucking movements in response to uncovering alone*. Thus it demonstrated its ability to elaborate conditioned reactions at this early stage of development when the alimentary functional system had as yet received only minimal insurance by selectively matured structural formations.

The above approach to the explanation of the acquisition of the first conditioned connections is, in our opinion, the most physiological one. We reject any measure of time starting from the moment of birth, since that moment, as shown above, cannot serve as a universal criterion for this purpose.

On the contrary, all our experiments and observations lead to the same conclusion : a conditioned reflex coupling can be established in all cases in which, *owing to the process of consolidation, a functional system with minimal insurance of any beneficial adaptive effect has already formed*. Such a functional system already has a reinforcing effect. From the moment of minimal consolidation of the functional system, there is a basis for the elaboration of conditioned reactions; it needs only to be determined which “indifferent” stimuli become meaningful to the functional system. However, only the *nearest afferent* stimuli which appear in the very realization of inborn activity become meaningful.

An exceptionally illustrative example of this situation is the transformation of the tactile stimulation of the tongue from an indifferent stimulus into a conditioned stimulus during the first feedings of a newborn infant with milk (see Chapter 2, Fig. 2.4, where this is discussed in detail).

Thus, in summarizing all the above data and considerations, we can formulate the following propositions governing the possibility of the elaboration of the first conditioned reflex connections during postnatal ontogenesis:

1. The only stable criterion for the elaboration of the initial conditioned coupling is the presence of a beneficial end effect, which is already adequate for this consolidated functional system.
2. The minimal adaptive effect is present long before birth. This is a purposeful adaptation ensuring the maximal probability of survival of newborn animals of all species.
3. The presence of many functional systems with a beneficial end effect in the newborn of all higher animals creates conditions for the *immediate* involvement of all the afferent mechanisms nearest the nucleus of the system, which in one way or another participate in the implementation of inborn activity. This gave us reason even long ago to assert that conditioned connections are actually formed as early as the first hours after birth.
4. The search for that decisive time at which conditioned reflexes appear "for the first time" after birth was based on the lack of sufficiently clear concepts concerning the fact that the very presence of a *reinforcing factor* (beneficial effect of the functional system) automatically creates a situation for the elaboration of a conditioned connection.

The point is merely to demonstrate which afferent "indifferent" impulses arise during implementation of an inborn activity and consequently, on a purely morphogenetic basis, are the first to be involved in the conditioned reflex control of a given functional system. Depending on the rates of maturation of the neural relationships and the abundance of these relationships in different animals, the initial conditioned reflex connections can, of course, be different. Essentially, however, they must arise immediately after birth.

5. In evaluating this principle from a broader evolutionary point of view, we must note that it is a logical incorporation into individual life of the processes and mechanisms of the *anticipatory reflection of the environment* which is characteristic of even elementary life and constitutes the basis for the formation of all stable structures of the organism (see Chapter 1). This completes the great cycle of transformations which organically unites the phylogeny and embryogenesis of organisms.

* * * *

The early data from our laboratory, as well as the most recent investigations, enable us to assert again that systemogenesis is indeed the regulator of the selective development of cerebral structures and functions, and consequently of unconditioned reflexes.

This development always proceeds selectively and with acceleration in accordance with the immediate environmental influences on the newborn animal. We have seen that this *well-timed* consolidation of the vitally important functional systems of the organism is continuously guided by the anlage, growth, and consolidation of the system. Heterochronous maturation of the brain involves more than just the various components of a functional system; it concerns the molecular combinations and the

processes of selective maturation of synaptic formations, as was clearly demonstrated at the cortical level.

There is no doubt that the systemogenic character of maturation and growth is most distinct in those functional systems of the organism which must be mature exactly by the moment of birth. Undoubtedly they are inborn, since their preparation and consolidation obviously occur during embryogenesis. They closely harmonize with ecological factors, i.e., factors characteristic for the newborn of a particular species. Can it be said that the exact "timing" of the consolidation of a functional system to the moment of birth is *purposeful*? This is true indeed. Classifying the newborn into viable and unviable, natural selection fixed in the genetic codes all those growth processes, and especially their rates, which are ready exactly at the moment of birth. Ever since the appearance of life, the decisive criterion of purposefulness has been *survival*.

In the broad Darwinian sense, all that promotes survival in the organism is purposeful, and all that leads to the destruction of life is not purposeful. In the course of millions of years, natural selection has perfected a form of interrelations of phylogeny and embryogeny, in which the experience of the species is realized in the perfection of the maturation processes before the moment of birth. Pavlov believed that in such cases purposefulness is not just a factor, but is the initial basic consideration of research. To interpret this as "teleology" in the philosophical sense would certainly be unreasonable (Fig. 3.21). Less conspicuous is the unification of the components of later and more delicately organized functional systems, on the basis of which various behavioral acts

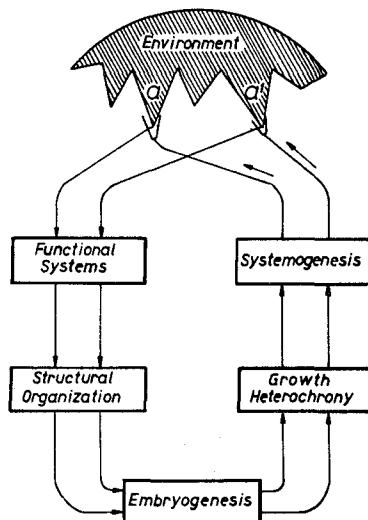


FIG. 3.21. Diagram illustrating the place of systemogenesis in the overall cycle of development of the adaptive functions of the newborn in relation to the conditions of its existence. It can be seen that systemogenesis, as part of the cyclic processes of embryogenesis, ensures the most delicate adaptation of the newborn to the environment. a and a' represent those ecological factors which the organism encounters immediately after birth.

develop during the postnatal ontogenesis of animals and especially man. In this case, where the peripheral apparatuses are fully mature, the maturation of new synaptic formations in the brain takes on the greatest importance, even though at this late stage the maturation of the synaptic formations is an implementation of the same genetic process as before birth. However, these synaptic formations develop in connection with, and on the background of, the implementation of the adaptive functions of the entire organism. Our experience in the study of the rates of maturation, the localization, and the nature of the synaptic formations during early postnatal ontogenesis convinces us that there are extensive opportunities for interesting and inspiring investigations of inborn activity. This fact is of special interest for the physiologist studying higher nervous activity: it guides him in the study of the general principles of the development of acquired, i.e., conditioned, reflex activity.

CHAPTER 4

Recent Theories on the Coupling of the Conditioned Reflex

PAVLOV once said that all our knowledge and working hypotheses are directly dependent on the delicacy of the investigative methods and the stage of development of a given science during the given period. This point of view is especially applicable to the gradual perfection of our concepts of the delicate physiological mechanisms of coupling of the conditioned connection.

It is natural that every investigator who attempts to understand how the conditioned reflex is elaborated, uses those data which have been obtained by neurophysiology up to his time. The first observations on conditioned reflexes in Pavlov's laboratory served as an impetus for the development of a hypothesis concerning the most probable and most acceptable mechanism of actual coupling on the basis of the information available at that time on cerebral function in general.

In order to more thoroughly understand the meaning of the first propositions concerning the mechanism of the conditioned reflex, we must first visualize the nature of neurophysiology at the beginning of this century, since Pavlov could utilize the necessary information only from the neurophysiology of his time.

It was known that the central nervous system implements adaptive activity on the basis of two opposing processes: excitation and inhibition. Inhibition in the central nervous system, the discovery of Sechenov, began to be widely utilized for the explanation of complex neural coordinations. All these interpretations, however, dealt basically with the spinal cord. Only Sechenov, in his famous book *Reflexes of the Brain* (1863b, see Bykov, 1952a, pp. 143-211), made use of the concept of central excitation and inhibition for the development of theoretical concepts concerning the reflex nature of cerebral function. This was a bold application of the materialistic principle to the explanation of the delicate mechanisms of mental activity which had previously been interpreted primarily on the basis of idealistic concepts. However, the delicate mechanisms of the activity of the higher parts of the central nervous system, including the cerebral cortex, had until recently not been sufficiently explained. An experimental analysis of all parts of the central nervous system is essential for understanding the conditioned reflex, a universal form of activity of the entire brain.

Early in this century Sherrington did the most extensive and precise work on the problems of cerebrospinal coordination. In 1906 his monograph *The Integrative Action of the Nervous System* was published. And yet, Sherrington did not actually deal with the

true integration of nervous processes, even though he made extremely important discoveries in the field of individual mechanisms of the central nervous system (the theory of the common path, the allying of reflex arcs, the reciprocal interaction of antagonistic muscles, the condition of central excitation, etc.). Essentially, Sherrington's interests involved the investigation of the *specific mechanisms* of integrative action but did not concern the laws of integration itself as a function of the integrated organism. Moreover, although the concepts of the significance of the trans-synaptic propagation of impulses had already fully matured, they could not yet be applied to the central nervous system.

The conditioned reflex, which ensures the adaptation of the integrated organism to the environment, constitutes in the true sense an integrative act of the organism since no aggregate of nervous processes can be called an integration if an adaptative end effect has not resulted.

Thus, Pavlov had to either develop a new and original concept of the mechanisms of the conditioned reflex, or limit himself to a purely phenomenological explanation. Bound to physiological traditions, Pavlov rejected a phenomenological description of the conditioned reflex and, interpreting the entire problem physiologically, he presented the first model of conditioned reflex coupling. In the first of his *Lectures on the Function of the Cerebral Hemispheres* he says: "Up to the present, however, there has been one essential point of difference between the American School and ourselves. Being psychologists, their mode of experimentation, in spite of the fact that they are studying these activities on their external aspect, is mostly psychological—at any rate so far as the arrangement of problems and their analysis and the formulation of results are concerned. Therefore—with the exception of a small group of 'behaviourists'—their work cannot be regarded as purely physiological in character. We, having started from physiology, continue to adhere strictly to the physiological point of view, investigating and systematizing the whole subject by physiological methods alone" (Pavlov, 1927, see Pavlov, 1960, p. 7).

What facts on the general physiology of the nervous system provided a basis for this concept?

At the beginning of this century it was predominantly thought that the central nervous system functions on the basis of strictly localized centers. This point of view was particularly furthered by the experiments of Munk, Fritsch, and Hitzig, who strongly supported the concepts of a strict localization of the various sensory projective regions in the cerebral cortex. At the same time, the entire neurophysiology of that day was founded on the concept of the threshold stimulus and the strength of the excitatory process. It was established that, starting with a threshold stimulus, the stronger the stimulus applied to the central nervous system, the more generalized is the reaction of the animal. A classical expression of this significance of stimulus strength was Pflüger's experiment with the irradiation of excitation along the spinal cord.

Thus, the principle of localization and the relation of an increasing area of excitation to stimulus strength were fully entrenched concepts which considerably determined both the formulation of the problem and the interpretation of the results. Therefore, it was natural to expect that an understanding of the relation between the indifferent

and the unconditioned stimulus had to be based on general physiological concepts.

At the same time it is important to keep in mind that the actual situation of the conditioned reflex experiment was quite definite: two simultaneous environmental stimuli, one "indifferent" and the other "essential," act upon the central nervous system sequentially and independently. The initial independence of the two stimuli can be realized when we arbitrarily select any indifferent agent for the elaboration of a conditioned connection. This agent may be visual, auditory, cutaneous, olfactory, etc.

In all these cases it is easy to ascertain that, except for the orienting-investigative reaction which always appears when a new stimulus acts on the sense organs of an animal, the initially chosen external stimulus has no relation to the vitally important activities of the organism. After several such successive coincidences, if the previously indifferent stimulus begins to evoke that vitally important activity which always follows it, some kind of material connection has obviously been established between the first and second stimulus and, of course, within the substrate of the nervous system.

As is known, in his 1908 publications Pavlov presented the first diagram of a conditioned reflex, in which the cortical focus of the indifferent stimulus was connected with the alimentary center of the medulla oblongata (Fig. 4.1). It was demonstrated

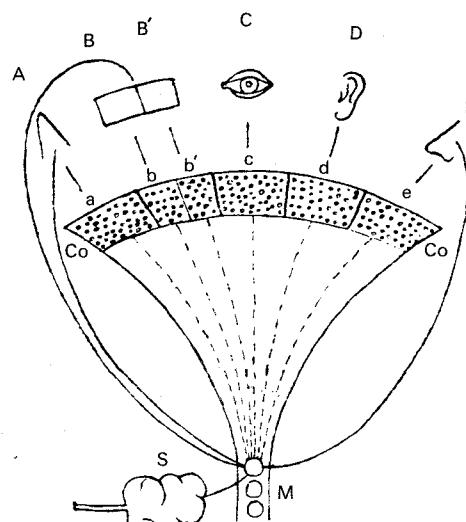


FIG. 4.1. Diagram proposed by Pavlov to explain the mechanism of formation of the conditioned reflex. As can be seen, this first hypothesis assumes that the corresponding cortical end of the analyzer is connected directly with the center of the salivary gland. From Pavlov (1908; see Pavlov, 1949a, p. 76). Co, cerebral cortex; M, medulla oblongata; S, salivary gland.

that after several pairings the indifferent stimulus alone began to evoke salivary secretion. In regard to this Pavlov wrote: "From this fact it is evident that if very strongly excited foci arise in the nervous system (in the given case, in the salivary reflex centre), the formerly indifferent stimuli from the external world, acting on the receptors and

thus exciting the receiving centres of the cortex, are conducted toward these strongly excited foci; in this way the impulses concentrate and open a path leading to these foci" (Pavlov, 1908, see Pavlov, 1967, p. 101).

Thus, Pavlov formulated the concept of the *attraction* of a weak excitation by the focus of a stronger excitation caused by an unconditioned stimulus.

Apparently it would be natural to think that even from the beginning of stimulation, the excitation from an indifferent stimulus by some means proceeds to the structures of the as yet unused unconditioned stimulus, i.e., feeding.

However, the concept of a strict localization of the "focus of excitation" which was dominant at that time prescribed that the propagation of an indifferent stimulus be restricted to proceed from the projection zone, i.e., an entirely limited focus of excitation. Logically, then, an excitation evoked by an indifferent stimulus had no way of uniting with the focus of an unconditioned excitation other than by being attracted by it. In accord with the concepts of the strict localization in the central nervous system of the excitation from both of the stimuli applied, the hypothesis of the "attraction" of the indifferent excitation originated. The idea of "Bahnung," which supplemented the general concept of a connection between two foci of excitation, originated in the same way.

The hypothesis presented above was historically the first, and therefore it naturally reflected only very general features of conditioned reflex activity.

As new experimental results were being obtained in Pavlov's laboratory, investigators became increasingly convinced that the contact between indifferent excitation and unconditioned excitation is established not via the route "cortex-medulla oblongata," but rather via the route "cortex-cortex." Such an approach to the problem became possible only after the concept of cortical representations from various unconditioned reflexes had been formed. Owing to this addition, the coupling process changed from cortico-subcortical into cortico-cortical, i.e., it occurred between two representations—that of the indifferent stimulus and that of the unconditioned stimulus.

It must be noted, however, that this change in the localization of the coupling of the conditioned connection did not change the concepts of the actual nature of the coupling. Just as in the first hypothesis, the strong focus of excitation of the cortical representation of the unconditioned stimulus "attracted" the excitation from the indifferent stimulus.

This concept of a connection between the projection zones of unconditioned and indifferent stimuli ("focus of excitation") has in essence survived up to the present time. Even now we explain the coupling of a conditioned reflex as an association between two foci of excitation of the cerebral cortex, as an association between two foci of excitation of the cerebral cortex. Just as before, the main point of the mechanism of this coupling is the difference in strength of the excitations to be united: as before, the strong focus of excitation of the unconditioned stimulus attracts the weak stimulation from the indifferent stimulus.

In this generally accepted concept, however, there are some contradictions which have never been the object of special neurophysiological discussion. For example, in the concept of cortico-cortical coupling the question has never been discussed as to how and along what pathways the conditioned excitation, having formed between two afferent

cortical points, is then accomplished in the operation of *efferent corticofugal mechanisms*.

Indeed, the cortical representation of an indifferent or an unconditioned stimulus is by its very essence an afferent representation. This representation is merely a focus for receiving information and perhaps for processing this afferent information. Since, however, as a result of such a connection a complete conditioned alimentary reaction must form, it is natural to suppose that from one of the afferent representations such a complex of efferent impulses must form which evokes the alimentary behavior of the animal. However, it is precisely this mechanism that is puzzling: how can an afferent representation form a fully integrated and directed complex of efferent impulses? At present we do not know of any neurophysiological mechanisms which could explain this process at the level of the cerebral cortex.

Consequently, the concept of the coupling of a conditioned connection between two cortical foci of afferent impulses leaves many unsolved purely neurophysiological contradictions. The basic reason for these contradictions is that the concept of the coupling of a conditioned connection between two foci of excitation remains unrelated to existing neurophysiological concepts. The formation of the conditioned reaction itself, as a complex mechanism of the efferent integral, was not included in the overall concept of coupling, and for that reason purely neurophysiological contradictions arose.

The above-described concept of the coupling of the conditioned connection stated the actual fact of coupling between two cortical foci of excitation, but neurophysiologically it did not explain how this association may be effected in the operation of the efferent part of the conditioned reflex. We know that at its efferent end the conditioned reflex is a highly organized complex of impulses engaging the functioning mechanisms in such a way that the responsive act is purposeful.

Recently several more concepts of the coupling of the conditioned reflex have been proposed. These present variations of the basic principle of coupling formulated by Pavlov in 1908 (see Pavlov, 1967, pp. 100–102). For example, on the basis of the well-known fact that the indifferent stimulus evokes the orienting-investigative reaction, Asratian (1953) assumes that the cortical representation of this reaction becomes connected with the representation of the center of the unconditioned reaction. In Asratian's concept the focus of indifferent excitation was replaced by a focus of unconditioned excitation of an orienting-investigative nature; consequently, the process of coupling itself must occur between the cortical representation of two unconditioned reflexes.

A closer analysis of these views shows that with their acceptance we find several new contradictions in addition to those already existing. For instance, it is difficult to conceive of the actual physiological mechanism which brings about the coupling of the connection between the cortical representations of two unconditioned reflexes. A quite deterministic basis is evident in Pavlov's concept of the *attraction* of the weak excitation from the indifferent stimulus by the excitation of the unconditioned stimulus: *the focus of the strong excitation attracts the weak excitation*. It is, however, entirely unclear on what neurophysiological basis a temporary connection can be established if both are cortical representations of unconditioned excitations of approximately equal strength.

In fact, observations under experimental conditions show that an animal's orienting-investigative reaction evoked by some stimulus may interrupt the course of an unconditioned alimentary reaction. In other words, at some moment in the interaction of these two unconditioned reactions, the orienting-investigative reaction may be a stronger "focus of excitation" than the unconditioned alimentary excitation.

In addition, observations of human behavior show that the orienting reaction may completely suppress the alimentary, the sexual, and even the defense reaction. In what direction will the temporary connection then be formed in response to a signal? Here we have an obvious disagreement with the logic of correlations included by Pavlov in his original concept of the coupling of the conditioned reflex.

It should be added that the orienting-investigative reaction by its physiological nature cannot have the distinctly outlined "focus of excitation" which one usually has in mind when speaking of the coupling of the conditioned connection. In fact, it is well known that during the formation of the orienting-investigative reaction there occurs an active gathering of information entering the central nervous system through various analyzers. This means that during multilateral orientation in the environment the cerebral cortex acquires several active foci of excitation. Therefore, it is difficult to imagine that this multifocal and undoubtedly integrated process of searching for the afferent synthesis most complete for a given moment can be "connected" with the focus of excitation of an unconditioned stimulus.

The contradictions discussed above are quite sufficient to show how difficult it is to agree with the coupling of a conditioned connection between two cortical foci of unconditioned excitations.

Moreover, the above-described concept preserves the most characteristic feature of all previous concepts: *the presence of two separate foci of excitation in the cerebral cortex between which coupling is formed*.

The first concepts of the coupling of the conditioned reflex pertain to that period when the brain as a whole appeared to the investigator as a peculiar "black box" for which the most diverse schemes and relationships could be surmised. However, the latest advances of neurophysiology in the direct investigation of intracerebral relationships considerably limit the possibilities of such hypotheses. I have in mind the discovery by Moruzzi and Magoun of the physiological role of the reticular formation as a powerful channel of ascending information and its activating influence on the cerebral cortex (Magoun, 1952a, 1952b, 1953; Moruzzi and Magoun, 1949). Since these physiological investigations, our concepts of the passage of afferent impulses into the cerebral cortex have changed considerably.

On what were all the original concepts of the coupling of the conditioned reflex based? Providing the basis for them was the assumption that all afferentation entering the cerebral cortex proceeds on one channel, i.e., along the lemniscal pathways and through the specific thalamic nuclei, and that later in the cortex it forms clearly defined foci of excitation (projectional) of a given sensory modality. The discovery of the physiological role of the reticular formation has to some degree extended our knowledge of the mechanisms of the entry of afferent information into the cerebral cortex. It has become evident that the processing of afferent information entering the brain is considerably

more complex. There is not as yet a sufficiently clear idea of what changes these new results have introduced into our former concepts on the coupling of the conditioned reflex. Briefly, these new results may be formulated in the following postulates:

1. Any stimulation, either indifferent or unconditioned, enters the cerebral cortex through two different channels. One of these channels—the lemniscal system, the thalamus, and the projection zones of the cerebral hemispheres—has served as the basis for the creation of our concepts on the mechanisms of the conditioned reflex. The other, more powerful channel for the passage of afferent impulses into the cerebral cortex was discovered by the investigations of Moruzzi and Magoun (1949). They revealed a new collateral pathway for the propagation of the same impulses through the reticular formation of the brain stem. These impulses, however, undergo a considerably greater qualitative transformation.

2. One of the remarkable characteristics of the impulses branching off collaterally from the lemniscal pathways into the reticular formation is that while they are to some degree a *copy* of the impulses directed into the thalamus and the cortex, they nevertheless spread quite extensively over the subcortical nuclei. In one form or another, actually all subcortical structures become involved in the processing of this information. Only after this processing is the afferent information converted largely into generalized series of ascending impulses which arrive in the cerebral cortex only 5–25 msec later than does the direct information over the lemniscal systems. This postulate contradicts the sense of the concept of the “focus of excitation.” In Chapter 5, which discusses the convergent theory of coupling of the conditioned reflex, I shall attempt to elucidate this most significant contradiction in the description of the neurophysiological nature of the conditioned reflex.

3. Especially important and interesting results for the comparative evaluation of both input channels of afferent information into the cerebral cortex were obtained by means of general anesthetics. It was shown that while putting an animal to sleep, a general anesthetic eliminates the activating effect of all the above-mentioned collateral impulses. At the same time the impulses of the lemniscal systems, to which all our theoretical concepts were related, are not only not eliminated by the general anesthetic, but are even more pronounced than in the waking state. In other words, the “focus of excitation,” with which our working hypotheses are concerned, is not subject to the action of the general anesthetic and thus cannot be correlated with the state of wakefulness and consciousness and with all that accompanies these active states of the brain.

It is quite obvious that this comparative evaluation of both input channels of afferent information to the cerebral cortex confronts the investigator of conditioned reflexes with an enormous number of new and highly interesting research tasks.

4. The fact that impulses propagating over the second, so-called “nonspecific” channel are of a generalized nature, i.e., are addressed to all regions of the cerebral cortex, is of special importance in the problem of the coupling of conditioned reflexes. This means that this generalization of excitation over the cortex is of a special character: it is formed in an *ascending direction*, i.e., according to a vertical principle and not according to a horizontal one as we had assumed for all our working hypotheses concerning the irradiation of excitation from a “point of origin” of excitation.

It is clear that in view of these new neurophysiological discoveries an alternate solution appears before the investigators of higher nervous activity: either the addition of the input channel into the cerebral cortex is of no importance to the generally accepted concepts on the coupling of the conditioned reflex, or else the input channel must be included as something new which expands our concepts on the mechanism of the coupling of conditioned reflexes and especially on the mechanisms of the propagation of nervous processes over the cerebral cortex.

In Chapter 5, I shall try to reveal the physiological meaning of the changes introduced into the problem of the coupling of the conditioned reflex by the theory of the physiological role of the reticular formation and the latest neurophysiological advances.

The new problems which arise in connection with the latest neurophysiological data have been the cause of numerous attempts to create a model of the conditioned reflex by using physiological data on the reticular formation or, more accurately, by using data on various kinds of nonspecific activation of cortical activity.

The most important attempt undertaken in this direction is the hypothesis of Fessard and Gastaut (1958) which deals with the mechanism and localization of the coupling process in the conditioned reflex. Their point of view is based on the premise that the process of the initial generalization of the ascending impulses through the multisynaptic reticular channel forms the basis for the appearance of the initial coupling of the temporary connection at the subcortical level. This conclusion is based on the fact that the initial conditioned reflex changes of the electroencephalogram during the elabora-

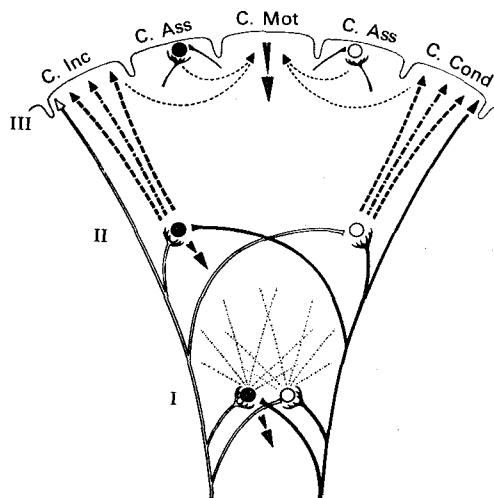


FIG. 4.2. Diagram of the coupling of a conditioned reflex connection at the level of subcortical formations with participation of the reticular formation and associative regions of the cerebral cortex. From Gastaut (1958, p. 266). I, Region of the reticular formation. II, Level of nonspecific thalamic pathways and nuclei of the third ventricle. III, Level of cerebral cortex where the final formation of the conditioned reflex connection takes place. C. Inc., cortical zones perceiving impulses of unconditioned stimulations; C. Cond., cortical zones perceiving impulses of conditioned stimulations; C. Ass., association areas of cortex; C. Mot., motor areas of cortex.

tion of a conditioned reflex arise in the reticular formation. According to Fessard and Gastaut, this deviation of the potentials is the most noticeable and the earliest to occur during the gradual growth of the conditioned reaction.

The electroencephalographic changes are actually the only supporting factor for the crucial conclusion concerning the initial subcortical coupling of the conditioned connection. In the investigators' opinion, this initial coupling process also subsequently takes possession of the cerebral cortex (Fig. 4.2; Gastaut, 1958, p. 266).

One can hardly deny the general proposition that any part of the brain is capable of associating two stimuli acting sequentially. In this lies the evolutionary meaning of the development of neural tissue as a substrate of the rapid chemical consolidation of the sequentially developing chemical transformations that occur during every action of external influences on the sense organs. In the case under discussion, however, we are dealing with a more complex phenomenon—a completely organized conditioned reflex behavioral act. For this reason it is necessary to make some remarks about the above concept of Fessard and Gastaut.

The role of the orienting-investigative reaction in the coupling process has long been clear to us: the high degree of activation of cortical activity arising during this reaction promotes both a more complete perception of afferent impulses and a more rapid processing of the information obtained due to a considerable facilitation of multilateral connections and comparison of ascending impulses at the cortical level (Anokhin, 1958b).

Returning to the observation of Fessard and Gastaut, we must say that their concept did not account for this initial period in the elaboration of the conditioned reaction.

In fact, even during the first applications of an indifferent stimulus, the cerebral cortex takes a most active part, extending its influence in a corticofugal direction far beyond the limits of the cortex itself. Therefore, it is natural to think that Fessard and Gastaut's index of coupling is merely a delayed result of the already widely developed influence of the cerebral cortex on all levels of the central nervous system (Hernández-Péón *et al.*, 1956; Shumilina, 1959, 1961; Gavlichek, 1958).

What constitutes this participation of the cortex in the determination of the initial coupling of the conditioned reflex? Several years ago, in relation to the study of the "switching"^{*} of conditioned reflexes, we demonstrated that the initial forms of new conditioned associations always arise with the participation of the cerebral cortex (Anokhin and Artem'ev, 1949). This participation, however, is extremely interesting. In bringing about the comparison and synthesis of the numerous and diverse afferent influences on the organism, the cerebral cortex can exert an active influence on the subcortical synapses over the corticofugal connections by either readdressing or completely suppressing the incoming impulses.

The essence of our experiments lay in the fact that an animal placed on a platform with two feeders at opposite sides was allowed the choice of either one of the feeders according to the presented conditioned signal.

In the experiment described, the conditioned signal represented by the tone "la" was reinforced at the right feeder, while a bell was reinforced at the left feeder. After

* Reference to Glossary.

prolonged training in this arrangement of signals, completely automatic conditioned reflexes were eventually established in the animal. At the tone "la," the animal would quickly rush to the right and there await the alimentary reinforcement. At a certain time, the location of the reinforcement was suddenly changed. The tone "la" was now systematically reinforced only on the opposite side, i.e., on the left side of the platform. This form of experiment was called "switching" in the Pavlovian laboratory.

Since in our experiment the conditioned stimulus did not lose its signal meaning and we have two indices of the conditioned reaction, secretory and motor, we have the opportunity to observe an extremely gradual transition from one motor reaction to the other.

It turned out that after the change in the location of the reinforcement, the initial conditioned motor reaction to the right began to change at the end of the former motor reaction. Initially the animal ran just as before to the right side of the platform in response to the tone "la." The animal began to run to the new side of the reinforcement at the end of the action of the conditioned stimulus, i.e., at the 15th second, then at the 13th, 10th, 5th, and 3rd second of the action of the conditioned stimulus. The *first second* of the reaction in the original direction, however, persistently resisted switching to the new meaning. For a very long time during the period of switching, upon presentation of the tone the animal would immediately rush to the right feeder. After 1-2 seconds, though, it would go to the new side, i.e., to the left feeder. We called this the reaction of the "first second." It persistently resisted switching and actually remained "unswitched." This extreme stability of the reaction of the "first second" compelled a consideration of its predominantly subcortical determination.

In a series of variations of the experiments we demonstrated, however, that a switching of even this part of the reaction is possible. It occurs on the basis of the *active involvement of the cerebral cortex in the control of subcortical processes*, redirecting them and thereby serving as a "switch." This could be seen from particular characteristic indices. For instance, if the cortical control was deliberately weakened by allowing the animal to go into a state of drowsiness, as a rule the reaction of the "first second," in accordance with the prior meaning of the conditioned stimulus (right side), was clearly manifested. This phenomenon could be reproduced even when the reaction of the "first second" had been eliminated by training by the time of the test.

On the other hand, during the stage when the reaction of the "first second" still remained stable, it could be completely eliminated by an orienting-investigative reaction occurring at the moment the conditioned stimulus is applied. In this case, however, the latent period of the motor reaction increased considerably. In all these cases the motor reaction was always correct, i.e., the animal ran to the left in accordance with the new meaning of the conditioned stimulus "la."

We have explained this case by saying that the most automatic component of the motor reaction (the "first second"), being the component of the switching, is the fastest one because at this moment the excitation spreads directly over the subcortical systems (Anokhin and Artem'ev, 1949). Extirpation of the sensorimotor zones of both hemispheres does not eliminate this kind of general excitation (Koriakin, 1959).

However, at the height of the synthetic activity of all the afferent influences of a

given moment, the cerebral cortex can easily alter the interaction of impulses at the level of the subcortical apparatuses and inhibit the unimpeded development of the rapid subcortical component of the "first second" of the conditioned motor reaction (Fig. 4.3).

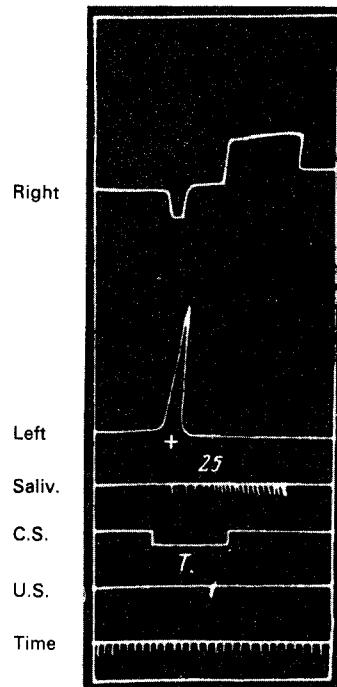


FIG. 4.3. Kymogram showing the residue of the old conditioned reaction to the left (marked by a cross). As shown by the record, even at their 25th presentation, feedings on the new side could not eliminate the reaction of the "first second." Right, Left, right and left side of reinforcement; Saliv., recording of salivary secretion; C. S., instant of presentation of conditioned stimulus; U. S., presentation of unconditioned stimulus. Time in seconds.

As is evident from the description presented above, we by no means reject the possibility of some form of coupling of a conditioned reflex nature at the subcortical level. However, with the development of the cerebral cortex and the increased complexity of the synthetic role of the orienting-investigative reaction during evolution, the cortex acquired the ability to influence any subcortical level, redirecting and inhibiting the excitation arising there.

It would be difficult to think otherwise. It is impossible to deny that the subcortical apparatuses, which receive a wealth of information from the environment and have an extraordinarily broad multisensory convergence, have an elementary coupling like that in temporary connections. This is my explanation for the observations of Fessard and Gastaut on conditioned electrical phenomena in the subcortical structures.

They could certainly have seen an electroencephalographic indication of conditioned

coupling in the subcortex, even though slow potentials are not a very reliable indication of this process. The appearance of this sign was undoubtedly preceded by a considerably prolonged orienting-investigative reaction with generalized activation of the slow electrical potentials of the cerebral cortex and with all those cortico-subcortical reverberations of impulses *which are an inalienable mechanism of the stage of afferent synthesis*. In other words, the cerebral cortex actively intervenes in the activity of the subcortical apparatuses even at the very beginning of the elaboration of a conditioned reflex.

Therefore, it would be imprudent to assert that the manifestations of a conditioned reaction shown on the electroencephalogram at the level of the reticular formation indicate that the initial coupling of the conditioned reflex occurs exactly here.

Our analysis of the coupling of the conditioned reflex performed long ago according to the view of the participation of the cerebral cortex and the subcortical apparatuses in this process has shown that such interrelations are formed over the entire brain. Conditioned coupling is undoubtedly of a *vertical* nature, but only the temporary connections of different levels of the brain have a different behavioral significance and a different physiological composition which is determined by the extent of afferent synthesis essential for the elaboration of the conditioned reflex (Anokhin, 1932a, 1932b, 1949c, 1955a, 1958a, 1959a, 1964a).

These data of our laboratory agree well with the latest neurophysiological demonstrations of the direct influence of the highest levels of the central nervous system on all points of synaptic aggregations located on the pathway of the reception of afferent signalizations from the periphery (Hernández-Péón, 1959; Livingston *et al.*, 1953; and others).

Admittedly, due to the methodological characteristics of their investigations (direct stimulation of the reticular formation), these investigators had no way of noticing this centrifugal influence on the series of the afferent impulses of the reticular formation. It would be physiological nonsense to ascribe to the reticular formation an *initiative role* in the active selection and active inhibition of individual series of ascending afferent information.

Actually, the active central action on the series of peripheral afferentations serves only the more general process of the entire brain, i.e., afferent synthesis, which is brought about, as we shall see below, by means of the multilateral convergence of impulses on the cells of the cerebral cortex. This synthesis, however, is not a disorganized pursuit after afferent environmental influences which give rise to millions of nerve impulses. It patterns the critical moment of behavior: *the making of a decision to act in a specific way and to pattern a specific behavioral act*.

This performance of the central nervous system can be brought about only where the initial incentive, the characteristics of a given situation, and the appropriate material available in the memory all become synthesized. Such a place is the cerebral cortex, which perceives all kinds of information in the form of extremely broad convergences and overlappings of impulses, with the participation of the same cortical elements in the same ascending series of impulses (see Chapter 5).

Thus, the concept of the coupling of a complex reflex as a function of the reticular formation developed only because the first stage in the elaboration of every conditioned

reaction, the synthesis of all afferent influences by means of the orienting-investigative reaction, was not taken into consideration. Developing as a consequence of the orienting reaction is the stage of afferent synthesis, which is based on the simultaneous action of both the indifferent and the unconditioned stimulus.

A direct confirmation of the above considerations on the levels of coupling are the highly interesting long-term experiments of Belenkova, who completely removed the cerebral hemispheres in cats and subsequently was able to elaborate conditioned reflexes in them (Belenkova, 1950a, 1950b, 1957, 1962; Belenkova and Chirkov, 1963). True, these conditioned reflexes did not have all the properties of normal conditioned reflexes, but nevertheless they give evidence of the presence of potential capacities for the formation of conditioned coupling in the subcortical nuclei.

Belenkova's experiments directly confirm the fact that those elementary processes of orientation, the formation of emotional states, and the capacity for association, which undoubtedly take place in the subcortical apparatuses, are capable of effecting a conditioned coupling. Belenkova presents a diagram in which he, just like Fessard and Gastaut, attempts to reconcile from his own data previous concepts on the exclusive cortical coupling of the conditioned reflex with the latest advances in neurophysiology, especially with the physiological properties of the reticular formation (Fig. 4.4).

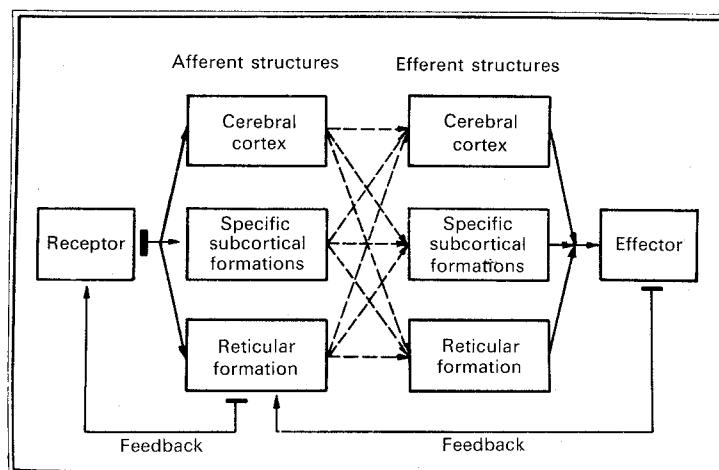


FIG. 4.4. Diagram of the levels of the central nervous system that participate in the formation of the conditioned reflex. As can be seen, this diagram introduces subcortical formations into the coupling process of the conditioned reflex, just as in the diagram by Gastaut (Fig. 4.2). In spite of the introduction of additional links, the diagram is constructed on the assumption of two foci of excitation in the cerebral cortex.

As can be seen from this diagram, the coupling of the conditioned connection is possible at all levels of the subcortex and the cerebral cortex. Naturally, this coupling is easier *the more complete an afferent synthesis by the rest of the cerebral mass in the cortex and the subcortical apparatuses is possible*. One must agree that all connections are of a multilateral nature but are especially facilitated in the presence of an ascending activation of cortical activity.

A conditioned connection, resulting from a previously developed afferent synthesis, can develop faster and more easily the more extensive the possibilities are of afferent synthesis in the nervous system. Probably this is the decisive factor in Belenkov's highly convincing experiments if, of course, it is assumed that *the entire cortical tissue was removed.*

CONCEPTS CONCERNING THE NATURE OF THE COUPLING PROCESS

In recent years in connection with the development of the morphology of the nervous system and of delicate electrophysiology, there arose the need to explain the detailed mechanisms of coupling itself, i.e., the very nature of the coupling process and its stability for long periods.

These new concepts illustrate in the best possible way the correctness of Pavlov's statement concerning the dependence of our views and hypotheses on the level of development of suitable methods of investigation and scientific concepts.

Lorente de Nó (1933a, 1933b, 1934, 1949) showed for the first time that impulses coming into the central nervous system do not always spread over it progressively and linearly from the point of entry to the point of exit onto the peripheral apparatuses. This is what is suggested by the classical definition of the reflex and the concepts formed concerning the function of the central nervous system. It turned out that there are special structures in which impulses, once having entered them, find themselves, so to speak, in a circular "trap," continuing to spread from element to element in a closed loop for a long time, as in a reverberating circuit (Fig. 4.5).

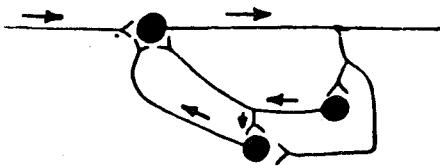


FIG. 4.5 Diagram showing the structure of a "trap of excitation".
From Lorente de Nó (1933a); see Magoun (1963, p. 16).

Since investigators were always seeking some structural equivalent of *prolonged functioning* when speculating on the mechanisms of memory and the coupling of the conditioned reflex, the morphological discoveries of Lorente de Nó immediately attracted attention. They were incorporated by some investigators into the concept of the coupling of conditioned reflexes. Actually, some process connecting two external stimuli could indeed become permanent after having entered such a "trap of impulses" and could subsequently be elicited arbitrarily as a result of acquired experience. This concept was quite favorably received by a number of investigators (Rashevsky, 1938; Young, 1938; Hilgard and Marquis, 1940, 1961; Householder and Landahl, 1945).

These investigators expressed the proposition that memory as a conditioned reflex experience is stored in the central nervous system in the form of such specific "traps" (closed self-reexciting chains). However, the support given this explanation can be understood only in the sense that Lorente de Nò, through his discovery, had offered the first realistic hope of finding the structural equivalent of memory and conditioned coupling.

There are, in fact, many contradictory data which provide convincing support that the "traps of impulses" cannot be the mechanism of memory and stabilization of past conditioned reflex experience.

First, as Eccles correctly points out (1953, pp. 218-219), this explanation could apply to short-term memories, i.e., to what in the physiology of the conditioned reflex has been called the trace process. It can hardly be considered possible that the organism, needing millions of memories, would perform this function so uneconomically in the cellular elements of the brain, as it would require at least millions of continuously circulating cycles of impulses.

From our point of view, the most important objection to this explanation is that not all kinds of impulses enter the "trap," but only those sensory impulses which have been reinforced by another excitation from some vitally important activity of the organism. Consequently, if we accept the explanation presented above, we must also explain how the unconditioned impulses "lure" impulses from the indifferent stimulus into the "trap."

Moreover, it is extremely difficult to accept the presence of such closed cycles of impulses without explaining by what pathways this "trap" can be connected with a conditioned stimulus which, acting on the central nervous system, can often exert its influence far away from this "trap." It is especially difficult, however, to assume that conditioned coupling takes place on the basis of the continuous circulation of impulses if one proceeds from data of anesthesia, fainting, hypothermia, etc. Numerous experiments show that none of these radical influences on the nervous system removes what has previously been elaborated in the animals as conditioned reflexes, even if this experience was acquired a year or longer before general anesthesia (Gerard, 1960). It is difficult to assume that the circulating impulses, which of course must first of all differ as to the parameter of frequency, would not be changed in any way by prolonged sleep or hypothermia.

Meanwhile, we know from medical practice that previously acquired experience does not lose its accuracy and adaptation to the corresponding external stimuli either after general anesthesia or after prolonged hypothermia. All these considerations enable us to conclude that the "traps of impulses" may be used to explain only some trace phenomena of short duration. They are, however, totally unsuitable for an explanation of the conditioned reflex experience of animals and man, which is highly stable and accurately retained throughout life.

In recent years, with the discovery of structural transformations in the synapses after prolonged conduction of the same impulses by them, the old views of Duval (1895) concerning the convergence and divergence of synaptic formations have been unexpectedly restored. As is known, Duval developed on this basis his theory of the alter-

nation of sleep and wakefulness. These at first purely speculative concepts acquired a definite significance in connection with the latest, highly refined investigations of synaptic activity. It was shown that after training of the synapse, its structure changes in the sense that the distance between the individual elements of the presynaptic and postsynaptic formations decreases considerably.

It was justifiable to think that such a convergence of structural elements that undoubtedly participate in the trans-synaptic propagation of impulses will create conditions for a facilitated conduction of impulses. Since most neurophysiologists dealing with the nature of coupling consider the formation of the conditioned connection to be a result of the facilitation of the conduction of impulses from an indifferent stimulus, the observations of purely structural changes in the synapses were applied to that problem. The course of structural changes may be observed for several weeks.

The investigations of Eccles and McIntyre on multisynaptic reflexes have shown that the presence of discharges over a prolonged time through these synaptic formations leads to a shortening of the latent period in the conduction of impulses and to closer contact between the neural elements. Eccles holds that this facilitated conduction of impulses may be a result of an excess accumulation of transmitter in the intersynaptic spaces (Eccles and McIntyre, 1953; Eccles, 1958a, 1958b).

In connection with this point of view, the question of the role of the dendritic spines of nerve cells in general and of the cerebral cortex in particular acquires special interest. From the classic work of Ramón y Cajal (1955), it is known that the long dendrites of the cortical pyramidal nerve cells are completely covered with formations which outwardly resemble spines and are especially visible upon preparation of the brain by the Golgi method (Fig. 4.6). Since then these spines have continually held the interest of both neuroanatomists and neurophysiologists. What is their functional significance? In recent years several works have appeared on the analysis of the fine structure of these spines by the method of electron microscopy. It was shown that each such spine has a quite specific structure and constitutes an organic whole with the protoplasm of the dendritic formations.

Taking into account the latest data on the structure of the neuromuscular synapse (De Robertis, 1958), we may assume that a spine is the external appearance of an extremely exaggerated postsynaptic membrane and an excessive increase in its structural chemical contacts with the substance of the dendritic protoplasm. A question arises requiring serious consideration: to what substrate does the synapse belong or, more accurately, its components, the presynaptic and the postsynaptic structure?

How are the trophic and the specific functional parameters of synaptic activity distributed?

In a large series of experiments with crossed anastomoses of nerve trunks of different functional significance we obtained impressive data indicating that we must change our concepts of the structure of the synapse and, most importantly, *of the functional affiliation of its various parts*.

For example, after a heterogeneous anastomosis of n. vagus with n. lingualis, the fibers of the vagus nerve grow into the peripheral branch of the lingual nerve and completely restore in the lingual mucosa the structure of those receptor formations

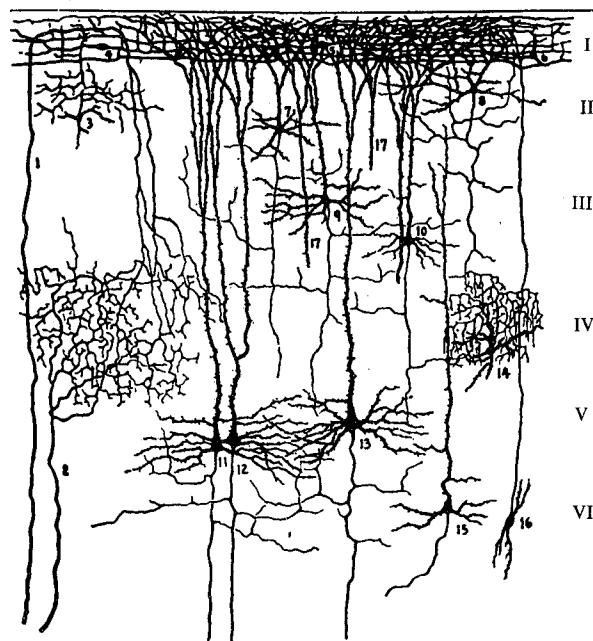


FIG. 4.6. Diagram after Lorente de Nò, showing the relationship of individual cortical neurons. Clearly visible are the "spines" on the dendrites of the large pyramidal cells, the recurrent collaterals of the axons, and the universal representation of all layers of the cerebral cortex in the first plexiform layer. From Chang (1951, p. 3). I-VI, cortical layers; 1-17, cortical structures.

which always occur in this zone of innervation of the lingual nerve. Moreover, these receptors functionally correspond completely to the ordinary lingual receptors that perceive the different properties of alimentary substances, though the impulses from them reach different nerve centers (Anokhina, 1946).

In exactly the same way, anastomosis of n. vagus with n. radialis leads to a number of phantom phenomena because there is a restoration after regeneration of those specific receptors in the skin which were always characteristic of the skin and muscles in the zone of innervation of n. radialis. As a result of these relations, streaked stimulation of the skin in the zone of the artificial innervation by the vagus nerve leads to immediate coughing spells which sometimes correspond exactly to the rhythm of stimulation. On the other hand, compression of the interdigital muscle gradually leads to vomiting (Anokhin and Ivanov, 1935a, 1935b). If we proceed from the quality of the stimulus applied, we can state correctly that the receptors of the skin and those of the muscles have been restored to their natural function, in spite of the fact that the cutaneous and the muscular zones of the radial nerve are innervated in this case by the vagus nerve.

If, however, we deal with the structure of the synapse, which in all cases consists of a presynaptic and a postsynaptic formation, experiments with heterogeneous anastomoses of *efferent nerves* are especially convincing. We obtained the most illustrative results in experiments with anastomoses between n. phrenicus and the chorda tympani. As is

known, n. phrenicus is a muscular nerve and innervates the striated muscles of the diaphragm by way of a neuromuscular synapse having an entirely specific function. The chorda tympani, on the other hand, innervates a secretory organ, the submaxillary gland, and has a neurosecretory synapse. What synapses are formed in the salivary gland after anastomosing n. phrenicus and the chorda tympani when the fibers of the phrenic nerve have grown into the salivary gland?

Experiments have shown that stimulation of the phrenic nerve above the site of anastomosis at a certain stage of regeneration yields a copious salivary secretion, *as if we were stimulating the chorda tympani* (Alekseeva, 1961). It is quite evident that the synaptic formations have regenerated according to their initial physiological specificity, even though fibers of the phrenic nerve had grown into the salivary gland.

How does one interpret the above-described results of experiments with functionally heterogeneous anastomoses of nerve trunks?

In order to understand the full meaning of the results presented above and their significance for the problem under consideration, we must note two important circumstances :

1. The descending Wallerian degeneration, which develops after severing the chorda tympani or the lingual nerve, encompasses all the peripheral structures, leading to the complete disappearance of both the receptors of the tongue and the neurosecretory synapses of the salivary gland. This results from the *trophic* influence of the central neuron on all peripheral structures.

2. Nerve fibers of an entirely different functional nature restore synaptic formations that correspond exactly to the previous tissue affiliation of the synapse. That is, the motor fibers restore to the secretory cell its previous function.

On the basis of these two propositions we can more confidently construct a diagram of the *twofold affiliation* of synapses, *the trophic and the functional* (Fig. 4.7).

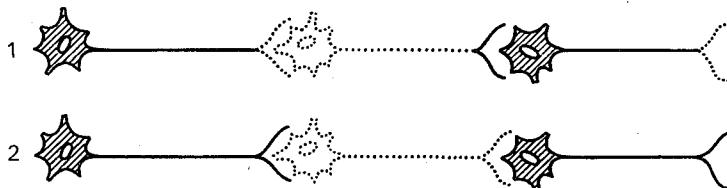


FIG. 4.7. Diagram of relation between individual neurons. 1 represents a functional affiliation of the synapse; 2 represents a trophic affiliation of the synaptic formations.

We can now return to the question of the role of those structures which are scattered over all the dendritic formations of the large cortical cells and are called spines. To what substrate do these spines *trophically belong*? Either they are related to those axons which terminate at these spines, or they are, in the molecular sense, a highly exaggerated structure which *trophically* and *functionally* belongs to the receiving substrate, i.e., in this case to the receiving neuron and its dendrites.

It appears to me that the spines, similar to postsynaptic formations in general, reflect to an extremely high degree the functional properties of the *subsequent* stage in the

transmission of information since they are under the continuous influence of the axoplasm of the neuron.

From these considerations we conclude that by its very nature the synapse cannot determine any sequence of two impulses destined for different points of the brain since we would then have to assume that several impulses differing in modality converge at the same synapse.

In fact, by examples of monosynaptic arcs of spinal reflexes, Eccles and other investigators emphasize only the simple training of the synapse with respect to the *same* excitation repeated many times. Consequently, we are confronted with two entirely different physiological mechanisms, since in the coupling of the conditioned reflex we are always dealing with the association of two excitations in the substrate of the nervous system. These excitations differ in physiological modality, localization, and biological significance for the organism. From this point of view, the so-called "post-tetanic potentiation" cannot assist us in explaining the coupling mechanism of the conditioned reflex either.

There are also many purely neurophysiological objections to the theory of "synaptic training" and the subsequent prolonged change in the structure of the synapse. Of course, in so far as there are numerous applications of the same stimulus, we cannot exclude some kind of "training" of the same synaptic formations; and yet this is hardly decisive for the establishment of vitally important conditioned reflex activity.

It is already well known that it is possible to perform very prolonged training by two stimuli, a bell and a light, without success in the sense of a permanent stabilization of this connection. On the contrary, with each successive exercise the initially formed connection between the bell and the light is extinguished.

On the basis of these considerations I feel that the most important factor in the coupling of a conditioned reflex is the combination of two such environmental stimuli so that the latter of them invariably provides the organism with a vitally essential advantage or with satisfaction. From this biological view, the "training" of the synapse is evidently relegated to a secondary position, since the whole meaning of the coupling activity of the brain lies essentially in the fact that in a number of cases the organism must secure a successful adaptation to environmental conditions *even during the first coincidence of external stimuli*.

Indeed, the life of a highly organized animal would be insecure if "training" were required to increase the conducting capacity of the synapses in order to avoid some mortal danger or the destruction of the organism. The animal would hardly need any more training after the first time....

As an illustration of this proposition I shall relate a case from my own observations. Once, while leading a dog to an experiment, I opened the entrance door so clumsily that the animal's paw was caught under the door and was quite badly hurt, as was evident from the animal's heart-rending scream. From that time on, upon approaching the door the animal always stopped far off and, looking warily at the door, went around it at a respectful distance.

It is quite evident that a single time is enough to establish a conditioned reflex connection between the sight of the opening door and the extremely painful stimulation

of the paw. What, however, would have happened to the animal if it had been necessary to repeat the "training" several times in order to establish this association?

The material presented in this chapter emphasizes that conditioned reflex coupling is not a consequence of mere "training" of the same synapse by the same stimulus. Neither is it the result of the mere sequence of any two stimuli. It is a sequence of stimuli invariably terminating in some vitally important activity or state which is important to the organism as a whole. The fact that in such cases the association is established as early as the first time shows that the crux of the matter lies solely in the *quality of the stimuli to be combined* and not in their purely quantitative parameters. It is the high biological activity of the latter stimuli that promotes in some not yet fully understood way (see Chapter 5) the firm "coupling" of two stimuli acting consecutively on the nervous system.

A few more considerations may be added to the observations presented above concerning the unsoundness of the theory of the training of the synapse in explaining conditioned reflex coupling. We know that each nerve cell, when it is a component of some highly versatile activity of the whole brain, participates in each specific activity with only a few of its synapses.

Thus, the training of any complex system of excitation within the limits of a given cell amounts to the training of a certain number of synapses. However, these same synapses in a completely different system of cells may also participate in a different activity which may not have any physiological or logical relation to the first one. The question naturally arises as to what influence these synapses that have been changed by training may exert on the other new activity in which they must take part. They will undoubtedly introduce a certain dissonance into the formation of this new activity.

All the considerations presented above lead us to the conclusion that the mere concept of the training of synapses and of their structural changes that facilitate the conduction of excitation cannot explain the intimate mechanism of the coupling of the conditioned reflex.

CHAPTER 5

The Hypothesis of the Convergent Coupling of the Conditioned Reflex

BEFORE I formulate an idea which I have been concerned with for several years, I must first define certain terminology related to the problem as a whole.

The problem of "the coupling of the conditioned reflex connection" in its pure form, as formulated in Pavlov's laboratory, has become increasingly complicated by other concepts adapted from various related sciences. Behaviorism, for instance, which examines the dependence of integrated behavioral acts on changes of external and internal factors, prefers to operate with the terms "learning" and even "conditioning." But actually any learning involves the formation of a new conditioned reflex connection. Admittedly, in integrated behavioral acts this formation of a conditioned reflex connection is not as physiologically evident as in the classic salivary reflex since it accumulates a great number of additional processes and mechanisms.

On the other hand, about 30 years ago a tendency appeared to call any sequential chain of processes formed in the nervous system by preceding training and reproducible on signal a "conditioned reflex." For example, the sequential action of the pair of stimuli "sound-light" is well known. As a result of the repeated presentation of these stimuli in the same sequential order, the connection between them in the nervous system is stabilized in such a way that even the presentation of sound alone leads to the appearance of a depression of the α rhythm in the occipital region, i.e., a depression characteristic of the actual presentation of light.

As was shown in Chapter 2, the analogy to the conditioned reflex is obviously not consistent. Here it is appropriate to recall these considerations once more. "Coupling" of two sequentially developing influences on the organism in its protoplasm is undoubtedly the most ancient feature of living organization, particularly of the nervous system, and is the mechanism created by evolution especially for the analysis and synthesis of external influences.

It was the historical role of the nervous system to specialize and considerably lower the organism's threshold of sensitivity to individual, vitally important influences. At the same time it also specialized as a substrate establishing an extremely rapid connection between two sequential influences on the organism; for, as we have seen, the organism is a direct consequence and reflection of this agelong sequential order of phenomena in the external world (see Chapter 1).

It is therefore natural that with the persistent repetition of any series of sequentially

acting agents we can initially elaborate a mechanism of anticipatory excitation, this being an elementary mechanism of any living substance. Subsequently, however, this initial fixation of the actual sequential order in the processes of the nervous system is invariably extinguished and can no longer be reproduced.

The experiments of Karazina (1958a, 1958b) cited above (see Chapter 2) completely confirm that by itself this *passive* sequential order of a number of influences on the organism is totally inadequate for a long-term stabilization of the initially established connection between sequentially excited elements of the nervous system.

As the experimental work of the Pavlovian school shows, it is absolutely necessary for *this sequential series of influences on the nervous system to finally become essentially important for the life of the organism, i.e., for its physiological and biological functions.* This requirement distinguishes the classical conditioned reflex. As we have seen, "coupling of the conditioned reflex connection" results only if, immediately after the appearance of any indifferent stimulus, there has occurred an effect on the organism which is accompanied by an activity of the *inborn* structures of the organism, exciting its emotional sphere and radically changing the general condition of the organism.

Having developed two biologically opposite reactions of the organism which, in the form of defense mechanisms, ensure the *maintenance* of life and its preservation, evolution also endowed higher animals with the ability to make an emotional-physiological evaluation of the *biological nature* of external influences as positive or destructive. This enabled the animal to rapidly evaluate the vital significance of any change in the environment according to one of these antipodal physiological processes. This reinforcement by a generalized inborn activity is the basis of true conditioned reflex coupling. Such coupling always has an adaptive significance which ensures the animal's ability to develop, on the basis of a signal alone, a reaction preparing it for a future situation: either to avoid destructive influences or to beneficially use conditions promoting life (see Chapter 1).

Thus, in analyzing the nature of the coupling process, we must explain the ability of the nervous system to associate *those sequences of influences on the organism which recur systematically* and lead to a positive result in regard to the preservation of life.

The object of our further analysis will therefore be "coupling" of this type, i.e., those mechanisms which constitute the conditioned reflex in the classical sense. This means that first those components forming the basis of the conditioned reflex, i.e., *the indifferent and the unconditioned stimulus*, must be analyzed at the level of neurophysiological processes. Such an analysis of these components, utilizing all modern neurophysiological advances, has unfortunately not yet been done. As a result, concepts and terminology have survived which often do not correspond to our present knowledge concerning the functional properties of the brain.

During the elaboration of a conditioned reflex there undoubtedly occurs a critical change in the biological significance of stimuli. The "indifferent" stimulus acquires a "vitally important" meaning.

**THE NEUROPHYSIOLOGICAL NATURE OF INDIFFERENT
AND UNCONDITIONED STIMULI***The Indifferent Stimulus*

Taking into account the above-described critical change in which the indifferent stimulus acquires a new role, we must submit this concept to a more profound and detailed physiological analysis than has previously been made.

With this analysis there first arises the question of the *composition* of the reaction to the indifferent stimulus as it can be conceived on the basis of the latest neurophysiological investigations. We must accept the initial hypothesis that the effect from an indifferent stimulus, at least during the first presentations of the stimulus, differs in no essential way from any sensory excitation spreading over the *lemniscal* pathways. The principal difference may be that the basic background of cerebral activity during which an indifferent stimulus acts may be different from that during which a simple sensory stimulus acts. However, for an evaluation of the central composition of the reaction to an indifferent stimulus, this may be of no decisive importance.

The question of the *composition* of this reaction has never been discussed in the literature, even though it would seem that we must know the composition of the physiological components involved in the mechanism of conditioned reflex coupling. Moreover, the most intimate nature of coupling cannot be understood if there is no knowledge available concerning the neurophysiological nature of that which is "coupled."

In the light of modern neurophysiological advances, we can best visualize the impulses arriving into the central nervous system, particularly the cerebral cortex, by combining three electrophysiological indices: the electroencephalogram, the evoked potential, and the discharge activity of an individual neuron, i.e., of a single nerve cell. A correlation of these three indices, though they are far from perfect and are not yet understood in regard to their physiological meaning (Anokhin, 1958a, 1959a, 1963), nevertheless provides a definite basis for judging the fate in the central nervous system of impulses evoked by an indifferent stimulus.

Since our laboratory was the first to begin electroencephalographic investigations of the conditioned reflex (Laptev, 1941) with chronically implanted electrodes under the conditions of Pavlov's classical experiment, we have developed some concepts and approaches to evaluate the above-mentioned electrophysiological criteria of cortical activity. Our knowledge concerning this problem has been supplemented by the experimental results of numerous other laboratories which have provided a wealth of material on the same problem (Livanov and Poliakov, 1945; Livanov, 1952; Kogan, 1949, 1956; Rusinov, 1947, 1953; Shumilina, 1949, pp. 561-652; Yoshii and Hasegawa, 1959; Yoshii *et al.*, 1960a, 1960b; Yoshii and Ogura, 1960). All this enables us to more accurately and thoroughly evaluate both our own experimental data and those obtained by other investigators in studying the mechanisms of the coupling of the conditioned reflex, including the role of ribonucleic acid in this process.

Jasper (1963), Jung *et al.* (1963), and many others have conducted correlative investigations of the behavior of individual cortical elements during the elaboration of

conditioned reflexes. Aside from the evaluation of certain overall simultaneous changes in potential for numerous cortical elements (Anokhin, 1964b), their results have rendered the electroencephalogram of little use for an understanding of intimate processes at the level of intercellular relations in the cerebral cortex.

For this reason, in determining the fate in the central nervous system of impulses from an indifferent stimulus, we shall concentrate on the distribution and change of evoked potentials and on the evaluation of cellular discharges. The question naturally arises: how adequate are these criteria for revealing the intimate and undoubtedly extremely delicate processes of the coupling of the conditioned reflex?

Since I have already discussed this subject elsewhere (Anokhin, 1958a, 1964b), I shall now evaluate these indices only in regard to their application to the general purpose of this chapter, i.e., the determination of the fate in the central nervous system of the impulses evoked by an indifferent stimulus.

First of all I should mention the tremendous importance of general anesthesia with respect to the form and distribution over the cerebral cortex of the evoked potentials obtained by means of the same incoming excitation. In the publications of French *et al.* (1955), King (1956), Brazier (1957), Albe-Fessard *et al.* (1960), and a number of other investigators, it was already indicated that the nature of the anesthetic and the depth of general anesthesia are significant for the evoked potentials. However, it was necessary to perform special experiments.

My collaborator Nabil' (1964) carried out a comparative evaluation of the distribution of evoked potentials over the cerebral cortex in response to stimulation of the sciatic nerve *during the administration of various anesthetics*. He used ether, nembutal,

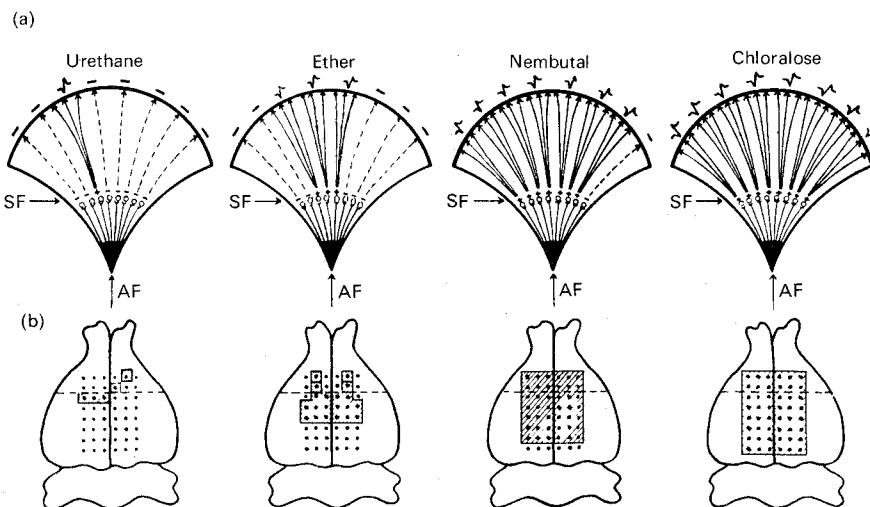


FIG. 5.1. Diagrammatic representation of degree of blocking of cortical evoked potentials resulting from a single stimulation of the sciatic nerve. Top row—blocking shown in the vertical plane; bottom row—blocking shown in its horizontal projection over the cerebral cortex on the basis of 48 lead-off points of the potential. AF, incoming afferentation shown by arrow; SF, level of subcortical formations.

urethane, chloralose, etc., i.e., those anesthetics which are most used in neurophysiological experiments. The evoked potentials were recorded from 48 cortical sites, which constitutes a standard network for all experiments and for all anesthetics.

One remarkable observation was made which unquestionably is of great significance for an understanding of the subcortical stage in the spread of any afferent impulses over the cerebral cortex (Fig. 5.1). As can be seen from the diagrams corresponding to the four different anesthetics, the evoked potentials exhibit extremely diverse distributions over the cerebral cortex. While chloralose permits their manifestation over the entire cerebral cortex, from the frontal to the occipital regions, urethane, as the antipode of this anesthetic, permits the manifestation of the evoked potentials only in a very small region of the cerebral cortex in the area of sensorimotor localization.

The comparative experiments of Nabil' make possible the following propositions:

1. It is essentially possible for impulses arising during threshold stimulation of the sciatic nerve to pass through the subcortical apparatuses and, upon reaching the cortex, create an appropriate evoked potential over the entire surface. The regions of destination *actually* receiving this information from the subcortical apparatuses and the form of information depend only on the various accompanying conditions (general anesthesia, wakefulness, natural sleep, emotional excitation, etc.).

2. Different effects of anesthetics on sensory impulses ascending to various regions of the cortex show that those sensory impulses which enter the nervous system over the lemniscal pathways are distributed to various nuclei even at the subcortical level and reach the cerebral cortex in the form of diverse information. This finding indicates the possible varieties of involvement by the subcortical apparatuses in the passage of sensory impulses (arising from an indifferent stimulus).

From the conclusions presented above it follows that the distribution of the evoked potentials over the cerebral cortex and especially the form of these potentials may indicate, although indirectly, how the influence of the afferent impulses spreads. We must now ascertain how those series of ascending impulses which are evoked by an indifferent stimulus are subsequently distributed at the level of the cortical synaptic formations. It is clear that the actual coupling process takes place in the final stage of the processing of the ascending impulses; therefore, to understand the ultimate mechanism of coupling means to know those processes into which all ascending impulses are transformed at the cortical level.

A serious obstacle, however, to understanding the more specific destination of these diverse ascending impulses was the uncertainty concerning the electrogenesis of the individual components of the evoked potential.

The heretofore dominant *monistic* theory in the explanation of the evoked potential maintains, as we know, that the entire diversity of the components is derived from one series of ascending impulses which formed postsynaptic potentials at the axosomatic synapses. From the point of view of this theory, all the remaining components of the potential are derivatives of this initial stage of excitation. The only difference between individual investigators is that they propose different mechanisms of propagation of a single initial ascending impulse for explaining the origin of the negative potential of the evoked response.

Eccles (1964), Grundfest (1959a, 1960), and Morison and Dempsey (1942) regard the negative potential of the primary evoked response to be a result of the propagation of the postsynaptic potentials over the long dendrites of the cortical cells to the apical dendrites where they then form the negative component of the evoked potential. Roitbak regards the negative component as the result of excitation which emerged onto the axon and, over the *recurrent collaterals*, returned to the apical dendrites of its own neuron. In other words, this concept assumes that the negative component of the evoked potential may form only when the neuron has already begun to discharge. In forming a new postsynaptic potential, this recurrent excitation then creates the negative component (Roitbak, 1956).

Recently, however, our concepts of the composition of the evoked potential have markedly and fundamentally changed. At the same time, extensive possibilities have become available for understanding the mechanisms of the distribution of excitation over the synapses of the cortical cellular elements. In regard to this I am referring to a whole series of investigations of the evoked potential which were carried out in our laboratory during the first days of postnatal development of animals.

Investigations of the evoked potential during ontogenesis had also been conducted earlier, such as those in Scherrer's laboratory (Scherrer and Oeconomos, 1954; Marty *et al.*, 1959). However, since their results were not related to an evaluation of the nature of the evoked potential, these investigators did not consider the problem of interest to us now. Through the systematic ontogenetic experiments of my collaborator Ata-Muradova, it was demonstrated that there are at least four separate series of ascending impulses which determine the usual configuration of the evoked (cortical) potential. Each of these series reaches the cerebral cortex by way of its individual ascending pathways and is selectively distributed on specific synapses (Ata-Muradova, 1961, 1963; Albe-Fessard and Fessard, 1963; Purpura, 1959).

Related to this are microscopic investigations of cortical structures during the early postnatal period (Purpura *et al.*, 1960b). In these investigations it was shown quite convincingly that the synapses of the plexiform layer mature earlier than the axosomatic synapses of the fourth layer. In essence, this sequence of maturation is the basis for the physiological phenomenon studied by Ata-Muradova, i.e., the *early appearance of the isolated negative component of the evoked potential*.

In special morphophysiological investigations by Ata-Muradova and Chernyshevskaia (1961), it was directly demonstrated that before the basal dendrites of the fourth cortical layer have matured (first day after birth), conducting pathways ascend from the white matter *directly* into the plexiform layer. They form terminal ramifications only in the plexiform layer and have a completely developed structure.

The *independent* nature of the negative component of the evoked potential leads to new concepts concerning the very nature of the evoked potential in the cerebral cortex. However, the main purpose of this analysis of the physiological *composition* of the evoked potential lies in the extensive possibilities, with the concept of the *multiple* nature of the ascending influences on the cerebral cortex, for answering the question: how does a sensory impulse arising from an indifferent stimulus spread over various regions of the cerebral cortex and even over its various layers?

An answer to this question is absolutely essential in order to understand the nature and fate of the reaction to an indifferent stimulus and also the mechanisms of its interrelations with the reaction to an unconditioned stimulus.

At present I would like to discuss the experimental procedure by means of which we could determine the affiliation of any one component of the evoked potential with the various layers of the cerebral cortex, i.e., we could determine the *functional architecture* in the distribution of the ascending impulses. This was accomplished by Ata-Muradova's work involving thermal action on the surface of the hemispheres in the zone from which the evoked potential is recorded. We have found that this means of blocking the cortical processes is the most acceptable for a number of reasons. It allows an exact graduation of the degree of blocking action from the reversible to the irreversible stage. Moreover, upon applying a heated object to the surface of the cerebral cortex, we are absolutely certain that first the plexiform layer will be blocked, then the second, then the third, etc. This is of great value for morphophysiological correlations of the results (Fig. 5.2).

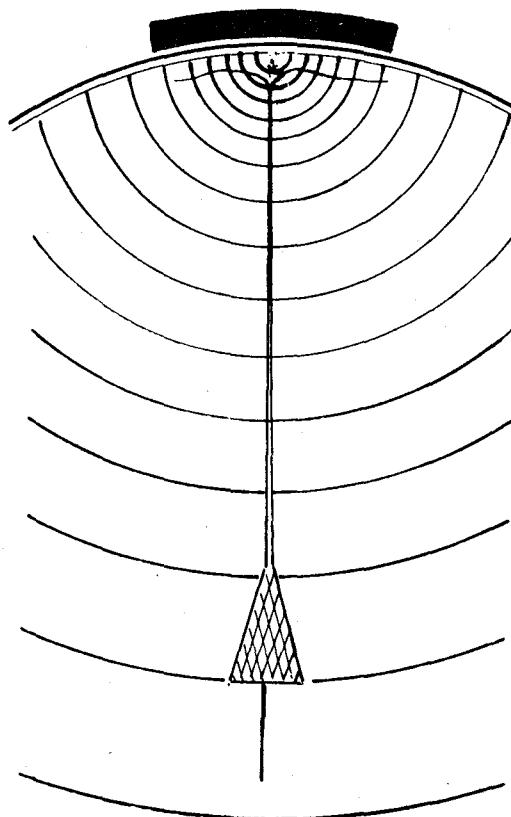


FIG. 5.2. Diagram of the action of a heating agent applied at the lead-off point of the evoked potentials. The heating gradient is shown in relation to the temperature of the heating agent and the duration of its action.

As was shown by this series of investigations, we have a quite definite picture of the whole dynamics of the distribution of ascending impulses in time and space, which essentially constitutes the basis for evaluating the fate of impulses from an indifferent stimulus.

In fact, if impulses from an indifferent stimulus enter the cerebral cortex as a sequential series aimed at various structures, it is by no means easy to indicate just which one of these several impulses has been "coupled" with unconditioned excitation. Therefore, only a detailed and purposeful investigation of the complete composition of an indifferent stimulus will allow us to answer this question.

An analysis of the results of heating the cerebral cortex has shown that in each of its sites several series of ascending impulses are distributed which form a definite configuration of the evoked potential on the cortical surface, depending on the strength of the individual series, the interval relations between the series, and the depth of localization of the terminal synapses (Fig. 5.3).

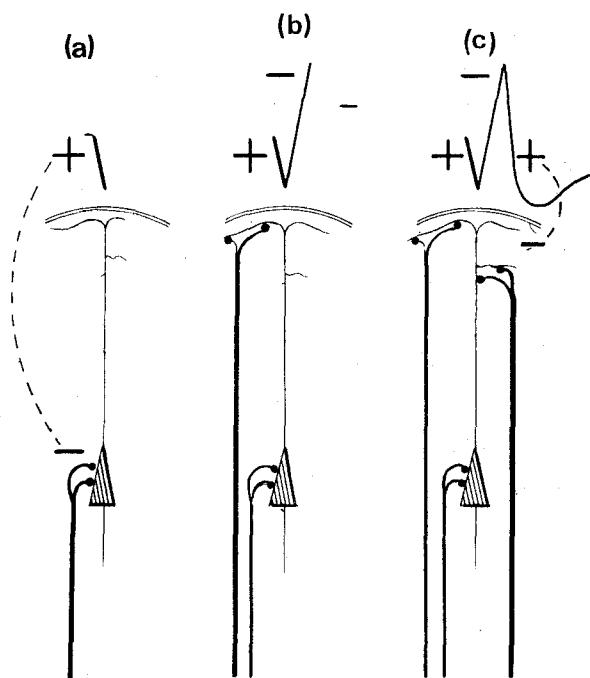


FIG. 5.3. Diagram of the gradual formation of the primary evoked potential in the cerebral cortex according to the investigations of our laboratory.

(a) Arrival of specific excitation at the axosomatic synapses, formation of the positive component of the evoked potential.

(b) Arrival of nonspecific excitation at the apical synapses of the cortical cells, formation of the negative component of the evoked potential.

(c) Arrival of nonspecific excitations at the central part of the long dendrite of the cortical cells, formation of the secondary Forbes discharge.

It was demonstrated that the secondary Forbes discharge, represented by the second positive wave of the evoked potential, is most probably formed as a dipolar result of the negative postsynaptic potentials that arise approximately in the lower part of the second layer, i.e., at the center of the long dendrites of the large cortical pyramidal cells (Fig. 5.4).

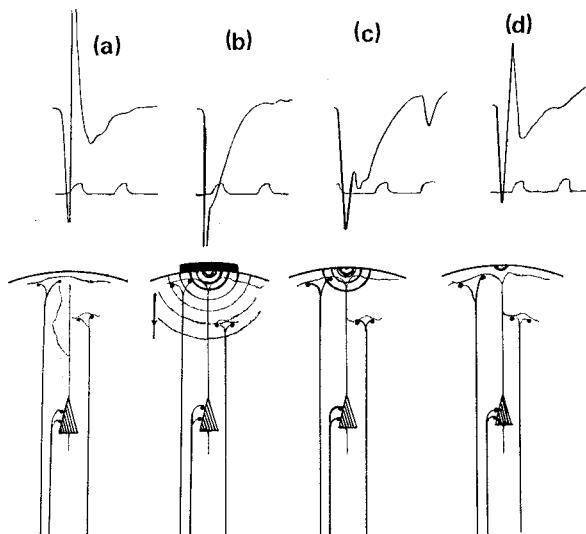


FIG. 5.4. Diagram corresponding to Fig. 5.3 explaining the changes in the true evoked potential upon application of a heating agent to the cerebral cortex.

- (a) Initial evoked potential and diagram of the ascending excitations corresponding to it.
- (b) Change in the configuration of the evoked potential half a minute after application of the heating agent to the cortex. The complete elimination of the negative component of the evoked potential and the unimpeded development of the positive potential from the axosomatic synapses can be seen.
- (c) Gradual disappearance of the heat block and return of the electric potentials. A condition was recorded in which two positive potentials, the axosomatic and the Forbes potential, were summed and formed positive fluctuations of very long duration. Only a part of the apical synapses, however, were released from the heat block, which is manifested on the actual evoked potential (top row) by a negative fluctuation in the ascending part of the potential.
- (d) Complete restoration of the initial relations with a somewhat decreased amplitude.

The latest investigations with a chemical analysis of the individual phases of the cortical evoked potential have shown that the differences between the series of ascending impulses extend far beyond the form of the electrical potential by which we usually evaluate and distinguish them. It is most probable that the same *seemingly homogeneous* electrical potential conceals a number of ascending series of impulses of diverse origin. Upon reaching a certain cortical site, they lose their individuality as they change into a uniform electrical phenomenon which may be either the summation of potentials of the same sign or some algebraic sum of two opposite electrical signs. Naturally, such combi-

nations (and there are quite a few of them in the electrical activity of the cerebral cortex) cause difficulty for the investigator when he is correlating the electrical phenomenon with true neurophysiological mechanisms.

It is known, for example, that by the direct application of GABA to the cerebral cortex, one can completely block the formation of the negative component of the evoked potential at this site (Purpura, 1960). This has led to the generally accepted opinion that GABA is a specific blocking agent of synapses becoming depolarized, since the negative potential of the evoked cortical response is of this origin.

Thus, the classification of potentials and their explanation are also based on the *electrical parameter* of an integrated neurophysiological process. Special investigations of the evoked potentials at various stages of postnatal development have shown, however, that blocking the negative component of the evoked potential by the application of GABA by no means occurs as a result of depolarization in its true sense. Rather, this blocking is caused by the suppression of the *given polarization* which has a neurochemical nature sensitive to the effect of GABA. Therefore, the focal point in the evaluation of the nature of the effect of GABA has shifted from the sphere of electrical specificity to the sphere of neurochemical specificity.

These conclusions may be drawn from Ata-Muradova's experiments. Having applied GABA to the site of the recording electrode, she obtained a suppression of the negative potential of the known evoked response. At the same time, however, GABA activated a new negative potential which had not been observed before the application of GABA but was now clearly manifested (Ata-Muradova, 1963).

Moreover, by the application of nembutal and strychnine, either separately or simultaneously, one can evoke a further splitting of the negative potential and show that there exists a whole "family" of negative potentials which are combined in the one generally known negative wave. With the application of specific chemical agents to the recording sites, there appears a dissociation of these combined negative potentials on the basis of their selective response to the applied substance (Ata-Muradova and Chuppina, 1964).

It is quite important for the problem being discussed to emphasize that each kind of negative wave in the cortex apparently has its own chemical specificity and is evoked by a separate series of ascending impulses.

If we consider that a single evoked potential results from a single impulse, then we can imagine how diverse the evoked potentials are when many series of impulses, or even whole complexes of these series, arrive simultaneously from several receptors. Each of these complexes may take on the role of an indifferent stimulus if it happens to coincide with an exceptionally strong, vitally important effect of some subsequent factors and becomes influenced by evoked or ascending impulses.

All the above data and considerations concerning the processes of excitation which are evoked in the cerebral cortex by any stimulus compel us to believe that the participation of the reaction from an "indifferent" stimulus in the coupling process is not as simple as it appeared to be. In fact, the very concept of "coupling" assumes something quite definite, a specific "focus of excitation." As it turns out, however, the indifferent stimulus brings about generalized series of ascending impulses. These series are of a

diverse chemical nature and enter the various layers and regions of the cerebral cortex at different time intervals. Thus the question arises: *which one of these numerous impulses forms the coupling of the conditioned reflex, and what characteristics must it possess for this purpose?*

As can be seen, the problem of the concrete mechanisms of the coupling of the conditioned reflex cannot be solved in a simple way, i.e., as some definite synaptic contact between specific sites of the brain. If to this multiplicity of cortical and subcortical processes of excitation which occur at different sites and different time intervals in response to indifferent stimuli one adds the inevitable orienting-investigative reaction with its highly generalized activation of cortical activity, the neurophysiological prerequisite for the subsequent coupling process will prove to be rather complex.

We must, however, evaluate all those conditions which are essential to the coupling process so that we may untangle the complex of diverse excitations. This can be done only after an equally detailed consideration of the second influential participant in the coupling of the conditioned reflex—the reaction to an unconditioned stimulus.

What is the fate of impulses arising in response to an unconditioned stimulus? What forms do they assume and to what regions of the cortex do they spread upon arriving there just after the impulses from an indifferent stimulus which also arrived as a series of ascending impulses?

We shall now attempt to answer this question.

The Unconditioned Stimulus

The decisive factor in characterizing the unconditioned stimulus, and the reaction in the nervous system to it, must be its biological role in the life of the animal. According to the generally accepted terminology developed by Pavlov, the unconditioned excitation, or the unconditioned reflex, eventuates on the basis of inborn structures of the central nervous system. Hence the identity of the two concepts of "unconditioned reflex" and "inborn reflex." It is assumed that in the evolution of animals only a vitally important reflex could become inborn.

In Chapter 2, I have already indicated that the two concepts of "inbornness" for the unconditioned reflex and "signalization" for the conditioned reflex may in certain cases overlap. Consequently these criteria may sometimes apply to both.

The electrophysiological analysis of the impulses entering the central nervous system, however, provides us with still another way of comparing inborn and indifferent excitation. Inborn excitation, which constitutes the basis of vitally important activity of the organism, as a rule leads to a generalized activation of the electrical activity of the entire cerebral cortex. This indicates that ascending impulses formed at the level of the subcortical centers of vitally important functions are capable of acting extensively on the apical dendrites of the cortical cells. We must assume that these generalized ascending impulses overlap in separate regions of the cerebral cortex.

The experiments of Shumilina (1964) in which the evoked potentials from a conditioned stimulus in the presence of unconditioned reinforcements of diverse biological modality were recorded show that both conditioned and unconditioned excitation converge on the same neural elements of the cerebral cortex. This can be shown when

a strong unconditioned excitation, such as the defense excitation, suddenly changes the degree of its activity under the influence of a selectively acting drug. As is known, the defense reaction of an animal is brought about through the mobilization of its sympathoadrenal system. That is, the adrenergic substrate located in the reticular formation and the hypothalamus sends impulses into the cerebral cortex (Agafonov, 1956; Anokhin, 1960b).

In Shumilina's experiments conditioned defense reactions to flashes of light were elaborated. Recording the electrical activity of the cerebral cortex showed simultaneously both the basic background electroencephalogram and the evoked potentials in response to the flashes of light. This enabled us to compare the overall electrical activity with the reaction evoked in the cerebral cortex by a single flash of light (Fig. 5.5a, b).

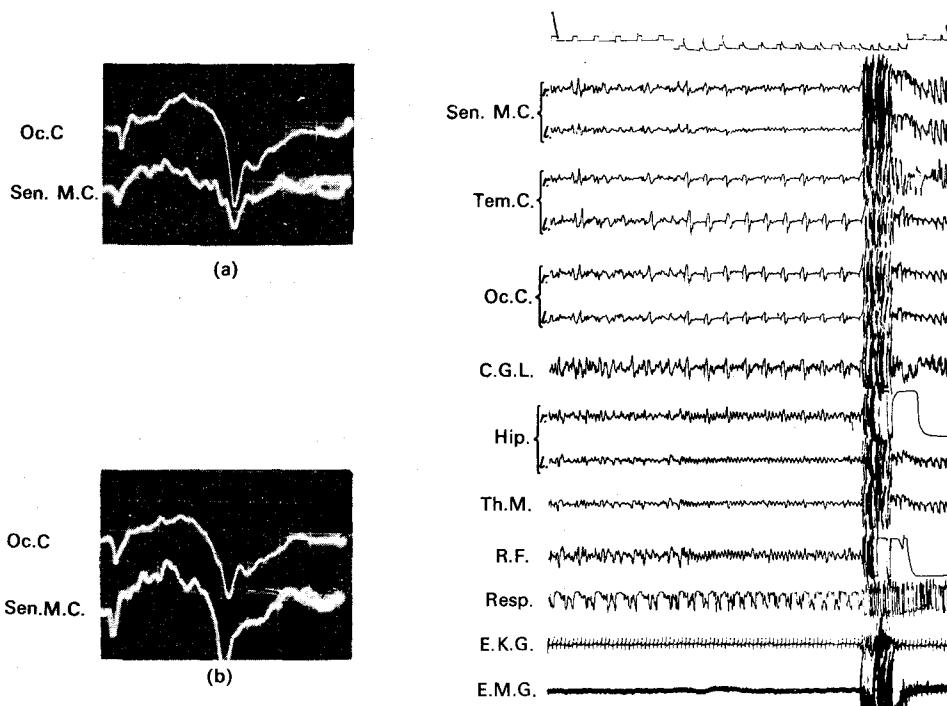


FIG. 5.5. Two examples (a and b) are given of the reaction of the cerebral cortex to flashes of light which act as conditional stimuli for a motor defense reflex. At left, evoked potentials; at right, records of electrical activity from 11 points of the cerebral cortex and of the subcortex. Sen. M.C., sensorimotor cortex; Tem. C., temporal cortex; Oc. C., occipital cortex; C.G.L., corpus geniculatum laterale; Hip., hippocampus; Th. M., thalamus medialis; R.F., reticular formation; Resp., respiration; E.K.G., electrocardiogram; E.M.G., electromyogram of hind extremity.

As can be seen from the above figure, the evoked potential in response to the flash of light has a rather stressed appearance since the flash of light is the signal of a defense

stimulus and corresponds to the stressed condition of the electroencephalogram, which indicates a maximum synchronization of the ascending series of impulses from the subcortical structures. However, the dependence of the form of the evoked potential on the overall emotional state of the animal directly proves that both the flashes of light, which once had been "indifferent," and the ascending impulses, which reflect the involved subcortical complex corresponding to the defense state of the animal at a given moment, are directed to the same nerve cells of the cerebral cortex.

The result of selective chemical action on the defense state of an animal validates these considerations. For example, if an animal in such a state is given a certain dose of chlorpromazine, both the behavior of the animal and the form of the electrical activity in the cerebral cortex change drastically (Fig. 5.6a, b).

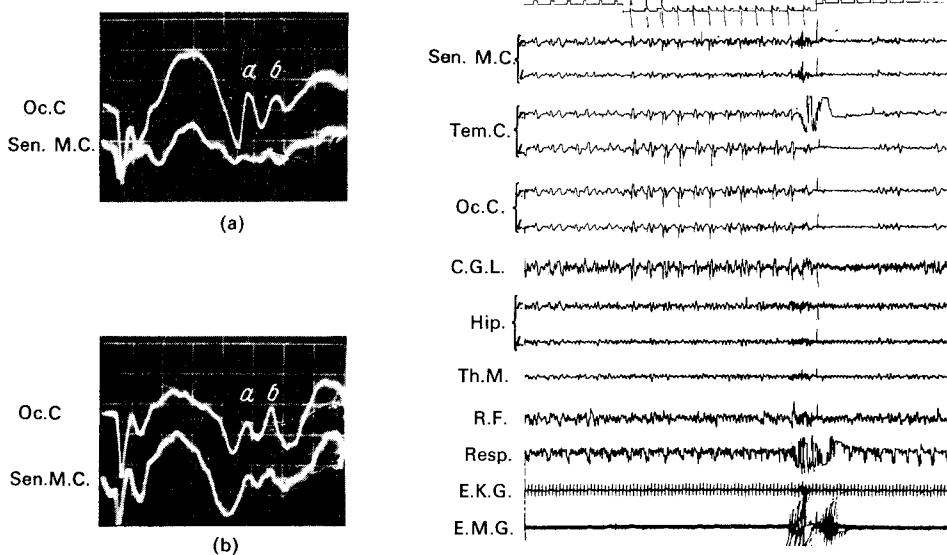


FIG. 5.6. The influence of chlorpromazine on the reaction of the cerebral cortex to flashes of light (a and b) in an experiment similar to the one described in Fig. 5.5. Chlorpromazine was injected 20 min before the recordings were taken. Significant changes can be seen. A dispersion in the descending phase of the evoked potential appears, and also a new fluctuation (a, b) appears which gives evidence of the release of a number of subcortical centers from the general stress of the defense reaction. Designations are the same as in Fig. 5.5.

The evoked potential in response to a flash of light loses its stressed character and is superimposed by a number of additional electrical waves which indicate the release of the series of ascending impulses (a, b). The appearance of separate negative electrical waves on the background of the first phase of positive waves indicates that the positive potential permits the formation of additional negative evoked potentials on individual neural elements. Consequently, the entire process of the transition from the stressed curve of the evoked potential to the other curve can be explained as follows.

In response to the flash of light a potential forms in the visual cortex at approximately the level of the afferent (axosomatic) synapses of the fourth field. According to the principle of the dipole, this concentrated postsynaptic negative potential induces a positive potential on the surface of the cerebral cortex. We use this as a criterion of the stressful state of the animal. If this potential is sufficiently strong, i.e., the potential is evoked by a strong ascending impulse and excites the cortical elements, it neutralizes any other negative potential which could originate in the plexiform layer on the background of the already existing positive potential. This situation is characterized by the stressed condition of the electrical activity at the moment when the animal is in a defense state (see Fig. 5.5).

In agreement with these considerations, any weakening of the subcortical stress, i.e., the elimination of the defense state, must also lead to a weakening of the postsynaptic potentials which, according to the principle of the dipole, form the positive potential at the cortical surface. This means that now the impulses entering the cerebral cortex from the other subcortical cells can break through the positive charge and manifest their negative character. This is what we see after application of chlorpromazine in the second case (see Fig. 5.6) (Shumilina, 1964).

Thus, any mobilization of synapses on the cortical cells must involve the elimination of competing impulses which reach the same cells by way of other synapses. On the other hand, when the cortical cells are no longer influenced by strong ascending impulses, they can then be influenced by other combinations of impulses formed by other synapses.

These competitive interrelations of impulses arriving from various functional systems make the electrical activity of the cerebral cortex extremely labile. It is important to note that strong ascending influences, such as those in the defense state, synchronize the activity of many elements and unify the cortical electrical activity, for example, the arousal reaction. An analysis of the activity of individual neurons shows that in this case most of them increase their discharge frequency (Jasper, 1963; Jung *et al.*, 1963).

To illustrate such a dependence of cortical activity on ascending impulses of a specific biological modality, the experiments of my collaborator Sudakov (1962) may be cited. As is known, during general anesthesia animals exhibit slow electrical activity of the cerebral cortex. It turned out, however, that the presence of slow electrical activity is directly related to the alimentary condition. If a hungry cat, for example, is placed under urethane anesthesia, the electrical activity of its cerebral cortex will differ appreciably from the electrical activity of a cat which had been fed before being placed under general anesthesia. The frontal lobes of the cerebral cortex of the cat will be in a state of desynchronization. It was shown that this desynchronization of the frontal lobes is substituted by slow electrical activity if an influence is exerted on the alimentary centers of the animal. The introduction of milk into the stomach and the injection of a glucose solution into the blood eliminate both the desynchronization of the frontal lobes and that of the hypothalamic lateral nuclei (Fig. 5.7).

This demonstrates that the initial facilitating factor for the cortical synaptic formations in this case is the excitation of the alimentary centers of the hypothalamus,

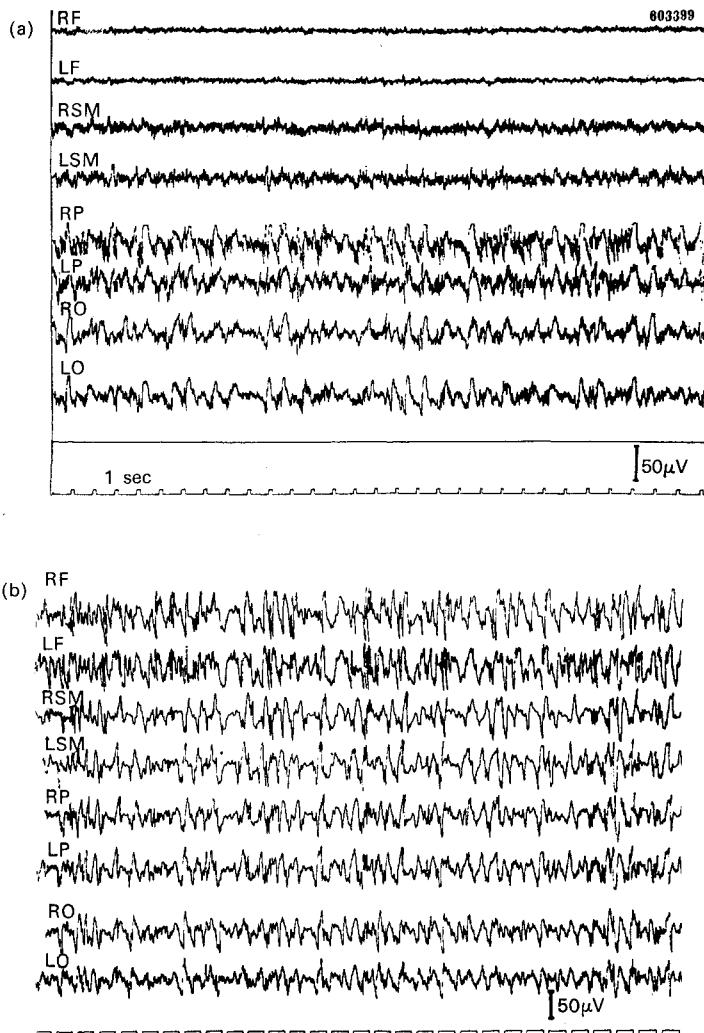


FIG. 5.7. (a) shows the electroencephalographic recording of a fasting cat under urethane narcosis. The desynchronization in the anterior areas of the cerebral cortex can be distinctly seen.

(b) Electroencephalographic recording from the same points of the cortex in a cat that has been fed before the experiment. The slow electric activity in the anterior areas of the cerebral cortex can be seen. RF, LF, right and left frontal cortex; RSM, LSM, right and left sensorimotor cortex; RP, LP, right and left parietal cortex; RO, LO, right and left occipital cortex.

which are well described in the works of Anand *et al.* (1955) and Brobeck (1957, 1960). Perhaps this dependence of generalized cortical activation on primary excitation of the subcortical centers by unconditioned stimuli is even more evident during local interference in the hypothalamic alimentary centers. Sudakov coagulated and polarized these hypothalamic centers with direct current (anode), whereupon the activation

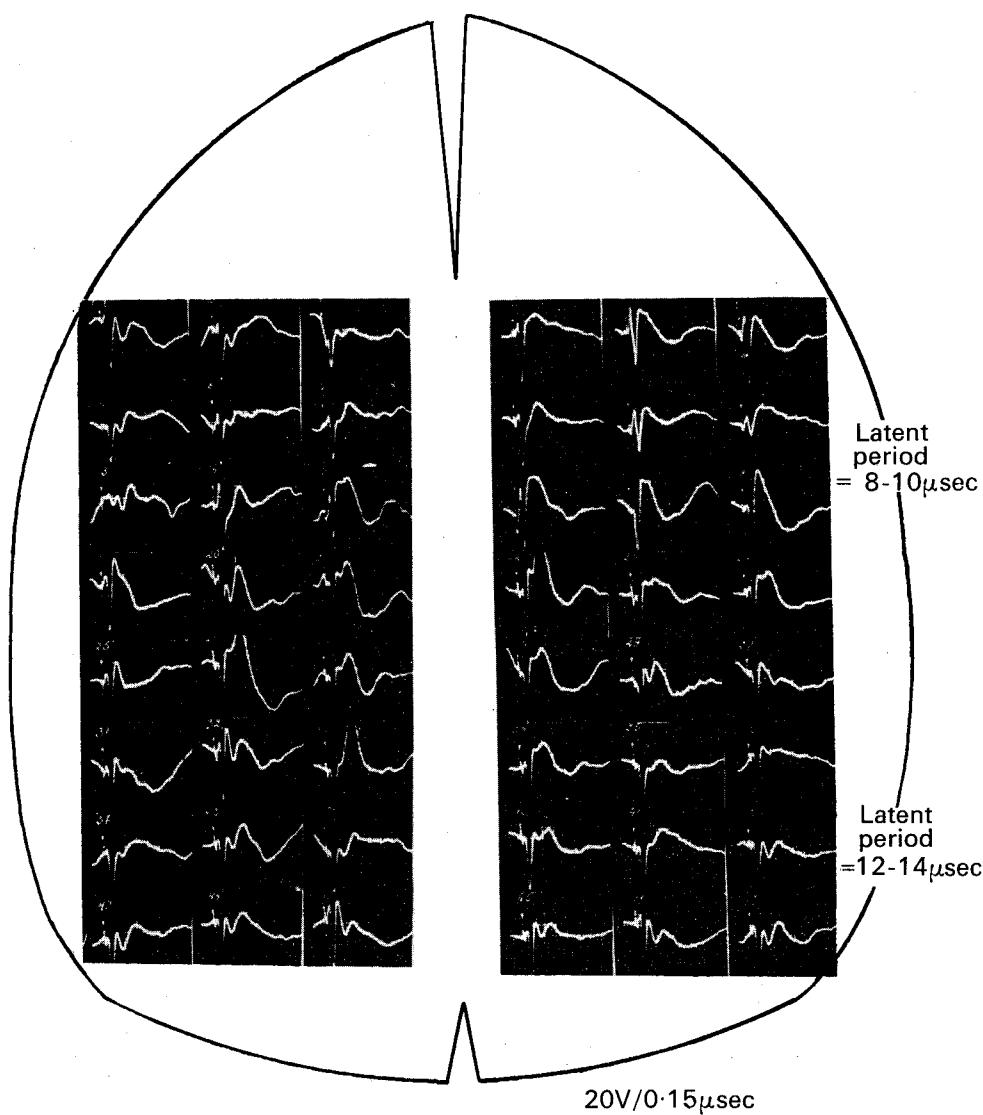


FIG. 5.8. Generalization of the evoked potential over 48 points of the cerebral cortex upon stimulation of the lateral nucleus of the hypothalamus. A 20-volt stimulus was applied for 0.15 μ sec. Nembutal anesthesia.

of the cortical neurons in the frontal lobes immediately disappeared, and the electrical activity of these lobes was transformed into the usual slow background activity characteristic of an animal under general anesthesia (see Fig. 2.14).

All the experimental data presented above suggest that the excitation of a center of

an unconditioned reflex of a specific biological modality terminates in an activation of cortical electrical activity widely distributed over the cerebral cortex. Thus, the subcortical centers, in this case the hypothalamic centers are a type of energy "pacemaker" for the synaptic formations of the cortical level. Since this generalization of unconditioned excitation over the entire cerebral cortex is of decisive importance to us, we specifically investigated this activation. In regard to this investigation we asked: are the ascending impulses from a defense reaction identical in composition for all regions of the cerebral cortex, or do they change in relation to localization?

The best method for evaluating the nature of incoming impulses is based on the form of the evoked potential. Therefore, it was necessary to choose the subcortical regions most suitable for direct stimulation. In view of the universal role of the hypothalamus in the formation of unconditioned excitation, we examined the evoked potentials over all areas of the cerebral cortex as they responded to stimulation of various nuclei of the posterior hypothalamus (Badam Khand, 1965).

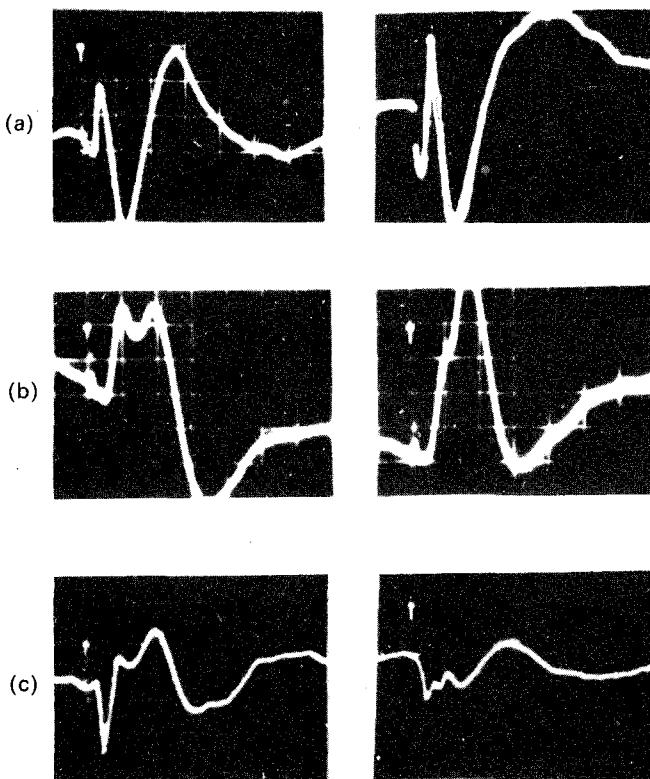


FIG. 5.9. An example of three configurations of the evoked potential from different areas of the cerebral cortex. (a) sensorimotor region; (b) parietal region; (c) occipital region.

Evoked potentials were recorded from 48 sites of the cerebral cortex, including areas from the frontal to the occipital regions. This enabled us to easily evaluate the difference in the ways in which ascending impulses affect the synaptic formations of the cerebral cortex. These effects could be evaluated both temporally (latent period, duration) and spatially (according to cortical layers). The results of stimulating two hypothalamic nuclei are presented in the composite chart in Fig. 5.8.

Electrical stimulation of the hypothalamus cannot, of course, be identified with the natural unconditioned excitation of any specific biological modality. And yet the nature of the distribution and the form of the potential may be the basis for evaluating a possible encounter of various impulses on the same neuron.

As can be seen from the forms of the evoked potential, the composition of the impulses arriving at each individual site of the cerebral cortex is most diverse. Stimulation of the hypothalamus in the sensorimotor area evokes a full potential with well-marked positive and negative phases, while in the occipital region there are predominantly positive waves and afterwards a very slow wave of negative potential. Using our procedure of the analysis of ascending impulses, we can compare the resulting form of hypothalamic impulses arriving at different cortical sites (Fig. 5.9).

The influences of the amygdaloid nucleus, which were recently discovered in our laboratory by E. Bogomolova, should also be mentioned in this connection. Electrical stimulation of the amygdaloid nucleus produces remarkably uniform evoked responses in all areas of the cerebral cortex (Fig. 5.10). These responses do not resemble any of the responses evoked from other subcortical structures.

As the previously mentioned experiments of Badam Khand have already shown, stimulation of any hypothalamic nucleus also produces a generalized response over the cerebral cortex; however, there is a distinct difference in both the intensity and the qualitative composition of ascending impulses in individual cortical zones (see Fig. 5.9).

In contrast with this, the evoked cortical potentials which arise upon stimulation of the amygdaloid complex are entirely uniform. They have a highly conspicuous positive component with a high amplitude and at the same time a weak negative component with a low amplitude and slow development.

We may characterize the evoked potential very completely if we apply our considerations concerning the independent origin of the positive and negative components to the analysis. In fact, the appearance of such a strong positive potential with an extremely high amplitude can be explained by the fact that the area of the axosomatic synapses of the cortical neurons of the fourth layer, or some other neurons of a deeper layer, is reached by a powerful series of ascending impulses from the point of stimulation of the amygdaloid complex. The sharpness and magnitude of these axosomatic discharges may be explained by the high degree of synchronization of this ascending series of amygdaloid impulses and by the unhindered development of the dipole potential on the cortical surface. This potential is generally interrupted by the immediately developing negativity from the negative component of the primary evoked potential (Anokhin, 1961c).

However, if the effect of the ascending impulses from the amygdaloid nucleus is so generalized, then its impulses must overlap with impulses from other modalities coming

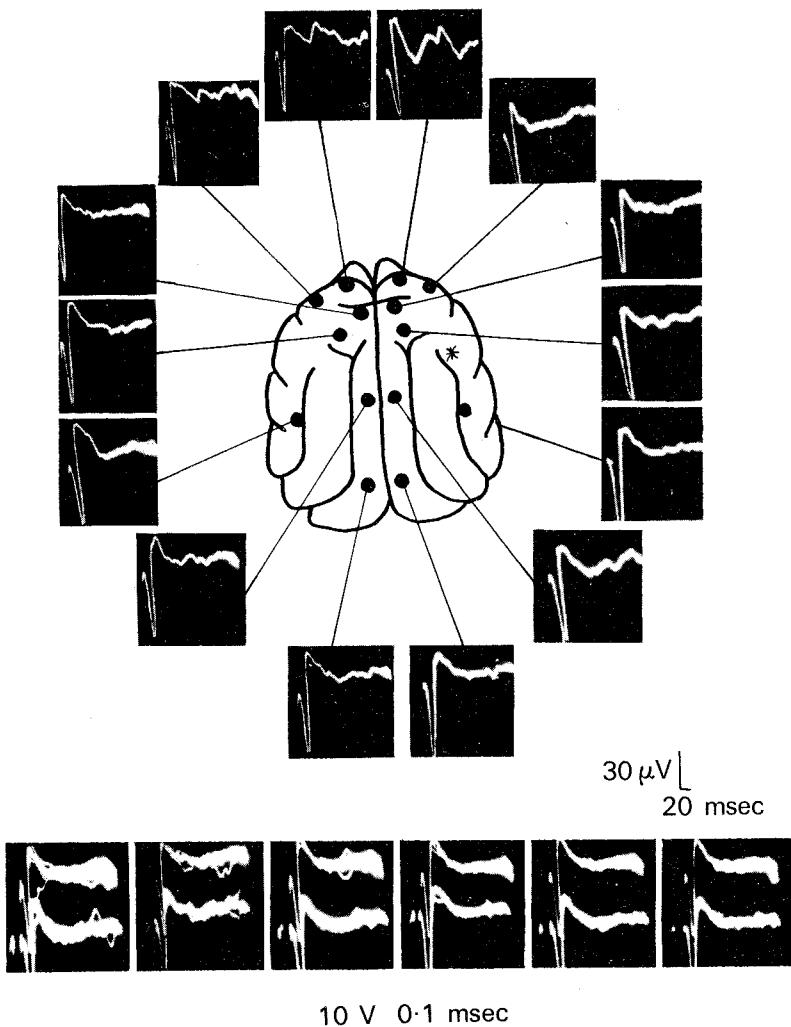


FIG. 5.10. Distribution of evoked potentials over the cerebral cortex of a cat upon stimulation of the anterior area of the amygdaloid nucleus. Uniform configurations of the evoked potential in all areas of the cerebral cortex can be seen.

from other subcortical structures and from various receptor surfaces of different sensory modalities.

Thus, all the material presented above, both that of our laboratory and that of other laboratories, agrees that in each neuron several ascending impulses meet after they have formed in different subcortical structures and have spread differently over the cortical areas, over the cortical neurons themselves, and finally over the cortical layers. Some are directed at the axosomatic synapses in the fourth layer of the cerebral

cortex (rapid, specific), others at the apical dendrites of the plexiform layer (nonspecific), and still others (highly generalized) over the cerebral cortex to the central part of the long dendrites (Forbes discharge), etc.

It is highly possible that many of these ascending impulses are aimed directly at the synapses of the large cortical neurons with long dendrites which ascend to the plexiform layer. These ascending impulses can also mobilize all internuncial neurons, particularly the stellate neurons. Nevertheless, in the final analysis the ascending impulses in one form or another invariably excite the pyramidal neurons at the decisive moment of processing all the ascending information entering the cerebral cortex.

Let us try to imagine the interactions of all those impulses reaching the cerebral cortex at different time intervals, differing in intensity and frequency, being differently generalized over the cerebral cortex, and having a different localization on the neuron, etc. What is the functional result of this extremely diverse convergence of different impulses at the cortical neurons?

Proceeding from the elaboration of the conditioned reflex, we must first visualize the action of an "indifferent" stimulus of some specific sensory modality on the cerebral cortex. Here we will use a visual stimulus. This stimulus immediately excites neurons of a highly diverse functional nature and even the individual synaptic formations on the neurons of the visual area. In the beginning this stimulation of the visual area of the cerebral cortex is neither isolated nor merely specific. Even in the anesthetized animal the sensory impulses are accompanied by nonspecific impulses which pass through the reticular formation and arrive by other routes. The specific sensory excitation manifested in the evoked potential is not homogeneous either in genesis or functional properties. It has at least four different components which together constitute the primary evoked response of the cerebral cortex.

This primary information concerning the action of an external stimulus includes series of rapid impulses relayed to the synapses of the nerve cell. Evidently it constitutes that most differentiated "local" information which, having appeared at later stages in the evolution of animals, favors the selection of the particular stimulus from among the multitude of stimuli in space and time.

After a few milliseconds this first rapid influx of impulses is met on the same neuron by another series of ascending impulses which is just as strictly localized in action and may be classified in the category of nonspecific impulses. It is aimed, as we have seen, at the first layer of the cerebral cortex at the apical dendrites of the cortical neurons. The plexiform layer, remaining from ancient primordial forms of cerebral organization, even now participates in the very first identification of a stimulus. It is most likely that the negative component of the evoked potential, i.e., the series of nonspecific ascending impulses, has maintained its potentiating influence on the specific component by acquiring a relatively high speed of propagation.

Just after this complex of ascending impulses, very powerful but scattered series of ascending impulses are sent from the rostral part of the reticular formation and from the hypothalamus. These impulses are evidently directed at the central part of the long dendrite of the fourth-layer pyramidal cells. On the evoked potential this series of impulses is manifested as a positive potential lasting for 30–100 msec and has been

called the secondary Forbes discharge. The subcortical structures responsible for the arrival of these ascending impulses into the cerebral cortex are highly sensitive to urethane and chlorpromazine.

The entire complex described above is merely the beginning of the action of the indifferent stimulus and lasts approximately 0.1 sec.

After the above sequence has occurred, the brain almost automatically develops an orienting-investigative reaction dispatching the powerful series of ascending impulses which produce a desynchronization of the widely generalized cortical electrical activity.

Thus, at this first stage in the elaboration of the conditioned reflex, the functionally highly diverse impulses which have reached the cerebral cortex retain a definite localization with respect to neuronal parts and cortical area. They are potentiated and united because of new series of ascending impulses having a high energy output and the capacity to facilitate other systems of excitation of the cerebral cortex that have already developed.

The physiological significance of the orienting-investigative reaction consists of most accurately identifying the external stimuli by means of the central cyclic circulation of peripheral impulses (Anokhin, 1958b). With this in mind it is clear that even before the arrival of the decisive series of impulses arising from an unconditioned stimulus there is a broad generalization of excitation from the first peripheral stimulus and the convergence of many kinds of impulses on the same cortical neurons.

The *actual generalization* occurs over the entire cerebral cortex, whereas *statistically* each particular area of the cortex varies greatly with respect to the composition of the ascending impulses reaching it and to the degree of their manifestation. Thus, the positive component of the evoked potential, which indicates the arrival of an impulse of a given sensory modality at the axosomatic synapses, seldom occurs outside of the given sensory projection, although, generally speaking, neural processes of a given modality may also occur in other areas of the cortex, for example, visual discharges in the sensorimotor area (Buser and Borenstein, 1959; Buser *et al.*, 1959; Jung *et al.*, 1963).

Nevertheless, *statistically* the projection area for the indifferent stimulus of a given sensory modality will always differ in regard to the complex of ascending impulses that have arrived here even at the stage of application of the indifferent stimulus alone. This integral from the same stimulus will be distinct also in the associative zones and in other projection areas of the brain, even though they would have a different sensory modality.

The unconditioned stimulus considerably adds to the complexity of this situation in the cerebral cortex which has developed as a result of the action of the indifferent stimulus and of the orienting-investigative reaction which has arisen in response to it.

What does the unconditioned stimulus contribute to this situation?

It adds one more series of ascending impulses which generalizes the cortical excitation even more and increases the variety of impulses that converge on the cortical neurons. These impulses, however, having a vitally important biological modality, decisively influence all the above-described kinds of impulses which converge in various combinations on the cortical neurons even *before the arrival of impulses arising from the action of the unconditioned stimulus*.

As the previously discussed investigations of Jung and his collaborators have shown, stimulation of the labyrinths with direct current (polarization) leads to a potentiation of the discharges of cortical neurons of any modality, mainly the auditory.

This potentiating property of the vestibular influences is increased by their generalization over the cerebral cortex. Those ascending impulses which have a quite specific biological modality have an even greater capacity for potentiation. This becomes evident upon consideration of the discharges of a single neuron in the case of ascending series of impulses in hungry animals. I refer again to the experiments of Fadeev (1965) in our laboratory. When considering the discharges of a single neuron from the frontal lobes of the cerebral cortex, he showed that under urethane anesthesia the high discharge activity of the neuron immediately decreases if artificial "satiation" of the animal is produced by means of an intravenous injection of glucose (Fig. 5.11).

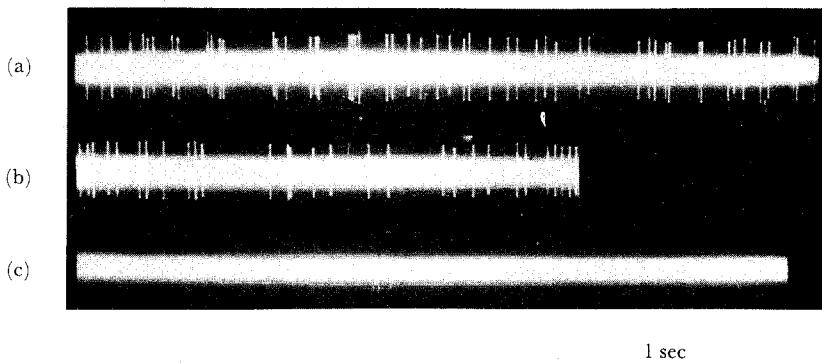


FIG. 5.11. Microelectrode recording from one of the cells of the anterior areas of the cerebral cortex. (a) background discharge activity of a cell in a fasting cat. (b) activity of the same cell 15 sec after administration of glucose. (c) complete cessation of the discharges of the cell 25 sec after administration of glucose.

TABLE 5.1. SUMMARY TABLE CHARACTERIZING THE RECORDED RESPONSES OF NEURONS TO STIMULATION OF THE SCIATIC NERVE. THE NEURONS ARE DIVIDED INTO 4 TYPES OF REACTIONS, AND THEIR QUANTITATIVE DISTRIBUTION IS GIVEN FOR THE STATES OF FASTING AND SATIETY.

Condition of animal	Reaction to stimulation				Total
	Type I Inhibition	Type II Excitation	Type III No reaction	Type IV Response of "silent" neuron	
Fasting	84 28.9%	114 39.2%	74 25.4%	19 6.5%	291
Satiated	14 11.8%	60 50.4%	29 24.4%	16 13.4%	119

As can be seen in this figure, the discharges of the neuron, having had a regular frequency of 9 impulses/sec before the injection, gradually disappear. This convinces us that the neuronal activity was caused by ascending impulses originating in the hypothalamic nuclei. It is interesting that the ascending alimentary impulses originating in the hypothalamus are by no means widely generalized. With a comparative statistical analysis of the neuronal discharges in both a sated and a hungry animal, it can be seen that there is a very marked diversity of functional conditions in the different neurons (Table 5.1).

From this table we see that there are neurons which conduct several types of impulses. Upon stimulation of the sciatic nerve, for example, neurons of the second type considerably increase the frequency of the background discharges previously evoked by ascending alimentary impulses. This interesting observation is evidence for the convergence of impulses of several biological modalities on this particular neuron. The fact that impulses of two different and even antipodal biological modalities can reach the same neuron of the cerebral cortex is paradoxical from the point of view of generally accepted concepts. However, upon considering the entire problem of the convergence of impulses of different modalities on the same neuron, this finding proves to be physiologically entirely feasible (Fig. 5.12).

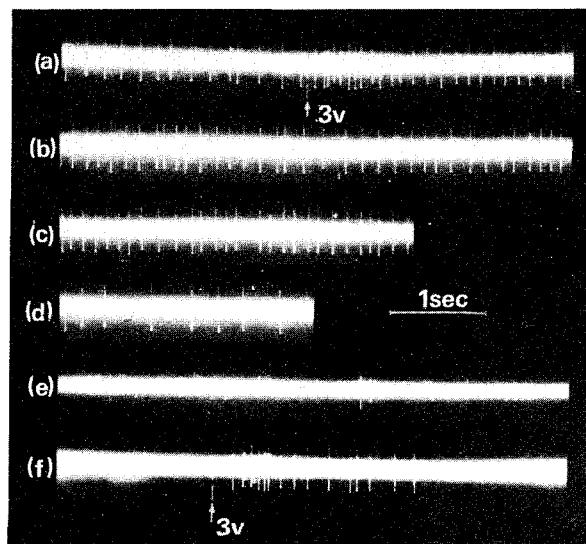


FIG. 5.12. Demonstration of the possibility of convergence of two biological modalities on the same neuron.

- (a) Electrical stimulation of the sciatic nerve on a background of the regular discharges of the neuron in a fasting cat.
- (b) Background activity of the same neuron before the administration of glucose.
- (c, d, e) Consecutive stages in the elimination of discharges at periods of 15, 28, and 43 sec after the administration of glucose.
- (f) Reaction of the "silent" alimentary neuron to stimulation of the sciatic nerve (3 volts). A distinct reaction to painful stimulation can be seen just as in (a), although the alimentary excitability has been eliminated by the injection of glucose.

We have only to change our previous concepts of the interaction of the impulses entering the brain. These concepts were developed during the period when the experimenter thought of the brain as something like a cybernetic "black box." Now, due to advances in electronics it has become possible to enter into this "black box." Thus we should naturally encounter many mechanisms which do not fit into our concept of the functions of the brain. The discovery of the physiological characteristics of the reticular formation may serve as a good illustration of this.

THE CONVERGENCE OF DIVERSE IMPULSES ON THE RETICULAR AND CORTICAL NEURONS

From the preceding material it follows that all forms of ascending impulses are to some degree of a generalized nature. This pertains especially to the impulses from an unconditioned stimulus that utilize the hypothalamic as well as the thalamic and reticular mechanisms of ascending activation. In all cases of cerebral activity, then, there are significant encounters of ascending impulses on the cells of the cerebral cortex.

The study of evoked potentials suggests that these encounters are distinct for each individual zone of the cerebral cortex. This is indicated by the difference in the configuration of the evoked potentials obtained both from purely sensorimotor stimuli and from stimulation of the hypothalamus and the reticular formation.

As we have seen, the true nature of the individual components of the evoked potential is shown to be the result of a special ascending series of impulses that have a definite localization in the cerebral cortex. Consequently, from the same point of view we must also understand the nature of the configuration of evoked potentials in each individual zone of the cerebral cortex and their summation in different zones. These configurations undoubtedly reflect the sequential order, intensity, and localization of the impulses reaching the cerebral cortex.

The presence of extensive encounters of impulses in the cerebral cortex must lead us to the conclusion that the ultimate effect of such encounters must be caused by their convergence upon the same cortical neuron and by their interaction on its synapses. We are thus confronted with the imperative task of analyzing all the data concerning convergence upon various neurons.

The idea of the convergence of impulses upon a single neuron became especially attractive after the discovery of the physiological properties of the reticular formation and the development of the microelectrode technique. Since 1954 certain investigations in Moruzzi's laboratory have shown that the neurons of the reticular formation have a remarkable property: impulses from all modalities (conditioned), and impulses from nociceptive stimuli (true unconditioned) as well, converge upon the same neuron (von Baumgarten and Mollica, 1954; Moruzzi, 1954; Scheibel *et al.*, 1955; Mancia *et al.*, 1957; Rossi and Zanchetti, 1957).

This somewhat unexpected result of the microelectrode technique naturally gained the interest of a number of investigators, both neurophysiologists and neuromorphologists. Investigations were conducted to determine whether this ability to receive different impulses is a specific ability of the cells of the reticular formation alone, or

whether it is also characteristic of other subcortical structures.

Morphophysiological investigations of the synaptic apparatuses of the reticular neurons, especially of their giant cells, have also appeared. Among these investigations, those of Kositlyn (1964) from the laboratory of N. G. Kolosov are of special interest since they showed that the number of synapses on the giant cells of the reticular formation is so great, and extends to all the dendrites, that we can fully understand the physiological result obtained by the microelectrode technique. Of most importance to us, Kositlyn also showed the extreme diversity in the forms of the synaptic knobs which implement the trans-synaptic propagation of impulses (Fig. 5.13a).

If we proceed from the completely practicable premise that the synaptic knob is the place of formation of slow chemical processes in the transmission of impulses, the morphological diversity of the structure of the knobs may serve as indirect evidence of just as great a diversity in the chemical characteristics of trans-synaptic propagation. Here it must be remembered that any method of cytological investigation, particularly using silver impregnation, is to some extent a differentiating histochemical method.

Leontovich and Zhukova (1963) came to essentially to the same conclusions, having shown that the cells of the reticular formation differ specifically from the cells of other nuclei at the same level of the brain stem in the tremendous ramification of the dendrites and in the reception of an enormous number of endings converging on them. It is appropriate to recall here the earlier work of Scheibel and Scheibel (1958), who have shown that each reticular cell can have up to 12,000 contacts with other neural elements. The systematic work of Brodal (1957) leads to the same conclusions.

Soon after the first microelectrode investigations, the results of the work of various authors were published in quick succession. The extensive convergence of various impulses from different sensory systems to the same nerve cells was shown. Perhaps the most persuasive work in this regard was performed by Starzl *et al.* (1951).

These investigators stimulated the sciatic nerve and recorded the evoked potentials from different regions of the reticular formation of the brain stem. Simultaneously they stimulated the auditory system by a click and were thus able to observe the distribution over the brain stem of those neural elements at which both somatic and auditory impulses converge. It turned out that these modalities are rather extensively represented in the region of the reticular formation and, at the same time, *there are points which react to both modalities within the entire reticular formation*. This convincingly demonstrates that the collaterals of the lemniscal pathway are quite widely branched over the reticular formation. This pertains especially to the region of the nuclei of the giant cells.

In subsequent work Machne *et al.* (1955), using the microelectrode technique, showed that in the reticular formation there are many elements which react to a variety of stimuli by a considerably increased number of impulses.

Many publications have appeared that present evidence of the existence of an extensive convergence of impulses from stimuli of different modalities upon the same neurons of the reticular formation (Bremer and Terzuolo, 1952, 1953; Bremer, 1966; Jasper *et al.*, 1952; Amassian, 1952; Livingston *et al.*, 1953; and others).

The work of Scheibel *et al.* (1955), who compared the influence of several stimuli on the discharges from one reticular neuron, deserves special attention. They used pola-

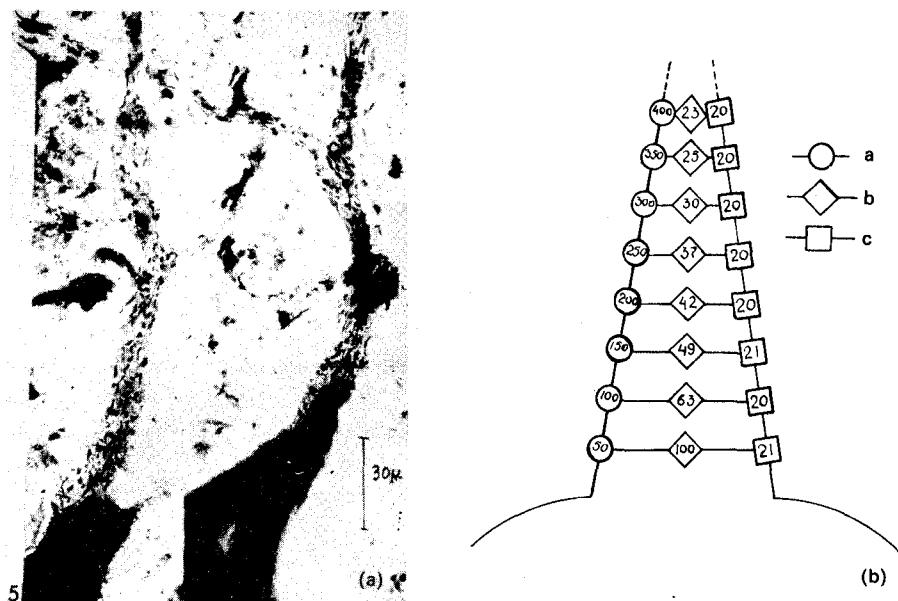


FIG. 5.13. Synaptic formations on the dendrites of a giant cell of the reticular formation (a). From Kositzyn (1964, p. 14). The higher saturation of the surface of a dendrite by synaptic end plates can be seen, although calculation shows that the number of end plates is more or less uniformly distributed over the different segments of the dendrite (b). From Kositzyn (1964, p. 11).

rization of the cerebellum, tactile stimulation of the skin of the nose, a clicking sound, and the application of strychnine to the sensorimotor region of the cortex. As a result of quite numerous experiments on 161 cats and on nearly 1000 individual neurons, they showed that *an individual reticular neuron was the point of convergence for all the stimuli selected.*

Subsequently, the convergence of impulses upon reticular neurons was studied by a number of other investigators. From these studies it was concluded that impulses from the most diverse modalities, as well as those evoked by direct stimulation of the cerebral and cerebellar cortices, converge upon the reticular neurons (Mancia *et al.*, 1957; Rossi and Zanchetti, 1957).

It has thus become quite evident that the cells of the reticular formation receive all the afferent impulses propagating along the lemniscal systems from various receptors. This extensive convergence is undoubtedly of great physiological significance. The indisputable fact that the reticular neurons gather impulses from different modalities, which can therefore interact in the protoplasm of the same cell, opens up immense possibilities for the synthesis of all afferent influences that impinge upon the organism at a given moment. I shall try to elucidate this process here.

The morphological correlation of these physiological data was provided by Brodal (1957) and Scheibel and Scheibel (1958). Investigations of the ascending sensory pathways showed that the passage of the series of impulses to the reticular neurons proceeds

by several pathways. First of all, the direct sensory pathway proceeds from the segments of the spinal cord and enters the caudal section of the reticular formation. It is true that a similar direct sensory pathway from the region of the medulla oblongata into the reticular formation had already been described by Bekhterev (1885) as a result of work performed in Flechsig's laboratory.

However, these direct sensory impulses converging upon the reticular neurons are few in number and evidently have some special physiological significance. Quite possibly they are a residue of the more ancient lemniscal systems described by Herrick and Bishop (1958).

Most of the afferent impulses enter the reticular formation through collaterals of the lemniscal systems which supply information to the cerebral cortex through the specific thalamic systems. These collaterals originate from all the conducting sensory pathways in such an enormous quantity that they penetrate the entire region and ensure the above-described convergence of sensory impulses upon one reticular neuron. One only needs to examine the diagram presented by Kositzyz (1964) in order to realize the enormous density of synaptic endings on the dendrites of the reticular neurons (Fig. 5.13b).

Immediately after the first discoveries of this convergence upon the reticular neurons, investigations were made to detect a similar convergence upon the cells of other subcortical structures. Using the same methods, the nucleus caudatus, the putamen, the centromedian nucleus of the thalamus, the lateral thalamus, the amygdaloid complex, and the hippocampus were examined (Green and Machne, 1955; Machne and Segundo, 1956; Segundo and Machne, 1956; Borenstein *et al.*, 1959; Albe-Fessard *et al.*, 1960; Albe-Fessard and Gillet, 1961).

Since these subcortical nuclei are greatly specialized, the convergence of different modalities is not so extensive. However, because the same nerve cell is able to accept several modalities, we must ask: how is this diverse information processed on the membrane and in the protoplasm of the same cell? Into what kind of final information on the axon are all those diverse impulses integrated which have entered the dendrites?

We shall return to this question after discussing the entire problem of convergence. Now it is necessary to explicate the problem of the convergence of the subcortical impulses upon the cortical neurons. This type of convergence has not been investigated as fully as that of impulses on the reticular neurons.

Extensive material in regard to the convergence of subcortical impulses upon cortical neurons was provided by Jung and his collaborators, who conducted their investigations by using stimuli of several different modalities (Jung *et al.*, 1963). They used the following stimuli: visual, auditory, cutaneous, and polarization of the vestibular apparatus. These stimuli have been studied most thoroughly in Jung's laboratory.

Jung attempted to classify the individual neurons into two large categories. Cellular discharges having a very short latent period and breaking off with termination of the stimulation were attributed to specific impulses, whereas discharges having a long latent period and leaving a trace after termination of the stimulation were attributed to nonspecific impulses. According to either an "on-effect" or "off-effect" kind of reaction, both types of impulses were further subdivided, which is, however, not

significant for the problem we are presently examining. In regard to Jung's experiments, the role of general anesthetics in the microelectrode technique should also be mentioned.

As could be seen from the experiments of Nabil' (1964), evoked potentials are most extensively manifested in the cerebral cortex during chloralose anesthesia. This explains the complete dependence of the success of experiments with evoked potentials using the microelectrode technique specifically during chloralose anesthesia. This was repeatedly observed by Albe-Fessard (1963), Jung *et al.* (1963), and others.

What is behind this marked manifestation of the microelectrode effect on the cerebral cortex under chloralose anesthesia? Is this distinct manifestation of neuronal activation in the cerebral cortex equivalent to the natural activity of the neurons, or is this merely a side effect of the specific character of this general anesthesia? Such a question is especially justifiable since the weakest manifestation of evoked potentials in the cerebral cortex was observed in our experiments involving urethane anesthesia (see Fig. 5.1), and at the same time, under this latter anesthesia the ascending painful activation spreads freely over all areas of the cerebral cortex. Thus, the impulses which produce the evoked potential in the visual area were not present in the cerebral cortex, while those producing the arousal reaction, or desynchronization (nociceptive stimuli), were present.

The direct investigations of my collaborator Serbinenko, who coagulated various subcortical structures, demonstrated that the group of parafascicular nuclei of the nonspecific thalamus is chiefly responsible for this pain-induced desynchronization (Serbinenko and Belova, 1964).

Among the findings presented above, Jung's experiments are closest to natural conditions since they were performed on Bremer's "encephale isolé" preparation, even though in this experiment the cerebral cortex was deprived of the strong series of proprioceptive impulses from the entire musculature. The results of the investigations by Jung and his collaborators are highly complex and will probably require serious statistical analysis in the future. The main conclusions he arrived at on the basis of his data are directly related to the problem under discussion.

First of all it was shown that according to the reaction of the neuron to the stimuli applied, there are two types of responses which appear in all neurons in various degrees, regardless of the modality (visual, auditory, or vestibular).

The first type of response involves a rapid increase in the number of background impulses of the neuron after a very short latent period, the action usually being limited to only the period of stimulation. This type corresponds, to a certain extent, with the projection zone for the given modality, although for some modalities, such as the visual one, there is considerable scattering over other regions of the cerebral cortex. Keeping in mind that these cells respond only to an appropriate stimulus, one sees that the results of these microelectrode investigations quite closely harmonize with Pavlov's concept of the "nucleus of the analyzer" and its "scattered elements."

The second type of response of the cortical neurons is more variable and differs from the first type in a number of parameters. For example, the latent period of this response is always rather long (30–400 msec), and the response itself is not as strictly dependent

on the duration of the stimulus. The response may change several times during stimulation and, in addition, may have a prolonged aftereffect.

The physiological characteristics of these two types of response of the cortical neurons to stimulation are such that Jung was justified in classifying them according to the generally accepted standard of "specific" (first type) and "nonspecific" (second type). The most significant parameter of the second type of response is the ability to facilitate the discharge activity of both the stimulated neuron and other neurons as well, whereas it is strikingly apparent that this facilitation does not occur when the discharge activity of the first type of response is completely unfatigued.

However, as soon as the discharge activity becomes "fatigued," i.e., decreases in frequency, the facilitating effect of the nonspecific activity of the neuron immediately appears: the frequency developing according to the first type is restored to its original value. Stimulation by direct current (polarization of the vestibular apparatus) evokes a very strong facilitating effect. For example, if the discharges of the visual neurons of the second type start to become fatigued and to respond with decreased frequency due to the prolonged stimulation by flickering light, additional polarization of the vestibular apparatuses immediately restores the original frequency of the discharges of the visual cells (Jung *et al.*, 1963).

This assumes special interest since there is a manifestation of the facilitating effect of responses of the second type within the same neuron only if its discharge activity (of the second type) decreases gradually. I must particularly emphasize the significance of this in regard to the formulation of our hypothesis of convergent coupling.

As we know, unconditioned excitation of the nociceptive or alimentary type substantially facilitates the spread of processes over considerable areas of the cerebral cortex. This is undoubtedly connected with the specific chemical action of the cortical synapses of these ascending impulses.

One more problem should now be discussed. The above examples of simultaneous generalized excitation aimed at the cerebral cortex are interesting and important because of their fundamental content. We must, however, always keep in mind the results of the previously discussed experiments of Nabil' (1964), since they are important for the problem under discussion. As we have seen, these experiments showed that the general anesthetic determines to what extent, into which regions of the cerebral cortex, and in what form the series of ascending impulses evoked by a single stimulation of the sciatic nerve will "break through."

Moreover, the effect of the general anesthetic is not directly correlated to the other forms of ascending impulses, especially those caused by thermal nociceptive stimuli (Agafonov, 1956).

The considerations above compel us to carefully evaluate the degree of generalization over the cerebral cortex of various influences on the brain revealed by means of various indices (EEG, evoked potential, discharges of single neurons). In particular, the excellent results of Jung and his collaborators in the study of the density of neurons with different convergence must also be regarded from this point of view.

The recent experiments of my collaborator Shumilina (1965), performed on animals in the normal waking state, caution us in regard to the transfer of results obtained

during anesthesia to those obtained under normal conditions. Shumilina studied the extent of propagation over the cerebral cortex of electrical potentials evoked by a flash of light in waking rabbits in a setting for conditioned reflex experimentation. The evoked potential propagates more extensively in a conscious rabbit than during the onset of the effect of a general anesthetic (Fig. 5.14).

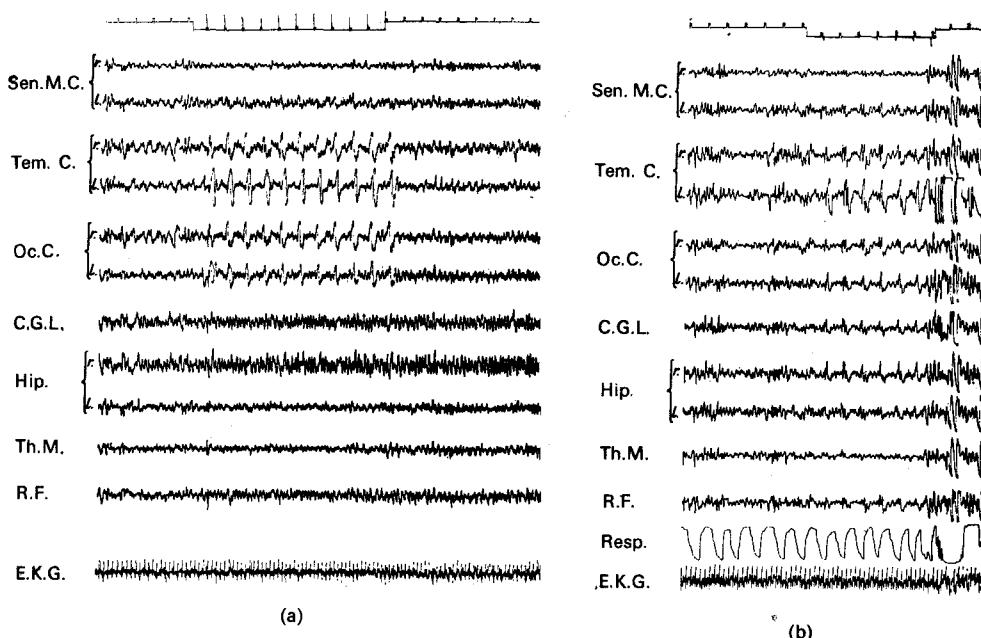


FIG. 5.14. Two electroencephalograms showing the reaction of the cerebral cortex to rhythmic flashes of light.

- (a) Distribution of the evoked potential under anesthesia.
- (b) The same potential recorded in a waking state. The considerably more extensive generalization of the evoked potentials over the cerebral cortex and over the subcortical formations up to and including the reticular formation can be seen. Designations the same as in Fig. 5.5.

Other similar experiments convince us that, due to the presence of a number of additional ascending activations, the waking state considerably expands the degree of generalization of the evoked potential over the cerebral cortex.

The data previously presented are entirely sufficient to prove the presence of a considerable summation of various ascending impulses. Correlating the distribution of activation over the cortex with the evoked potentials and the discharges of individual neurons, one may conclude that essentially there is a universal convergence of different ascending impulses to all or most of the cortical neurons. Moreover, each series of ascending impulses consists of many components, and consequently this convergence may occur in the most diverse combinations of components from various potentials.

This convergence becomes especially evident when considering that the ascending impulses from the unconditioned stimulus are deliberately directed to all regions of the

cerebral cortex. Generally speaking, those impulses which are directed chiefly to the synaptic formations of the first layer (apical dendrites), as well as those impulses which are directed to the axosomatic synapses of these cells, can converge to the same cell of the frontal lobes. Such combinations of ascending impulses of different origin, aimed directly or through the stellate cells at different parts of the same dendrites of a giant cell of the fourth layer, can be considered only statistically. However, it is important for us to note that the convergence of these various impulses upon the same cortical cell poses a number of important questions.

This convergence could be regarded as a purely summational phenomenon of uniform impulses, as occurs in modeling the neuron. Then we would deal with a pure summation of series of impulses. This would deprive each particular series of its individuality, imparting a homogeneous nature to them as suggested in Gesell's theory of electrotonus (1940), which explains the generative activity of the neuron. Acceptance of this point of view would make the multiplicity of specific influences to which each cortical cell is subjected incomprehensible and functionally meaningless.

However, this special diversity of series of impulses reaching the same cell acquires a profound functional significance as soon as we grant that each of these series not only has a characteristic frequency but also evokes on the postsynaptic membranes of the receptor neuron a chain process of chemical reactions specific for it. In this case the processes initiated at different synapses of the same neuron by different incoming impulses could serve as stimuli for the development of distinctive chemical patterns in the axoplasm of the neuron itself. Naturally we should ask whether we can gain anything from modern neurophysiology and neurochemistry to help us understand this postsynaptic process in order to agree with such a hypothetical possibility.

Upon careful analysis of the presently available data of neurophysiology at the neuronal level, it will be found that this assumption is not at all unlikely. We probably even have every reason for accepting it as a working hypothesis.

Indeed, let us remember the comparative analysis of neuromuscular and neurosecretory synapses in view of the significance of the postsynaptic processes for determining the specific nature of the functional end effect, secretion or muscular contraction. The above-discussed experiments with the anastomosis of functionally heterogeneous nerves quite clearly indicate that the synaptic formation at the receiving organ has chemical characteristics which, by means of a continuous chain of transformations, leads to the specific function of that organ (either contraction or secretion). If the generation of impulses is considered to be a specific function of the neuron, the postsynaptic processes on its membrane must have equally specific properties since they must transform one form of incoming impulses into impulses of a different specificity.

Thus we have arrived at the assumption that probably even the synaptic processes, which are formed by different impulses converging upon the same neuron, can differ in chemical specificity.

The investigations and theoretical concepts of a number of scientists significantly support these views. In this respect the abundant material obtained in the investigations of Bullock (1959, 1961) should be particularly mentioned.

In our subsequent considerations the problem of the heterogeneity of the membrane

of the nerve cell will occupy an especially important place. Therefore, I would like to discuss in some detail Bullock's point of view, since he is perhaps the only investigator who is fully and systemically studying this problem. The question of the heterogeneity of the neuronal membranes was clearly specified for the first time by Grundfest. Since 1940 he has believed that certain parts of the dendritic system of the neuron are not excitable by electrical stimuli, whereas they are capable of producing electrical potentials in response to specific chemical agents. In other words, the dendrites have a specific sensitivity to chemical agents. On the other hand, other parts of the neuron, especially the point of generation of discharges going out to the axon, are particularly sensitive to electric current. Thus, the membrane of the nerve cell is not homogeneous in regard to its physiological properties but represents an integrated unit based on the interaction of specific components, the properties of which were created in the process of differentiated evolution (Grundfest, 1959b).

It is interesting that a comparison between impulses propagating along an axonal conductor and those passing through a synapse shows their basic difference in a number of parameters. A table and figure taken from Grundfest (1959b) are presented below. They show the distinctive features of the synaptic process (Table 5.2 and Fig. 5.15).

TABLE 5.2. PROPERTIES WHICH DISTINGUISH TRANSMISSIONAL FROM CONDUCTILE ELECTROGENESIS. FROM GRUNDFEST (1959b, p. 52).

A. Conductile Response with Impulse (Spike)	B. Transmisional Responses (p.s.p.s)
1. Excited by depolarization, including electrical stimuli	Cell membrane not responsive to electrical stimuli
2. As above	Component of cell response not excited by electrical stimuli
3. Absolute and relative refractoriness	No refractoriness
4. Characteristic duration, never summated	Prolonged, sustained electrogenesis (a) to repetitive neural stimuli (b) to chemical excitants
5. Conduction at specific rate	Nonpropagating ("standing") response
6. Vanishingly brief latency	Long, irreducible latency
7. Blocked by hyperpolarization	Response during hyperpolarization
8. Inactivated by depolarization	Response during depolarization
9. All-or-none (except in special circumstances)	Graded, reversible in sign
10. Low sensitivity to drugs	Sensitive to pharmacological agents in two ways: (a) synapse activation, (b) synaptic blockade
11. Always depolarizing, overshoot	Hyperpolarizing or depolarizing

This aspect of the investigation, which emphasizes the diversity of the properties of different points on the neuronal membranes, has been extensively and delicately developed in recent years by Bullock. He regards the neuron as an integrated formation which has points of different physiological significance and an unlimited number of

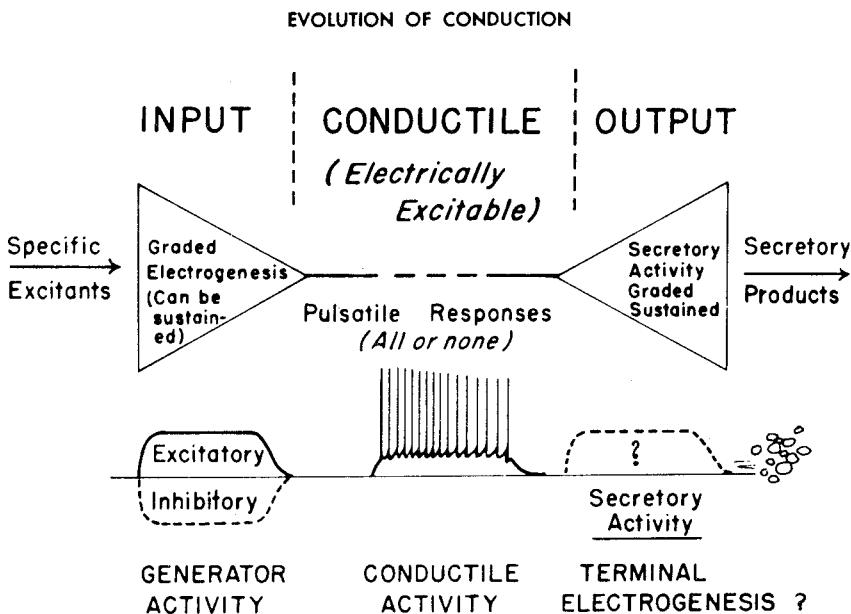


FIG. 5.15. Diagram of the different responsive components of an excitable cell. The input portion, not electrically excitable, and the output section are shown as distinct from the conductile part for schematic purposes. In many cells the electrogenic membrane of the input is interspersed with the electrically excitable, as at the soma of some neurons or in eel electroplax. In others, the conductile component is absent, as in some glands, muscle fibers, or electroplax. The types of electrogenesis are shown on the lower line of the diagram, the possibility of inhibitory, hyperpolarizing responses being indicated by broken lines. The response of the input is sustained, and the depolarization which it produces at the conductile, electrically excitable membrane is shown as initiating a train of spikes in the latter. The electrogenesis of the output is unknown, but the arrival of the messages at the output causes secretory activity, production of a transmitter substance. From Grundfest (1957; see Grundfest, 1959b, p. 55).

diverse chemical processes arising in the postsynaptic membranes of the same neuron. Bullock writes (1959, p. 1002) :

Physiologically, however, we have a new appreciation of the complexity-within-unity of the neuron. Like a person, it is truly a functional unit, but it is composed of parts of very different function not only with respect to metabolism and maintenance but also in the realms of processing diverse input and determining output—that is, of integration. The impulse is not the only form of nerve cell activity; excitation of one part of the neuron does not necessarily involve the whole neuron; many dendrites may not propagate impulses at all; and the synapse is not the only locus of selection, evaluation, fatigue, and persistent change. Several forms of graded activity—for example, pacemaker, synaptic, and local potentials—each confined to a circumscribed region or repeating regions of the neuron, can separately or sequentially integrate arriving events, with the history and milieu, to determine output in the restricted region where spikes are initiated. The size, number, and distribution over

the neuron of these functionally differentiated regions and the labile coupling functions between the successive processes that eventually determine what information is transferred to the next neuron provide an enormous range of possible complexity within this single cellular unit.

Bullock reaches this conclusion on the basis of an analysis of the properties of the neuron from the point of view of its physiological parameters. He considers two planes in the life of a single neuron. The first plane is the electrical activity of the neuron appearing as discharge activity; this is the plane to which we usually devote our attention and ascribe decisive significance. The second plane is the still inaccessible aspect of the neuron which determines the fluctuations of threshold excitability, the prolonged retention of trace processes, the electrotonic synchronization of actual discharge activity—in short, all those molecular processes which in the final analysis either facilitate or inhibit the observable activity of the neuron.

This approach to an evaluation of the activity of the neuron, compatible with the extreme diversity of the chemical properties of the neuronal membrane, represents a step forward, making it possible to explain some purely phenomenological observations of neurophysiology in terms of cellular and molecular mechanisms.

At present it is important to note that the correlation of the above-described approach to the function of the neuron with the data on the convergence of different impulses upon the same neuron opens many possibilities for understanding the integrative processes of the brain. Moreover, this point of view also has some degree of precautionary value regarding neurophysiological conclusions, since it emphasizes that the highly favored electrical phenomenon is not the only, nor by far a comprehensive, parameter of the activity of the neuron.

With these data Bullock recognized the neuron as an independent integrative unit, capable of dynamic plasticity and compensatory adaptations under diverse conditions of activity. This concept corresponds exactly with what we said above concerning the extensive convergence of different impulses upon the same neuron. Only the heterogeneous nature of the neuronal membrane, with respect to the electrical properties, chemical sensitivity, and generative capacity of the neuron, can functionally justify the arrival of the most diverse influences at the same cortical neuron, both from various nuclei of the subcortex and over special intracortical connections. Attention should be given to the ascending impulses generated in different subcortical structures. In their evolutionary essence they are heterogeneous both in the metabolic and in the neurohumoral sense. Thus, the two series of ascending impulses which evoke an indifferent and an unconditioned excitation, respectively, are physiologically different, i.e., in their formation at the subcortical level, in the extent of involvement of all functional systems of the organism (especially in the vegetative components of the reaction) and, finally, in the extent of their generalization over the cerebral cortex.

Due to this convergence of various impulses, each individual neuron becomes an arena of interaction of heterogeneous impulses, an interaction regulated by the sequence and biological significance of the converging impulses.

As we have seen above from the experiments of Fadeev (1965), two series of impulses,

even of different biological modality, can converge upon the same neuron. Under natural conditions of cerebral function such a convergence is not simultaneous, but occurs in the presence of only one of the series of afferent impulses. Nevertheless, the comparative evaluation of the chemical characteristics of those synaptic knobs which transmit these two modalities of impulses is of exceptional interest. For this problem we recently performed a series of special investigations which I shall analyze in detail below.

First it is necessary to consider what data we have in contemporary literature concerning the possibility of chemical diversity in the postsynaptic membranes of one neuron. I have already referred to the reliable data of Bullock and Grundfest. These investigators established a basis for solving this problem through a more specialized study, involving specific mediators and chemical agents, of individual synaptic formations.

Marrazzi (1958) made use of this possibility. Due to his work, the whole problem of different chemical properties of the postsynaptic membranes on the same neuron has shifted from hypothetical considerations to reliable principles. By means of stimulating presynaptic neurons and recording postsynaptic potentials, he showed that on the body of a single cell there are different chemical receptor points for the synaptic transmitter of different presynaptic axons. He demonstrated the possibility of the

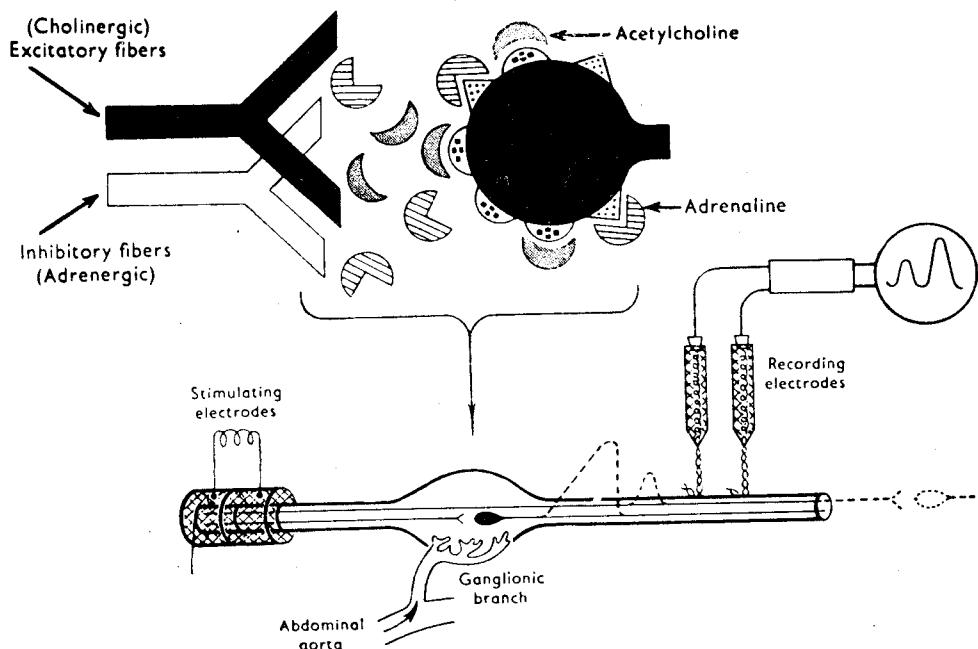


FIG. 5.16. Diagram of the results of the conduction of excitation through the synapses of a post-ganglionic neuron. The possibility of at least two chemically different subsynaptic formations on the same neuron can be seen. From Marrazzi (1958, p. 377).

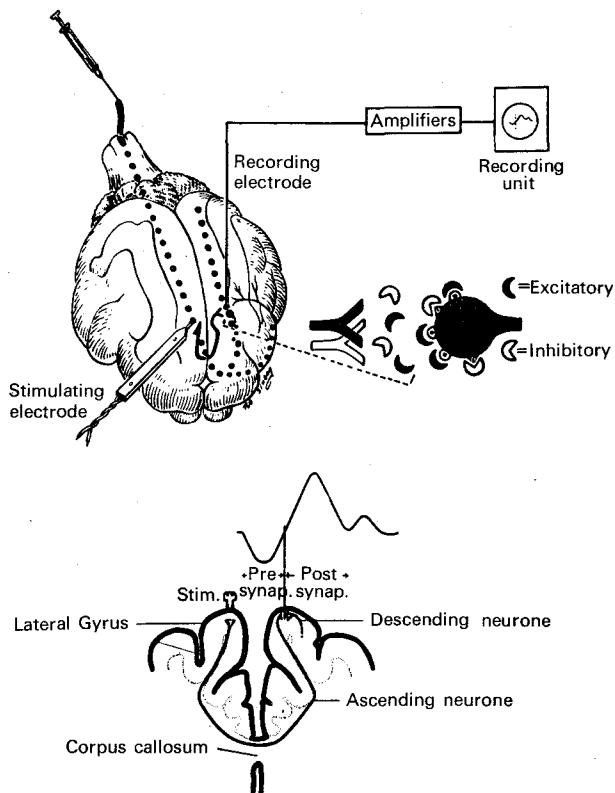


FIG. 5.17. Diagram showing chemically dissimilar synaptic formations on a cortical cell (explanations in text). From Marrazzi (1958, p. 378).

transmission of impulses, entering by two separate axons, through the cholinergic and adrenergic postsynaptic membrane of the same ganglionic cell (Fig. 5.16).

This finding is direct evidence of the multichemical organization of the postsynaptic membranes on the body and dendrites of the same ganglionic nerve cell. Of special interest to us, Marrazzi subsequently demonstrated such a possibility for the cortical neurons as well. He showed that a transcallosal impulse, spreading from one hemisphere to the other as a result of electrical stimulation, can also be directed at chemically different synaptic formations of the same neuron. By recording the evoked potentials of the visual cortex, he demonstrated that the same cortical neuron may have both cholinergic and adrenergic synapses on its membrane. He applied the most diverse substances which specifically affect the processes of trans-synaptic propagation, and thus revealed the different effects of these substances on synapses of the same neuron. Among those substances he used were noradrenaline, serotonin, LSD-25, and mescaline.

As a result of his experiments, Marrazzi concluded that his concept concerning the presence of adrenergic and cholinergic synapses on the same cortical neuron was entirely valid (Fig. 5.17). These data lead us to assume that the difference in the

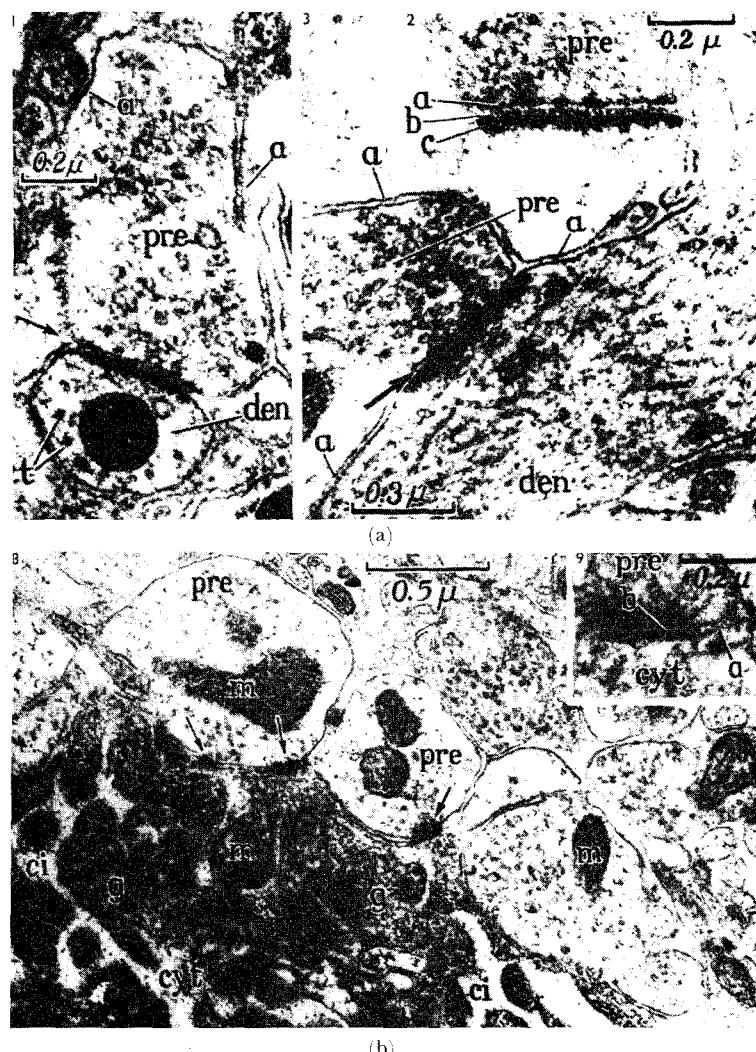


FIG. 5.18. (a) Synapses on the dendrites or, according to Gray's classification, "synapses of the first type." An example of three synaptic formations is presented in which contact is achieved at a great distance between the presynaptic and the postsynaptic membranes. Bands of dark substrate are easily seen which in all three examples confirm the importance of the chemical reactions precisely on the postsynaptic membrane. In addition, example 2 shows a strip (b) of extracellular material, in the form of a special fringe between the presynaptic membrane (a) and the postsynaptic membrane (c).

(b) An example of axosomatic synapses which differ considerably in nature from axodendritic synapses. All presynaptic endings (pre) contact the membrane of the cell body, the cytoplasm of which is filled with Nissl bodies and mitochondria. The arrows indicate points of thickening which occupy a considerably smaller part of the entire synaptic contact, thus distinguishing this second type of synapse from the first type, i.e., from axodendritic synapses. From Gray (1959).

configuration of the synaptic knobs (and spines), easily detectable by using even an ordinary microscope, is also a manifestation of the chemical specificity of the processes occurring on the postsynaptic membranes.

In connection with this, the data of electron microscopic investigation are of special interest. Palay (1956), for example, asserts that this type of investigation does not reveal a structural difference between the axodendritic and axosomatic synapses. The later data of Gray (1959), however, distinctly brought out these differences. Gray showed that the point of synaptic contact and the structure of the postsynaptic membrane itself differ appreciably for axodendritic and axosomatic synapses. Moreover, even at the same level of convergence there can probably be synapses of different morphological structure (Fig. 5.18).

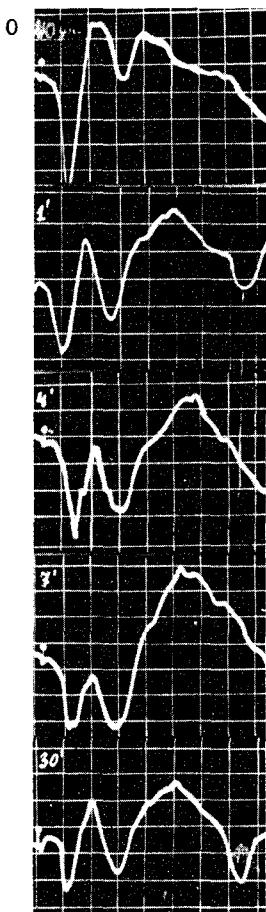


FIG. 5.19. Consecutive stages of the action of GABA on the depolarizing synapses of the cerebral cortex. The gradual suppression of the primary negative component and the growth of the secondary negative component can be seen. From top to bottom : min after the application of 1% GABA.

What we know about the heterogeneous chemical nature of the synaptic formations on the body of the same nerve cell is essentially limited to these data. Although they are sufficiently convincing with regard to this extraordinary property of the cortical cells, it was nevertheless necessary to make further verifications in relation to the generally known phenomena of the evoked potentials, the composition and physiological genesis of which has been sufficiently well studied. For this purpose numerous investigations were carried out in our laboratory on different forms of evoked potentials with the use of different substances of known pharmacological effect. In spite of the fact that this experiment is still in its very early stages, we can state various considerations which justify a hypothesis concerning a chemical basis for the convergence of different impulses into the protoplasm of the same nerve cell.

We first noticed that the electrical index alone is insufficient to approach the essence of the neurophysiological processes arising on the neuron while we were investigating the action of GABA on the synapses of the cortical cells. The generally held concept that GABA selectively blocks the depolarizing synapses has come about since the interesting investigations of Purpura (Purpura, 1959, 1960; Purpura *et al.*, 1960a). Being the end result of depolarization under an electrode, the negative component of the evoked cortical potential is eliminated upon the direct application of GABA to the recording site of the evoked potential.

However, as the investigations of my collaborator Ata-Muradova (1963) showed for the first time, this generally accepted point of view does not reflect fully enough the true essence of the actual neurochemical process resulting from the action of GABA. Upon application of GABA to the cerebral cortex, the negative component of the evoked potential is blocked. Simultaneously with the decrease in the amplitude of the usually occurring negative potential, another negative potential begins to appear near the decreasing negative potential (Fig. 5.19).

Observations show that this negative potential, which we have called secondary, also occurs under ordinary conditions but develops almost simultaneously with the primary one. Being of the same polarity, they summate and in most cases cannot be differentiated. Under any artificial conditions, however, such as heating, their difference appears. The application of GABA, as shown by Fig. 5.19, distinctly reveals this secondary negative potential.

Both these negative components undoubtedly result from depolarization. But what, then, could be the cause of this differentiation of seemingly identical types of depolarizing synapses? "Negativity" is not the decisive criterion for evaluating the effect of GABA. The data show that electronegativity can be the result of completely dissimilar neurochemical processes. One of these processes is chemically affected by GABA so as to preclude the possibility of depolarization, while the other is distinctly facilitated by GABA. Thus, there are two kinds of synaptic endings which have the same localization (the plexiform layer) and the same polarity, but a different neurochemical basis on which this negative potential is produced (see Fig. 5.19).

These differences in chemical properties can be produced even more distinctly if nembutal is applied under conditions of preliminary local strychninization of the focus of maximum activity of the evoked potential. With this procedure one can obtain a

distinct dissociation between the negative potentials, which, though having the same deflection, are the result of completely separate ascending series of impulses with different chemical properties of the apical synaptic formation for each respective series. Moreover, such a proportion of nembutal and strychnine can be selected that not only is a secondary negativity evoked by the application of GABA but also a "tertiary" negativity. All the negative potentials having individual chemical properties show that the mass of ascending impulses entering the cerebral cortex and having definite chemical individualities is considerably richer than can be expressed by the two signs of a simple electrical index (Fig. 5.20).

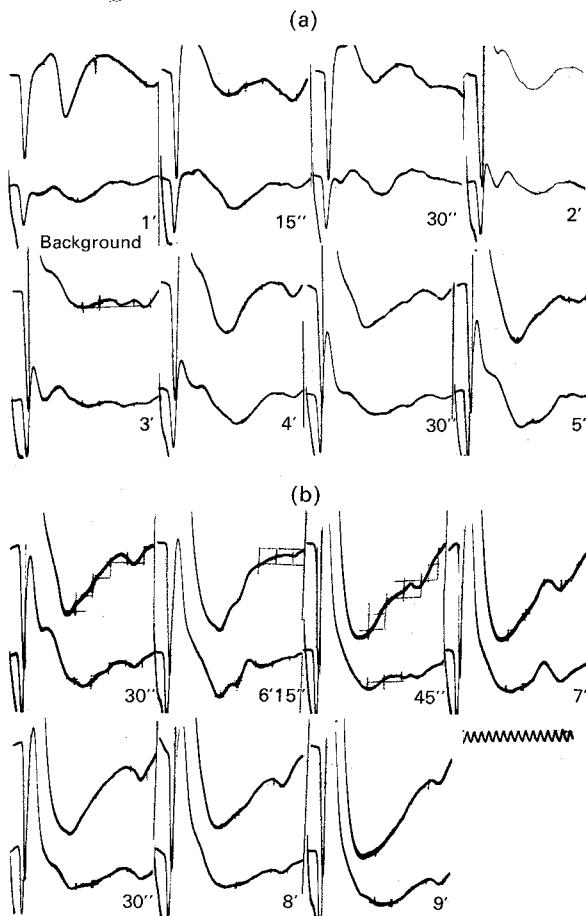


FIG. 5.20. (a)-(c) Illustration of the action of strychnine and nembutal on the negative component of the evoked potential. (a) Upon application of strychnine, a considerable increase in the amplitudes of both the positive and the negative component (background) occurs. The application of nembutal gives a considerable decrease and elimination of the negative component, starting from 15 sec after the application up to 3 min, when instead of the primary negative component, a secondary negative component appears. (b) The application of nembutal shows that, concurrently with the elimination of the primary negative component, an increase of the secondary negative component takes place.

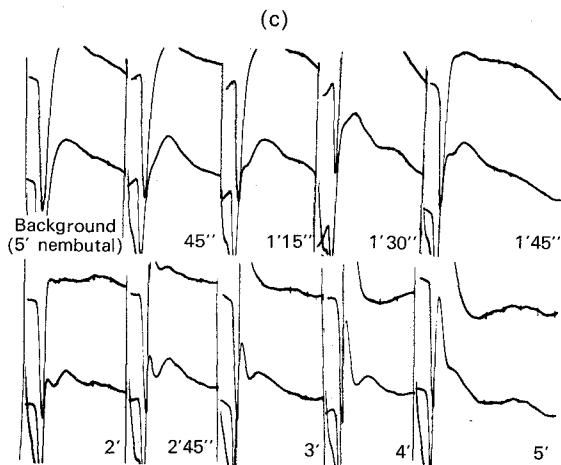


FIG. 5.20. (cont.)

(c) The same experimental conditions. The appearance of a tertiary negative component is shown on the curve.

What kind of impulses do the different synapses receive? In other words, do they transmit only specific ascending impulses which have arisen in different subcortical structures, or can they all conduct the same impulses?

We attempted to answer this question by several methods. First of all, we recorded the evoked potentials at the same point of the cerebral cortex. These evoked potentials, however, were of different physiological origin, i.e., they were obtained from the stimulation of different points of the central nervous system and the peripheral receptors. The subsequent course of the experiments was as follows: we applied different substances to the common recording site of both potentials and observed the change in the analogous components of the two different evoked potentials obtained as a result of physiologically different ascending impulses.

Chuppina, a collaborator in my laboratory, compared two evoked potentials by using the above-described method. One of them was obtained by stimulating the symmetric site of the contralateral hemisphere (transcallosal potential), and the other by stimulating the contralateral sciatic nerve (Fig. 5.21). As can be seen from the recordings of these two evoked potentials obtained from one cortical site, the composition of both potentials in regard to individual components is the same. Only certain parameters of these potentials differ in detail. However, the application of GABA or novocaine to the recording site of the potentials exerts a nearly opposite effect on the formation of the negative components of these potentials. The application of GABA almost immediately blocks the negative component of the primary evoked response and scarcely changes the similar negative component of the transcallosal evoked response (Fig. 5.22, a). Novocaine, on the other hand, after 1 min suppresses the negative com-

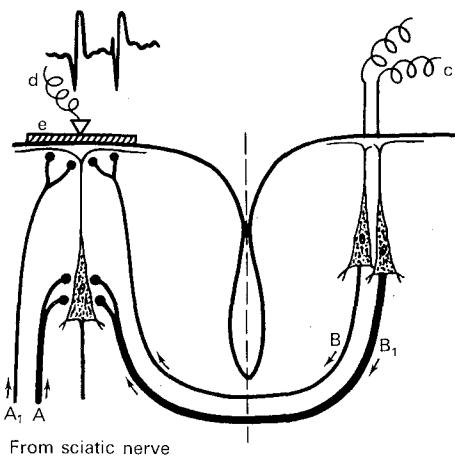


FIG. 5.21. Diagram of the convergence of two different emissions of excitations to the same cortical neuron. A, A₁, specific and nonspecific excitations from stimulation of the sciatic nerve; B, B₁, two pathways in the corpus callosum, which conduct excitations to the axoapical and to the axosomatic synapses. The point of stimulation (c) and the point of recording (d) and of the application of chemicals (e) are shown.

ponent of the transcallosal evoked response and hardly affects the negative component of the primary evoked response (Fig. 5.22, b).

Since all other experimental conditions (strength of stimulation, recording site, etc.) were absolutely the same as before, there remains only one explanation for the above-described difference: the chemical properties of the synapses to which both the peripheral and the transcallosal afferent impulses are directed are different (Ata-Muradova and Chuppina, 1964).

Among the many examples showing that the synaptic formations of the cortical neurons are considerably more diverse in their chemical properties than it previously seemed are the experiments of Badam Khand (1965) which have been analyzed earlier in this chapter. As we know, she studied the form and degree of generalization over the cerebral cortex of the primary potentials evoked by the stimulation of different hypothalamic nuclei. It was shown that (see Fig. 5.22) the configuration of the evoked potential changes appreciably depending on which nucleus of the hypothalamus is stimulated at a given moment. As it turned out, however, this difference in configuration is related to a distinct difference in the reaction of the synaptic formations at this recording site to the application of certain drugs (GABA, chlorpromazine, adrenaline, etc.).

Furthermore, a difference is especially apparent in the chemical properties of the postsynaptic membranes of those axodendritic synapses which are located on the apical dendrites, i.e., those in the plexiform layer. One may select that site of the cerebral cortex in which in response to stimulation of the hypothalamus two negative potentials of almost identical amplitude are formed. If GABA is applied to this site, the first negative potential is blocked, while the second gradually increases (Fig. 5.23). If

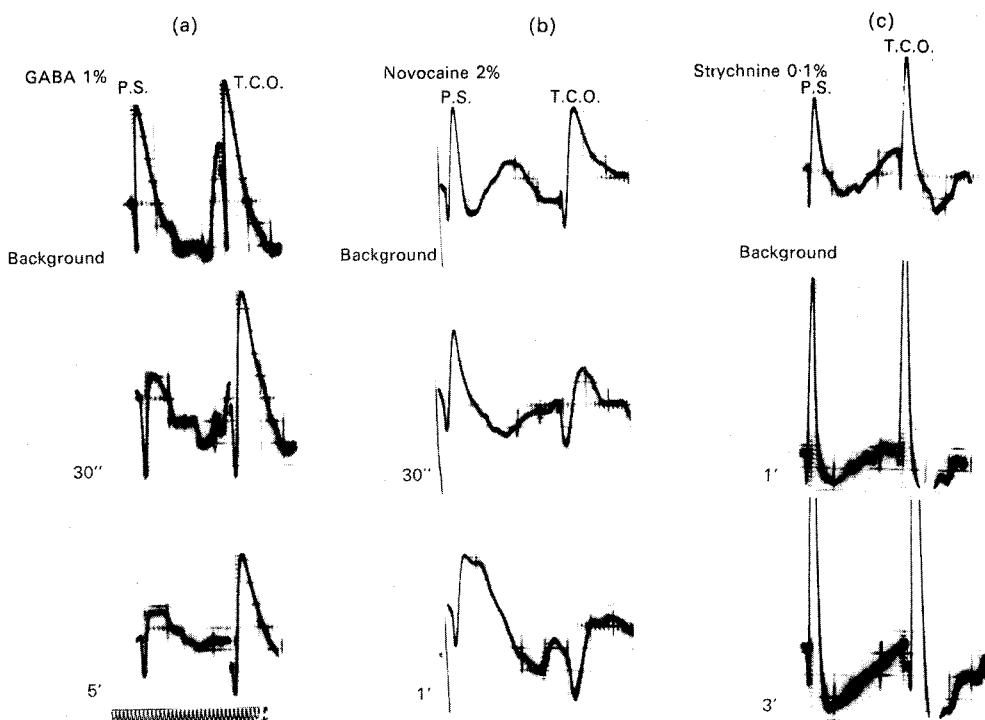


FIG. 5.22. Three examples of chemical actions on different postsynaptic membranes.

(a) The action of GABA on the evoked potential of the sciatic nerve (PS) and the evoked potential of transcallosal origin (TCO). The difference in the chemical sensitivity of the postsynaptic membranes of both evoked potentials can be readily seen. By the fifth minute, the potential from the sciatic nerve is completely eliminated, while the potential of transcallosal origin decreases only slightly.

(b) The application of novocaine under the same experimental conditions gives entirely opposite results. The negative potential of the transcallosal response is blocked, while the negative potential from the sciatic nerve remains.

(c) The application of a 1% strychnine solution leads to a marked increase in the amplitude of both evoked potentials.

chlorpromazine is applied to the same site in the presence of the same two initial negative potentials, the phenomenon develops in reverse order: the second negative potential disappears, while the first changes only slightly.

There is no doubt, then, that the hypothalamus sends into the plexiform layer several types of ascending impulses directed at synaptic formations with postsynaptic membranes having entirely different properties.

Thus, the difference in the chemical properties of the synaptic formations proves to be manifold. It varies according to both the type of ascending influences and the localization of the generating centers, and also appears in the application of paired stimuli to the sciatic nerve at critical intervals. Depending on the application of one substance or another to the recording site of the potentials, we have different forms of suppression of some potentials by others (Sun Ven-in, see Anokhin, 1964c) (Fig. 5.24).

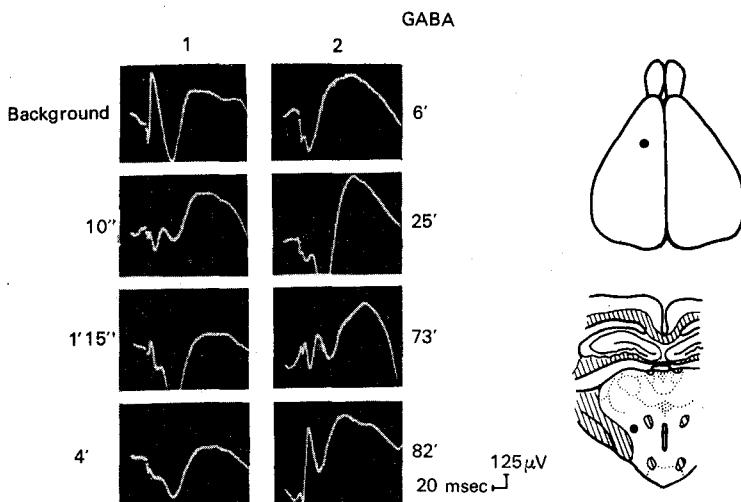


FIG. 5.23. The curves illustrate that in response to the application of GABA to the evoked potential during stimulation of the hypothalamus, one of the negative components is immediately eliminated (1). This can be seen as early as the 10th second of the action of GABA, while the second negative component (2) undergoes a considerable evolution toward an increased amplitude. It reaches its maximum increase during the 25th minute. At right, the figure shows the point of stimulation (bottom) and the point of recording (top).

Perhaps, however, this chemical diversity of the cortical synapses was brought out most clearly in the chemical analysis of the cortical activation obtained on the basis of both the ascending impulses of very definite biological modality and the evoked potential formed on this background. These experiments by a collaborator in my laboratory,

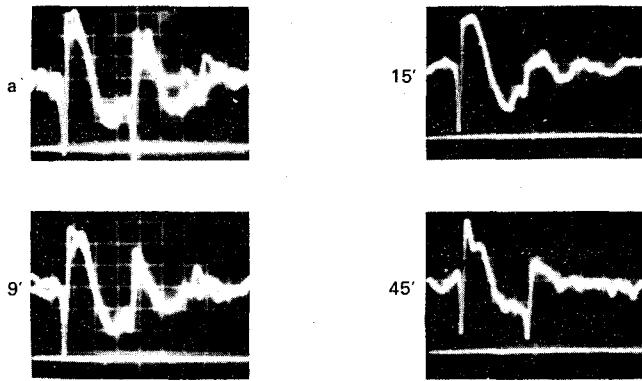


FIG. 5.24. The effect of an intraabdominal injection of chlorpromazine on paired evoked potentials obtained at the optimal interval. Recordings before the application of chlorpromazine (a), and 9, 15, and 45 min after its application are given.

Turenko, were performed on cats under urethane anesthesia after a two-day fast. As we already know from what has been presented above, a one- to two-day fast leads to the establishment of a constant ascending activation in the anterior parts of the cerebral cortex even during urethane anesthesia. This activation depends on the lateral nucleus of the hypothalamus which is excited by "starved" blood (Sudakov and Turenko, 1965).

Since our previous data had convinced us that desynchronization is established by

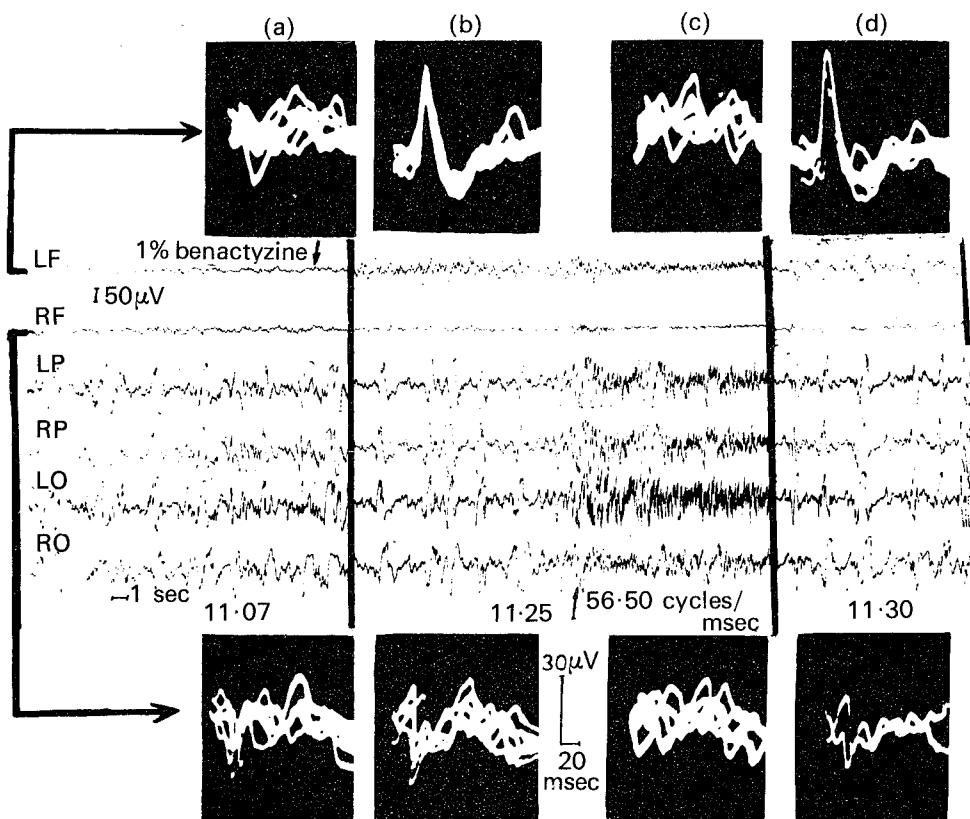


FIG. 5.25. Changes in the electroencephalogram and the evoked potential under conditions of initial excitation by hunger and the subsequent application of benactyzine to one of the points that are in a state of activation. At the top are shown the potentials from the point of application of benactyzine; at the bottom are shown the evoked potentials from the corresponding point of the opposite hemisphere, to which benactyzine was not applied. The application of 1% benactyzine leads to the elimination of desynchronization and to the appearance of a pronounced evoked potential (b), which differs noticeably from the masked evoked potential under conditions of desynchronization (a). After the electrical stimulation of the sciatic nerve was started, the slow electrical activity was again transformed into hypersynchronization, and at the same time the evoked potential proved to be masked again (c). Five minutes after the stimulation, the slow electrical activity is again restored at the point of application of benactyzine, as are also the evoked potentials (d). LF, left frontal; RF, right frontal; LP, left parietal; RP, right parietal; LO, left occipital; RO, right occipital.

means of the arrival of ascending impulses from the subcortex into the plexiform layer of the cerebral cortex, we wished to ascertain the chemical nature of those synaptic formations which form desynchronization (activation) in the cerebral cortex.

Experiments have shown that if a small piece of paper moistened with a 0.5–1.0 per cent benactyzine hydrochloride (amizil) solution is applied in the zone of alimentary activation, very interesting phenomena arise which shed light on the chemical properties of the cortical synapses that receive the ascending activating influences. At the site where benactyzine was applied, the desynchronization was replaced by slow electrical activity characteristic of the resting state of the cortex (Fig. 5.25, a).

As seen in this figure, the replacement of the activated state of the EEG by slow activity occurred only at the site at which the benactyzine was applied. Both in adjacent areas of the same hemisphere and in the contralateral hemisphere, ascending alimentary activation occurs as before.

If the evoked potential is concurrently recorded from the same site, characteristic changes may also be observed. During the activated state of the cortex the evoked potential has, as usual, a negative component of considerably decreased amplitude (the "masking phenomenon") (Fig. 5.25, b). This "masking" is related to the fact that the ascending activating influences, which mainly spread into the area of the apical dendrites, impede the mobilization of those postsynaptic potentials on the basis of which the negative component of the evoked potential usually is formed during a state of rest.

It is interesting that the above changes of activation into slow electrical activity at the site of application of benactyzine are accompanied by a concurrent restoration of the negative component of the evoked potential (Fig. 5.25, c).

Taking into account the data published by many investigators (Anichkov, 1960; Denisenko, 1960; Il'uchenok and Mashkovskii, 1961) that benactyzine blocks cholinergic synapses, we can interpret the results of our experiments as being a consequence of blocking the cholinergic synaptic formations situated in the zone of the apical dendrites, i.e., predominantly in the plexiform layer of the cortex.

This conclusion gives us reason to think that ascending alimentary activation affects the cerebral cortex through a cholinergic synaptic mechanism. If we compare this mechanism with the neurochemical characteristics of the subcortical center, which initiates the activation and is of a cholinergic nature (Shumilina, 1964), we see the striking chemical unity of an old synaptic formation (hypothalamus) and a new one (frontal cortex) which pattern functions of the same biological modality but at different levels of the central nervous system.

We are interested in still another aspect of Turenko's experiment. If the cholinergic synapses are blocked at the recording site where benactyzine was applied, is it not possible to reestablish an activated condition on the same cortical cellular elements through other synaptic formations?

It is clear that in this case it was necessary to use some other nonalimentary ascending impulse of a different biological modality. Since in our previous experiments we had often compared two biological modalities of ascending impulses, the alimentary and the nociceptive, in this case we chose nociceptive stimulation of the sciatic nerve. The

slow electrical activity which had set in at the point where benactyzine was applied changed, upon stimulation of the sciatic nerve, into a new activation, a nociceptive one (Fig. 5.25, c).

On the one hand, this experiment confirmed our previous concept concerning the different specific natures of ascending activations of different biological modalities. On the other hand, it showed that the cortical cell has several synaptic formations of different chemical specificities, i.e., several afferent "entrances." While some of them, such as the cholinergic ones, may be inoperative in this case due to the action of benactyzine, others not subject to the action of benactyzine can form the activated state characteristic of them (Fig. 5.25, d). Although these synaptic formations remaining unaffected by benactyzine and forming the activated noxious state are still under investigation, we have every reason to believe that they are of an adrenergic nature. At present it is only important to note that these synapses differ chemically from those which mobilize the alimentary reaction at the cortical level.

The differentiated sensitivity of the various synapses at the subcortical and cortical levels can be highly diverse and can be manifested under various specially created

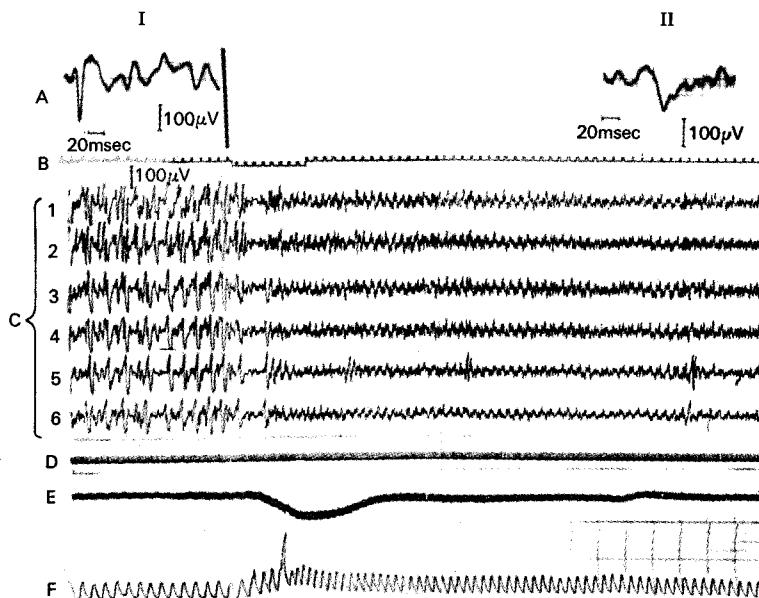


FIG. 5.26. Evolution of the evoked potential and of the electroencephalogram from a moment before the application of electrical stimulation of the sciatic nerve (I) until after the application of stimulation (II). The appearance of desynchronization in all leads from the cerebral cortex and the change in the evoked potential as a result of the elimination of its negative component can be seen. Recordings from top to bottom : A, evoked potential in the left sensorimotor cortex in response to a single stimulation of the right sciatic nerve; B, time in sec.; C, EEG in a unipolar lead from the sensorimotor (1—right, 2—left), temporal (3—right, 4—left), and occipital (5—right, 6—left) regions of the cortex of both hemispheres; D, EKG; E, arterial blood pressure; F, respiration. The depression of the time line corresponds to the period of nociceptive stimulation.

conditions. It is known, for example, that nociceptive activation of cortical electrical activity strongly masks the evoked potential in the cerebral cortex (Fig. 5.26). One might think that the nociceptive ascending impulses act on structures which are common to the evoked potential and to the activation of the cortex. Injection of chlorpromazine permits a chemical differentiation of the structures forming the nociceptive activation from those forming the evoked potential in response to stimulation of the sciatic nerve.

As we know, injection of chlorpromazine prevents desynchronization in response to nociceptive stimulation. This means that the subcortical structures which had formed the nociceptive activation are blocked. However, in spite of the absence of desynchronization (chlorpromazine), the evoked potential is suppressed under these conditions, as before, by nociceptive ascending activation (Fig. 5.27). Consequently, the chemical characteristics of the synapses of the two ascending influences are different (Kagramanov, 1964a, 1964b).

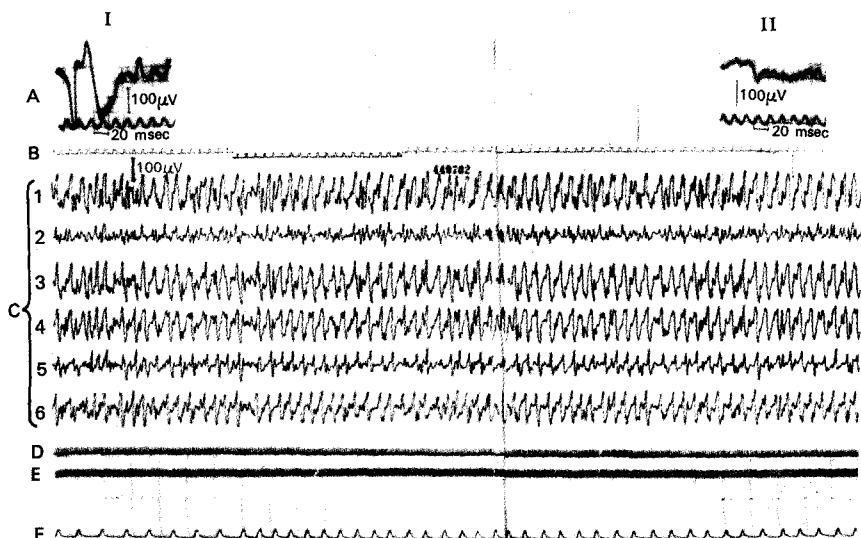


FIG. 5.27. Recordings of an experiment set up under the same conditions as in Fig. 5.26, but with the second part of the experiment performed on a background of chlorpromazine injection. It can be seen that before the injection of chlorpromazine the evoked potential was pronounced, especially its secondary positive discharge (I). However, in spite of the fact that electric stimulation on a background of chlorpromazine did not produce changes in the electroencephalogram, it nevertheless led to a masking of the evoked potential (II). Lines A-F, the same as in Fig. 5.26.

Evidence that the cortical synapses have different chemical characteristics and pertain to different subcortical structures can also be seen in the following phenomenon. In the above experiments of Sudakov on a fasting cat, under conditions of alimentary activation of the anterior parts of the cerebral cortex, the evoked potential from stimulation of the sciatic nerve proves to be masked. On the other hand, the

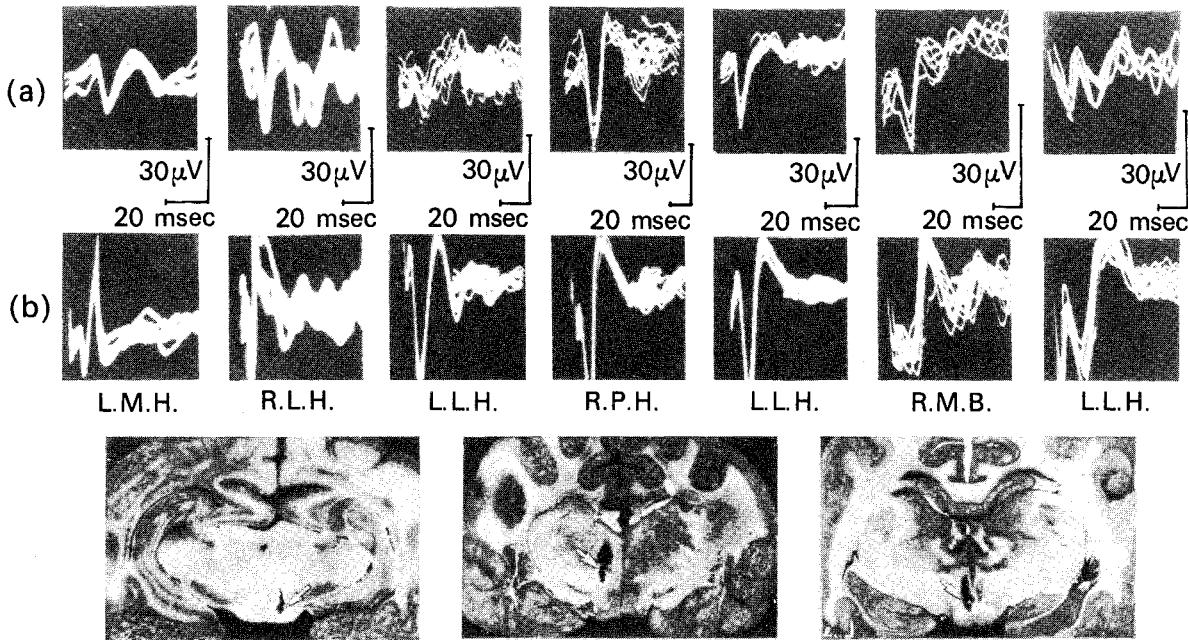


FIG. 5.28. Two series of stimulations, performed in seven separate experiments. The upper row of evoked potentials (a) was obtained on a background of desynchronization, evoked by electrical stimulations of the sciatic nerve. The lower row of evoked potentials (b) was obtained from the same point of the cerebral cortex upon stimulation of various points of the hypothalamus. L.M.H., left medial hypothalamus; R.L.H., right lateral hypothalamus; L.L.H., left lateral hypothalamus; R.P.H., right posterior hypothalamus; R.M.B., right mammillary body. At the bottom are three photographs of transections of the brain in the hypothalamic region.

evoked potential from the lateral nucleus of the hypothalamus that had formed this alimentary activation is clearly apparent (Fig. 5.28). This phenomenon could only occur if the impulses of the alimentary activation and those of the evoked potential (from the hypothalamus) are functionally homogeneous and interact on the synaptic formations of the same cellular elements.

The extent of chemical specificity of the cortical synapses can be seen from other experiments of Kagramanov (1966). He showed that by injecting various substances into the blood one can block the muscarine-sensitive synapses and activate the nicotine-sensitive ones. Apparently the chemical specificity of the cortical synapses is much more extensive and complex than we are able to detect by our present methods of investigation. This specificity certainly is established at the molecular level, but evidently, the morphological investigations which have determined the structural diversity of the synaptic knobs only roughly approach the specific processes of trans-synaptic propagation which develop and acquire their characteristics predominantly at the molecular level.

Now we can return to our initial question : where and how do the "indifferent" and the "unconditioned" impulses meet, if they follow each other in a definite order that is essential for the elaboration of the conditioned reflex? Considering all the possibilities for the encounter and convergence in the cerebral cortex of ascending impulses different in origin, as analyzed in this chapter, we can answer this question with a considerable degree of probability.

THE MOLECULAR THEORY OF MEMORY IN RELATION TO THE COUPLING OF THE CONDITIONED REFLEX

The material examined in the preceding sections of this chapter enables us to state two conclusions which require further analysis on a molecular level.

First, the impulses arising from indifferent stimuli that reach the cerebral cortex via two channels, the lemniscal system and the subcortical nuclei, overlap in various combinations, and finally a convergence of these ascending impulses upon the same cortical neurons occurs. This is relevant not only to the sensory projection of a particular stimulus, where the convergence of impulses is maximal, but also to other areas of the cerebral cortex which receive various fragments of the ascending impulses evoked by the indifferent stimulus. This pertains especially to the so-called associative areas and to the central parts of the long dendrites of the cortical neurons since the Forbes discharge and the positive potential ascending from the hypothalamus are of a generalized nature.

An unconditioned stimulus having a definite biological modality evokes a generalized activation of the entire cerebral cortex. We can therefore state the second important conclusion : at the moment of action of the unconditioned stimulus there occurs an extremely broad convergence of the two ascending series of impulses, the indifferent and the unconditioned, upon the cells of the cerebral cortex.

Considering the diverse nature of the ascending impulses which are aimed at different regions and different layers of the cerebral cortex and which excite these structures

with different intensities and at different time intervals, we can imagine the extraordinary interactions of these combinations of impulses at various cortical sites and on various nerve cells. We must assume that even the indifferent stimulus, potentiated by the orienting-investigative reaction, evokes an extremely extensive complex of excitation in the cerebral cortex, which can only be evaluated in detail by statistical methods.

Now it is important to understand that the first interaction of the processes evoked by the indifferent and the unconditioned stimulus occurs on the same neurons. Already during the first milliseconds after the action of the unconditioned stimulus, it develops on the background of the generalized activation evoked by the orienting reaction. Consequently, we must sooner or later answer a question concerning the chemical heterogeneity of the neuronal membrane.

What does this interaction involve? What kinds of chemical processes are evoked by the impulses arriving at the postsynaptic membranes of the same neuron?

These questions bring us to a discussion of those membranous and protoplasmic processes which are presently regarded as the most likely concomitants of any fixation of acquired experience. In other words, we must examine the molecular theory of memory as related to experience and elucidate the relation of this theory to the problems of interest to us.

By this time we have ample literature dealing with the role of the individual components of the protoplasm of nerve cells in the accumulation of life experience in animals and man (Hydén, 1943; Corning and John, 1961; Gaito, 1963; Dingman and Sporn, 1964; Eccles, 1966, pp. 314-344).

The fixation of acquired experience may be caused by molecular rearrangements in the cells of the organism, namely, by the transformation of ribonucleic acid (RNA) (McConnell, 1962; McConnell *et al.*, 1961). McConnell's experiments caused such a widespread sensation in the scientific world, especially among scientists working in the neurophysiology of the conditioned reflex, that there is a continuing interest in them. It should be said that McConnell's experiments have been the impetus towards the formulation of the contemporary molecular theories of memory and learning and therefore deserve special attention.

The planarian is distinguished by a marked capacity to regenerate after the infliction of various injuries, even after being completely cut into pieces. This characteristic of the planarian at one time served Child as he developed the concept of the physiological gradient (Child, 1921, 1924, 1941). After being cut in half, these worms regenerate a head on the tail section and a tail on the head section so that two separate planarians actually result.

McConnell made use of another characteristic of planarians. Although they are invertebrates, planarians can develop conditioned reactions during the reinforcement of light by electric current. Usually after only a few dozen pairings of light with the passage of electric current through the water of the aquarium, the planarian reacts quite distinctly to light alone in the form of spastic movements and a twisting of the entire body.

McConnell elaborated a conditioned reflex of this type in a planarian and then bisected it, expecting a regeneration of both halves. After a certain period of regenera-

tion, when two complete individuals had been restored, the conditioned reflexes to a flash of light were tested. Both individuals could elaborate conditioned reflexes more rapidly than could naive planarians. This finding caused a sensation which spread to all physiological and biological laboratories.

These experiments were repeated many times by both McConnell and many other investigators. In the overwhelming majority of cases, McConnell's results were confirmed. Experiments were then set up differently, emphasizing even more that the ability to elaborate a conditioned reflex in the regenerated planarians is a result of the acquired diffuse tissue specificity. These experiments were called "cannibalistic." They consisted of the following: a planarian in which a conditioned reflex to light had been elaborated was ground or cut into small pieces. This mass was fed to another planarian which had never before developed a conditioned defense reflex to light. The results were quite startling. After having eaten the other "conditioned" individual, the fresh planarian could more rapidly elaborate the conditioned reactions than is usually achieved by planarians.

It became quite evident that the ability to implement previously elaborated conditioned reactions in planarians is incomprehensibly fixed diffusely in the entire mass of the body and consequently can be transmitted to any other regenerating individual. The question arose as to what kind of substrate so miraculously fixes the connection between two sequentially arriving external influences on the organism.

By the time of McConnell's experiments the genetic code, which implements all the hereditary characteristics of animals via RNA, had been quite well understood. Therefore, the suspicion arose as to whether RNA was also responsible for the transmission of conditioned reactions to regenerating planarians.

There is an experiment which may substantiate this suspicion. This involves the action of an enzyme, ribonuclease (an inhibitor of ribonucleic acid), which paralyzes the information capacity of RNA. The experiment showed that ribonuclease almost completely eliminates the conditioned reaction in the regenerating tail section of a previously trained planarian if it was applied when the regenerated planarian was becoming a mature individual.

All these experiments provided a basis for the formulation of the so-called "molecular theory of memory," which can briefly be described as follows: on the basis of external influences that evoke a chain of chemical processes in the organism, any new experience establishes a specific code by rearranging the RNA (memory). With the appearance of a similar situation, this code is subsequently manifested in an appropriate form of behavior (recall).

Thus, as I have said, McConnell's data were an impetus for the development of a new trend in understanding the acquired associative activity of living beings. It was found that this activity is not as exclusively dependent on the nervous system as it was previously thought. It is highly probable that in lower animals these associations, i.e., temporary connections, become much more generalized and may involve all the elements of the body. McConnell's experiments made it possible to believe that the protoplasm of every cell in the body of these animals somehow receives a stimulus for the rearrangement of RNA, which subsequently serves as a basis for the reestablishment of their adaptive behavior.

Here, of course, many other problems arise which remain unsolved: by what means is the optical stimulation transformed into a stimulus for every cell of the body, and how do these cells subsequently transmit their coded RNA to the newly regenerated front end, thus making it sensitive to an optical stimulus which acts as a conditioned stimulus? In any case, the experiments themselves must also be verified by even more rigorous experimental procedures.

In connection with McConnell's findings it is appropriate to recall our concept concerning the biological roots of the conditioned reflex, which was presented in Chapter 1. In the development of this concept we proceeded from an apparent fact in the relation between the inorganic and the organic world: any sequence of several influences on the organism must invariably evoke the appropriate chemical reactions, proceeding in the same sequential order and specific for each of these influences. To avoid repetition I shall omit all the intermediate arguments and merely recall that a stable chemical connection is established between all these sequential reactions only if these sequential influences terminate in an event of vital importance for the organism. This connection, in the course of subsequent repetitions, assumes the nature of a temporary connection, ensuring the signaling nature of the adaptive activity of the organism.

Analyzing the data on the elaboration and regeneration of conditioned reactions in planarians, Hyden concluded that such a sequence of two external influences was fixed in the code of RNA (Hydén, 1960). Consequently, we may assume with a certain degree of probability that even in the case of primordial, primitively organized matter this connection can also be established by means of some codifying protoplasmic formation, possibly even on the basis of some kind of "precursors" of RNA.

In any case there is every reason to believe that during evolution there was formed in the protoplasm of living beings one universal form of fixation of vitally important, sequential, protoplasmic processes which reflect the sequential influences of environmental changes. It is entirely possible that RNA subsequently became this universal means of coding experience in the protoplasm.

The results of McConnell's experiments, which had shown the determining role of RNA in the fixation of sequentially developing protoplasmic processes, were subsequently tested on the model of the elaboration of conditioned reflexes in higher animals also. In this respect it is of special interest to point out the experiments of Hydén (1960), which further strengthened the concept of the role of RNA in the learning process.

Hydén's molecular theory of memory encompasses all those transitional processes which connect the series of impulses that have arrived at a nerve cell with the final transformation of this series into specific structural rearrangements of the protein molecule. According to Hydén's theory, a decisive role in this process is played by RNA, which is an intermediary between the external information reaching the cell as nerve impulses and the final product in the form of the rearrangement of the protein molecule, the true "memory engram."

Hydén's theory has been substantiated by a number of experiments involving the elaboration of behavioral conditioned reflexes in rats and the use of a quite delicate method for the detection of RNA in brain cells. In view of the complex nature of

Hydén's hypothesis, based on morphological, physiological, and chemical data, I consider it necessary to briefly state its basic postulates.

Hydén assumes that the primary distinguishing feature which makes a particular memory trace specific is the frequency of the impulses reaching the nerve cell. Depending on this frequency, a change in the position of certain nucleotides in the RNA chain is accomplished. Consequently, according to Hydén's theory, the initiation of association in the protoplasmic processes depends on a change in the informational significance of RNA. It is well known, however, from biochemistry that the central and perhaps even the only function of RNA is the synthesis of protein molecules. By assuming a change in the arrangement of nucleotides in the composition of RNA, we may also assume that this new RNA synthesizes protein molecules appropriate for a given situation (Fig. 5.29). In essence, Hydén believes that this new protein molecule is the repository of the information obtained, a kind of "memory engram."

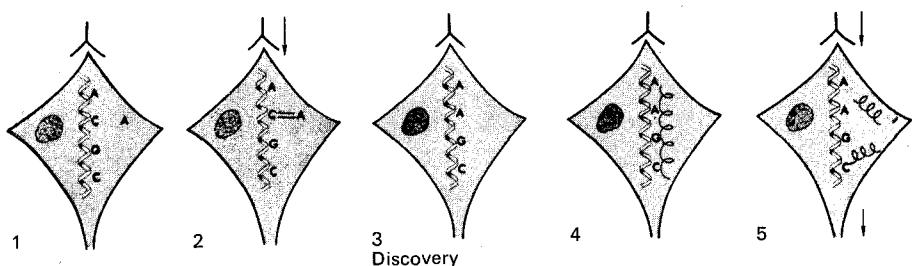


FIG. 5.29. Diagram of the coding of an acquired habit according to Hydén. From Rose (1964, pp. 42-43). A, C, G, C, the respective bases of the ribonucleic acid. 1, 2, 3, 4, 5, stages of change in the code of the ribonucleic acid and the formation of a new protein molecule which then is the repository of the acquired experience.

Any theory is intended to explain not only memory but also, what is especially important, recall, i.e., the extraction of information encoded in a protein molecule in the appropriate behavioral situation. For Hydén, recall is also related to the frequency of impulses which arrive at the same synapse and excite the same complex of chemical reactions as before. In this case, however, the incoming series of impulses does not promote the synthesis of a new protein molecule, but rather a sudden change in this memory molecule. This change serves as an impetus for the excitation of a given nerve cell which is part of an extensive neuronal complex that brings about some behavioral act.

Hydén's concept has now acquired wide circulation, even though its acceptance is hindered by certain unrealistic features. It is therefore interesting to analyze the experimental arguments on which Hydén based his concepts. First of all, experiments involving the elaboration of definite behavioral acts in rats should be cited (Dingman and Sporn, 1961). In a water maze, rats had to perform swimming movements so that they could obtain food after swimming through the maze. The rats quickly learned the simple movements and obtained the food, i.e., they elaborated a conditioned alimentary reflex (Fig. 5.30).

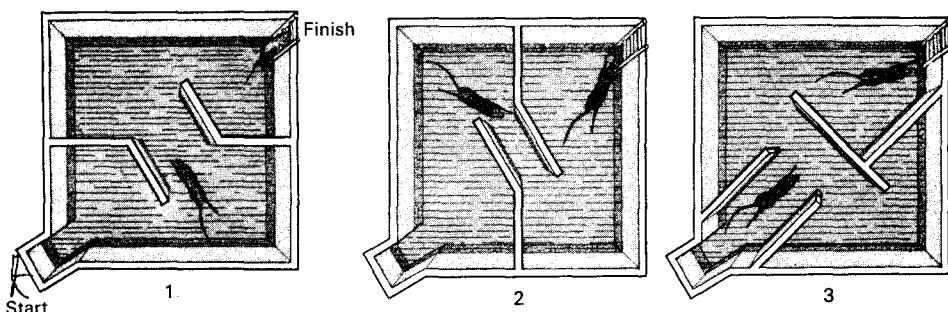


FIG. 5.30. Setup of experiments by Dingman and Sporn (1961) on the elaboration of skill in obtaining food. From Rose (1964, pp. 40-41). 1, 2, 3, different variations of the experiments.

Subsequently, the experiment was conducted in two variations. In the first series, before the start of elaborating the conditioned reflex, the rats received an RNA inhibitor (8-azaguanine), but in the second series of experiments they received this inhibitor only after the elaboration of the conditioned reflex. Since the inhibitor acts on the RNA by stabilizing its genetic code, it was quite interesting to determine the effect of the inhibitor in both above-mentioned cases of the elaboration of the conditioned reflex. Experiments have shown that 8-azaguanine considerably retards and even completely inhibits the elaboration of a new conditioned reflex pertaining to the maze, while it does not affect an already elaborated and stabilized conditioned reflex.

From these experiments it was concluded that in the process of fixation of acquired experience, RNA is especially important as a transmitter of information; already fixed acquired experience, stored in the specific codes of protein molecules, is not affected by the inhibitor.

The following remains unexplained: in that series of experiments in which the inhibitor was administered after the elaboration of the conditioned reflex, how can the reflex be manifested? The intermediary, RNA, should be paralyzed.

By means of a delicate surgical technique, Hydén (Hydén and Pigon, 1960; Hydén and Egyházi, 1962) was able to extirpate individual nerve cells from that region of the brain which was known to have participated in the formation of a conditioned reflex. He elaborated conditioned vestibular reflexes by subjecting rabbits and rats to rotation. Resisting the rotation, the animals elaborated the reflex via the motor analyzer. Thus, Hydén selected the cells of the motor area for an investigation by a delicate histochemical method. He showed that in the cells of the motor area there is considerably more RNA than in cells that did not participate in the elaboration of the conditioned motor reflexes (Fig. 5.31).

In regard to this, attention should also be given to the experiments of Kreps and of Morrell involving direct analysis of cerebral substance during the elaboration of conditioned reflexes (Kreps *et al.*, 1954; Morrell, 1961). Since it was shown that in all cases the amount of RNA increases, naturally one may be tempted to attribute to RNA the role of the principal participant in the fixation of the information obtained in the form of protein "memory engrams."



FIG. 5.31. Samples of cells extracted from the vestibular nuclei of rats which had undergone rotation. Explanations in the text. Preparation by Hyden and Pigon (1960). From Rose (1964, p. 38).

At present, numerous indications of such a role of RNA have accumulated in the literature. Here I would like to mention the experiments of Bråttgard (1952), who has shown that there is a close relation between stimulation of the retinal ganglionic cells and an increase in RNA. Of special interest in this regard are the experiments of John *et al.* (unpublished data), who have demonstrated the extreme selectivity of the action of ribonuclease. Injection of ribonuclease into the cerebral ventricles of the cat blocks only those conditioned reactions which had been elaborated on the basis of unconditioned alimentary reinforcement. On the other hand, those reflexes which had been elaborated on the basis of unconditioned defense reinforcement remained unaffected after the injection. This finding is, of course, of great interest since it demonstrates a definite chemical difference in the coding of associations formed on the basis of reinforcements by stimuli of different biological modalities. If we take into consideration everything stated above regarding the chemical specificity of different (nociceptive, alimentary) stimuli, this conclusion from the experiments of John *et al.* will no longer appear so improbable.

Indeed, if the ascending impulses from the reinforcing unconditioned stimuli form distinctive chemical reactions on the postsynaptic membranes of the cortical cells, there is every reason to assume that these chemical reactions for the alimentary and nociceptive impulses must be different. This, however, must be tested by special experiments.

Comparing all the data analyzed above, we must admit that there should be a closer analysis of the problem of the different impulses converging upon the synapses (having different chemical properties) of the same neuron. We must realize that the very process of fixation of the connection between the indifferent and the unconditioned stimuli, which meet on the same neuron, is most closely related to the interaction of the synaptic membrane with the axoplasm. The neuron, then, is perhaps an exceptional cellular structure of the organism in the sense that its crucial processes are formed not only in the protoplasm and the nucleus, as is the case with all other cells of the organism, but even at the periphery, i.e., at the chemically heterogeneous postsynaptic membranes (see Fig. 3.20).

In fact, electron microscopy shows that the synaptic endings are mainly comprised of mitochondria, the power stations supplying the cells with the energizing material intimately connected with the conduction of impulses (adenosine triphosphate). The same investigations show, on the other hand, that the ribosomes, which determine the synthesis of protein molecules, are very poorly represented in the synaptic formations. They are, however, abundantly present in the cytoplasm and even in the cell nucleus. This alone shows that the postsynaptic process evoked by the diffusion of acetylcholine through the presynaptic membrane is merely the initial stage of some long chain process which may terminate in the cytoplasm by the incorporation of the above-described synaptic process with the participation of RNA.

Recently there have appeared a number of considerations concerning the nature of this chain process thought to be the basis of memory. Smith (1962) believes that cholinesterase, which reacts with great sensitivity to the strength of the excitatory process by increasing its amount, could be the initiator of this chain of processes. From Smith's point of view, the nature of this chain of processes must consist of a series

of highly specific enzymatic processes that spread to the center of the cell. It is quite possible that the contact of these highly specific enzymatic processes with the transmitter RNA occurs here, thus forming specific protein molecules. In any case, considering the experiments of Hydén, McConnell, and others, there is a very substantial basis for this assumption.

* * * *

The material examined above and the considerations which arise from this analysis lead us to state the hypothesis that impulses arising from indifferent and unconditioned stimuli meet on the membrane of the same cell and that their postsynaptic processes, proceeding into the cytoplasm, undergo the most intimate chemical interaction. This assumption is a natural extension of what neurophysiology has achieved in the study of the convergence of impulses and of the chemical specificity of the postsynaptic processes. According to the opinion of biochemists, the processes of the cellular membrane are a part of the metabolic processes of the entire cytoplasm. The experiments involving anastomoses, which were discussed in Chapter 4, suggest that the postsynaptic process is a direct reflection of cellular metabolism, and I see no basis for denying the encounter of all impulses at the level of the molecular processes in the cytoplasm. This pertains especially to the encounter of impulses arising from indifferent and unconditioned stimuli. Still not completely understood is the ability of the impulses arising from the unconditioned stimulus to combine with the impulses preceding them and to form with them stable chemical bonds.

We must firmly realize that none of the past or present hypotheses adequately satisfy our current knowledge of the fine structure and the intimate processes of the nerve cell. We usually say that coupling takes place on the basis of the "interaction of foci of excitation" and on the basis of the "synaptic process" with the incorporation of "inhibitory and excitatory synapses," etc. Essentially, however, these figurative expressions do not supply an adequate concept of the nature of coupling at the molecular level, which is what actually occurs. The very fact of the formation of new temporary connections between two external influences which had never been connected led to the concept of the necessity of new material contacts in the cerebral substrate. All the above terminology reflects essentially these initial hypothetical concepts. However, further penetration into the electrophysiological, neurochemical, and genetic nature of the nerve cells compels us to seek answers to our questions at this considerably more intimate level.

It is no accident, moreover, that a number of investigators, having encountered the phenomenon of convergence of impulses upon the reticular and cortical cells, have already attempted to relate the convergence of impulses to the formation of the conditioned reflex (Fessard, 1960; Jung *et al.*, 1963). This is undoubtedly very significant.

The convergence of impulses upon a neuron was linked most closely with the elaboration of the conditioned reflex by Fessard (1960). He analyzed in detail the general physiological aspect of the interaction of different series of impulses arriving at the same neuron, emphasizing postsynaptic potentiation in particular. In his

concept, Fessard has attempted to combine the advantages of convergence with the merits of potentiation.

Fessard ascribes the main significance to the process of potentiation, which results from prolonged influence of nerve impulses on the synaptic formations. Postsynaptic potentiation, in his opinion, facilitates conduction through the synapses. Therefore, with prolonged training, a particular combination of synapses will always exhibit the least resistance and delay in the conduction of an impulse appropriate for it.

Fessard has calculated the interaction of individual neurons which, in the presence of a sufficiently strong initial excitation, may lead to the involvement of neighboring neurons. He believes that this makes it possible to explain the phenomenon, known from the physiology of higher nervous activity, of the generalization of conditioned excitation, which is manifested during the initial period of the elaboration of a conditioned reflex.

A number of other factors involved in the process of the formation of conditioned reflexes are indicated by Fessard. He takes the case of the synchronization of electrical activity in which several neighboring regions of the cerebral cortex become harmonized to the same rhythm. To support his argument, he presents the well-known experiments of Livanov (Livanov and Poliakov, 1945; Livanov *et al.*, 1951), who showed that during the elaboration of a conditioned reflex the projection zones of the conditioned and unconditioned stimuli in the cerebral cortex "synchronize to the same rhythm of electrical activity."

Fessard (1960, p. 169) cites the physical data of Pringle (1951) that, at the moment when wavelike changes of the same rhythm meet, there occurs a peculiar "locking" of the rhythms, on account of which one of the rhythmic processes, as it were, drags the other behind it for some time. I do not think that this physical law of the "locking of rhythms" can apply to the isorhythmic pulsation of certain regions of the cerebral cortex. Amassian, Scherrer, and Fessard showed that this pulsation intensifies the neuronal activity of the appropriate regions in a definite rhythm. It is most likely that this promotes the establishment of some as yet unknown form of connection.

In fact, no explanation based solely on electrical phenomena can explain the intimate nature of the coupling process.

Fessard gives special attention to those changes in the condition of the nerve cells which, although they cannot be detected by generally used methods of investigation, can nevertheless very extensively influence the interaction of neurons during the elaboration of conditioned reflexes. He also analyzes in detail the "previous history" which affects the level of excitability of the neurons involved in the formation of conditioned connections.

Proceeding from a number of investigations in his laboratory, Fessard asks where the coupling of the conditioned connection arises first: in the subcortical structures or in the cerebral cortex. He cites the data of Buser and Roger (1957), who showed that the rhythm of the electrical activity corresponding to conditioned stimulation arises in the nonspecific thalamus earlier than in the cerebral cortex.

If I have understood Fessard's concept correctly, it postulates that a primary convergence of impulses from a conditioned stimulus occurs at the level of the sub-

cortical apparatuses and then appears as peculiar "convergent patterns" on the cortical neurons.

All these interesting data, which resulted from Fessard's investigations, provide him with a basis for explaining the process of coupling of the conditioned connection at both the subcortical and the cortical level.

In the evaluation of Fessard's concept, it is difficult to ignore any of the parameters in the activity of the cortical neurons, since each of them undoubtedly participates in the formation of actual interneuronal relations. In the activity of the cortical neurons, occlusion as well as trace processes, potentiation, etc., occur. However, neither of these mechanisms can be the basis for the formation of a stable conditioned connection.

For example, a change in the polarity on the cell membrane can hardly cause the permanent connection between external stimuli. The organism is exposed to such a variety of life situations, evoking complex forms of cerebral activity, that no polarization can be stable. Moreover, we are well aware that the same nerve cell can become involved in a number of different activities through different synapses. Consequently, it is difficult to conceive that polarization established on the synapses at a certain moment in the life of the brain would not be affected by structural and functional changes in later life. It can nevertheless be stated with assurance that the parameters of excitation of the nerve cell described and worked out by Fessard are valid and participate in the establishment of the final association in the form of the conditioned reflex. While having a definite meaning and significance for the associative process, all these phenomena merely bring the impulses to that point at which the macromolecular and micromolecular processes of the cytoplasm anchor acquired experience in labile chemical patterns. In this sense the investigations of Fessard undoubtedly advance the formulation of a more complete and adequate hypothesis concerning the coupling of the conditioned connection, including neurochemical processes (see below).

Among the concepts of the coupling of conditioned reflexes based on the electrophysiological mechanisms of cellular activity is the hypothesis of Rusinov (1960, 1961), which links conditioned coupling with the dominant state of certain cortical regions (the dominant state being evoked by the polarization of these regions by direct current).

Rusinov's experiment was as follows: polarization of the sensorimotor area of the cortex by a direct-current cathode led to the condition that any additional stimulus ("indifferent") evoked a movement of an extremity on the opposite side of the body. As Rusinov explains, it appears that the excitation evoked at the site of additional stimulation, spreading over the cerebral cortex and arriving at the "focus of dominant excitation," promotes the excitation of the pyramidal neurons of the sensorimotor region, which leads to the movement of the extremity. At first sight this "coupling" process corresponds somewhat to the original explanation of the coupling of the conditioned connection.

However, the convergence described in terms of biophysics, which so recently satisfied our quest, provides very meager information concerning the essence of the subsequent cytoplasmic processes which inevitably result from both the electrical phenomena and the convergence of impulses. This is very significant. The true coupling of the conditioned connection is always a delicate protoplasmic process, and all the

anatomy, biophysics, energetics, transmission, propagation, and interaction of impulses are only a means of conveying diverse information to those points of the organism where it can be consolidated into stable chemical patterns.

The stability of these connections is remarkable. They are extremely resistant to various strong influences (anesthesia, hypothermia, convulsive seizures, etc.), and at the same time their content is retrieved with incredible ease as soon as an appropriate functional life situation arises. Such is the accuracy of the "tuning" of the signals in the retrieval from the memory of all that was deposited in it, often throughout an entire life!

The usual electrophysiological analysis of the propagation of nerve impulses is limited to a description of the postsynaptic potentials and to the generating capacity of the cell. The description of the electrical phenomena undoubtedly provides specific information concerning the localization of a process, its evolution, and the intensity of the interactions developing in the nervous system. Unfortunately, however, these phenomena, so very useful and essential for understanding the interaction and integration of neural processes in the central nervous system, become completely incapable of revealing anything when the neural processes change into the most decisive process—the chemical fixation of acquired experience.

The role of the nerve impulse in the nerve cell is usually quite underestimated, and attention is given only to the generation of nerve impulses of the cell in the region of the axon hillock. All the diverse processes of nervous activity, such as the transformation of impulses in the sense organs, propagation along a nerve, architectural systemic interactions, etc., ultimately store information in stable protein codes while they ensure the patterning of an adaptive act.

In concluding, I would like to mention one more important factor which is undoubtedly present in the elaboration of every conditioned reflex. I have mentioned that the unconditioned stimulus affects all those converging impulses which had been evoked by the indifferent stimulus; the activating action of the orienting-investigative reaction unquestionably also converges upon the same cortical neurons. From the investigations of Jung's laboratory and from those of the collaborators of my laboratory, we have seen how the indifferent and unconditioned stimuli appear in the cerebral cortex as very diverse single discharges and evoked potentials. It is therefore natural that the actual types of coupling activity for different regions of the cortex and for different neuronal elements will, of course, be different. Consequently, the unconditioned excitation actually stabilizes a pattern of *preceding excitations* with an extremely extensive area and complex configuration. If one adds to this that the situational stimulus, which as a rule is very complex, also becomes a conditioned stimulus, the complexity of the entire situation can be handled only by a broad statistical analysis.

Another important aspect of the elaboration of the conditioned reflex as an act of the entire brain remains to be discussed. Until now we have examined the problem in its aspect of the convergence of ascending impulses upon a single cortical neuron and subsequent neurochemical transformations within this neuron. At the same time it was pointed out that ascending unconditioned impulses involve the entire cerebral cortex and consequently exert their chemically stabilizing action in all those

neurons which obtained information from the indifferent stimulus in any form.

The orienting-investigative reaction is the powerful agent by which the brain and a given functional system rid themselves of excess external information, selecting only the information of the greatest significance. Thus, the series of ascending impulses arising from an unconditioned stimulus will catch up with only those impulses, or their residual trace processes, which were stabilized by the orienting-investigative reaction as essential for a given moment in the life of an animal or man (afferent synthesis).

The broad picture consists of the selectively excited elements in both the projection zones and the associative, often widely separated zones of the cerebral cortex, where the impulses from the unconditioned stimulus have entered into a stabilized chemical connection with some parameter of the excitation from the indifferent stimulus which has not yet subsided. As a result of these processes, there occurs a rather diverse stabilization of the connection in various cortical elements located in different sections of the cerebral cortex.

How are all these elements united into a single monolithic system which determines in an efferent direction all the specific features of a given conditioned reflex?

It seems that this is the purpose of the extensive intracortical associative connections which facilitate the establishment of functional contacts between cells that are either in close proximity or at a considerable distance from each other. Recognizing the significance of intracortical connections as a mechanism establishing contacts between simultaneously excited neurons of the cerebral cortex, we eliminate the apparent contradiction between the previous concept of a generalization of excitation over the cerebral cortex from its point of origin (horizontal aspect) and a generalization of excitation in connection with ascending series of impulses (vertical aspect).

Indeed, the intracortical associative pathways are selective and are responsible for the propagation of impulses over separate areas of the cortex. It is highly probable that these intracortical connections cause those integrative influences which arise between cortical cells associated on the basis of the concurrent effect of ascending impulses. The principal condition for the patterning of an integrated behavioral act would be achieved on the basis of a comprehensively integrated complex of impulses. Assuming this, we would have a highly coordinated system of relationships between the ascending, truly generalized impulses and the impulses spreading selectively over the cortex and uniting only individual groups of neurons into functional combinations.

In regard to this one cannot fail to see the biological meaning manifested in the evolution of these two forms of activity. On the one hand, the varieties of ascending impulses encompass without exception all the information available at a given moment, which is brought about by extensive generalization of excitation over the entire cerebral cortex and by various additional excitations of its different areas. This phase proceeds with a surplus involvement of various cerebral processes and mechanisms, bringing a very definite statistical success similar to that resulting from a blast from a shotgun. The very possibility of missing anything essential for the organism is eliminated. On the other hand, all the cortical elements related to the most important parameters of a given situation prove to be interconnected in a single integrated formation.

Summarizing the entire material of this chapter and all the arguments presented in

support of this material, we can formulate several fundamental propositions which characterize the concept of the convergent coupling of the conditioned reflex.

1. It has become quite obvious that earlier concepts of the coupling of conditioned reflexes, which are based on the connection of two foci of diverse excitations, are inadequate. These concepts do not determine the true nature of the coupling process, and, in postulating the actual coupling on the synaptic formations, thereby eliminate the possibility of explaining the prolonged stabilization of the process at the synapses.

2. Contemporary neurophysiological concepts of the electrophysiological parameters of an impulse (summation, potentiation, etc.) eliminate the possibility of accepting these parameters as decisive mechanisms in the stabilization of neural connections in relation to their dynamic variability and brief duration. It must be recognized, however, that all the electrophysiologically observed parameters of an impulse enumerated above are absolutely essential for conveying the nervous processes, which frequently originate at remote points of the organism, to those points which ensure the actual coupling of the conditioned reactions. These points are primarily in the neuronal cytoplasm where processes of protein synthesis occur.

3. As long as the concept of the uniformity of all synaptic processes on the membrane of the same cell prevailed, it was impossible to understand how the numerous and diverse impulses reaching a neuron could have any informational value in the formation of one single impulse on the axon. The concept of "homogenization" of impulses merely shows that we were unable to penetrate into the very essence of the cellular processes for an explanation of these mechanisms.

4. This gap between the arrival of an impulse at the surface of a nerve cell and the emergence of the impulse onto the axon is now being bridged by means of microchemical investigations on one single neuron. Data on chemical differences in the postsynaptic membranes of the same cell have allowed for the possibility of closing this gap. As shown by the experiments of our laboratory, the chemical differences in the postsynaptic membranes are much more extensive and diverse than is specified by the generally accepted classification of impulses as "depolarizing" and "hyperpolarizing," or "cholinergic" and "adrenergic." These chemical differences on the postsynaptic membranes are the starting point for the launching of various chains of enzymatic processes in the cytoplasm of the nerve cell. It is highly probable that this chain process ultimately leads to changes in the codes on the RNA molecule and to the stabilization of this new chemical pattern in a distinctive protein molecule. The assumption of such a process is in full accord with the latest investigations of the role of RNA in the stabilization of acquired experience. This also explains the "homogenization" of impulses. In reality "homogenization" does not exist as such, since each functional situation on a neuron is realized in the chemical patterns specific for it. This then is the basis for the evaluation of the informational significance of the impulse emerging onto the axon. In spite of their apparent uniformity, these impulses conceal within themselves a multitude of changes in the protein of the given nerve cell, which is always statistically characteristic of any functional situation.

5. It must be especially emphasized that an ascending impulse from an unconditioned stimulus generates on the postsynaptic membranes of the cortical cells some

particular chemical processes which possess enormous potential for the stabilization of converging impulses. There is reason to believe that this capacity of ascending unconditioned impulses (from alimentary, defense, sexual, and all other emotional stimuli) is a phylogenetic remnant from the stage of the primitive forebrain.

6. Thus, due to the convergence of impulses on the same neuron, conditioned reflex coupling actually consists of the entering of two distinct chemical processes into intimate dynamic interactions in the molecular organizations of the cytoplasm.

7. Modern concepts of the role of RNA in the transformation of the genetic code and in the associative processes of the body have closed the gap in the deterministic explanation of coupling, which for a long time existed between the electrophysiological manifestation of an impulse and cytoplasmic transformations. Most probably there is a change in the RNA code connected with the formation of protein molecules which are repositories of the association formed. This concept agrees very well with the observation that nonreinforcement of a conditioned stimulus leads to the elimination of the code formed. From this it follows that nature acted very ingeniously in having made the constant presence of a reinforcing as well as a chemical factor a basic condition for the preservation of newly formed chemical associations.

The hypothesis we are proposing concerning convergent coupling of the conditioned reflex on a molecular basis is merely the most convenient form we have at this time for an understanding of the integration of all the simultaneous and sequential processes in the nervous system which are involved in the formation of a conditioned reflex. It was our aim to present a continuous deterministic chain of scientifically understood processes which could in an acceptable form relate the electrophysiological data on the subject with that final stage which consolidates any relationship among external influences in time and space into stable chemical patterns in the nerve cell.

Of course, we do not consider this hypothesis in any degree complete and perfect. But it does eliminate a number of contradictions, promote the understanding of hitherto inexplicable facts, and open the way for setting up further useful experiments. When our hypothesis ceases to serve us in this way, it will have to be replaced by a new, more suitable one. This is the fate of any hypothesis, no matter how tempting it may be.

CHAPTER 6

The Functional System as a Basis of the Physiological Architecture of the Behavioral Act

ACCORDING to our concepts developed in 1932-5, the functional system is a selective integrative formation of the organism. It is a true unit of integration which arises during the dynamic development of any qualitative activity of the organism as a whole. We have always emphasized that the functional system is always a selective central-peripheral formation and not merely a formation of the central nervous system per se (Anokhin, 1935). The mere fact that this concept developed in our laboratory as the result of the difficulties which we experienced in 1932 in explaining the compensatory mechanisms of the organism as a whole solely on the basis of the generally accepted reflex arc, emphasizes its special physiological architecture. It turned out that systematic adjustments of motor acts in connection with compensation of disturbed functions proceed on the basis of continuous information from the results obtained. Consequently, to a certain extent the entire process of compensation acquires a *circular character*.

Since the concept of the functional system in its very essence is an integrative concept, before discussing the nature of the functional system it is necessary to outline the general concepts of integration in modern neurophysiology.

THE CONCEPT OF THE INTEGRATIVE ACTIVITY OF THE NERVOUS SYSTEM

The originator of the application of the term "integration" to biological phenomena was the English philosopher Herbert Spencer, who used this concept as the opposite of differentiation as applied to the evolution of material systems. Spencer regarded the entire process of the progressive evolution of life on earth as a harmonious combination of the integration and differentiation. His also was the concept of *levels of integration*, since in the process of evolution a gradual increase in the complexity of integrated processes takes place.

Applying the concept of integration to the evolution of the universe, Spencer believed that integration appears as a result of the concentration (increasing density) of matter and of its differentiation in the process of development. In his treatise "First Principles" he writes: "Evolution is an integration of matter and concomitant dissipation of motion; during which the matter passes from an indefinite, incoherent homogeneity to a definite, coherent heterogeneity and during which the retained motion undergoes a parallel transformation" (Spencer, 1904, p. 343).

Since for Spencer the use of the mathematical term "integration" was only a part of his philosophical concepts (*Weltanschauung*), his concept of integration did not exert an immediate and direct influence on physiology, even though he published a work entitled *Transcendental Physiology*. On the other hand, the general philosophical meaning of the concept of integration acquired widespread importance.

Perhaps the first follower of Spencer in the field of neurology was the neuropathologist John Hughlings Jackson (1931-2). Using Spencer's concept of integration as a basis, Jackson gave the first explanation of neural integration from the point of view of evolution, namely the accumulation of integrative complexes in a definite "hierarchy." Each level of this "hierarchy" forms its representation at a higher level of integration until the entire organism is integrated at the highest point of the central nervous system.

This concept of integration in the nervous system as a "condensation" of various properties and representations was used extensively by Jackson in pathology in order to explain a number of clinical symptoms resulting from "dissolution" of higher integrations under the influence of organic or functional pathogenic effects. Precisely in this sense his theoretical concepts were well formulated in the expression "evolution and dissolution," i.e., a return to lower levels of the hierarchical structure of the brain.

Subsequently the idea of integration was taken up by a number of scientists who interpreted Spencer in various aspects. In this respect we should refer to the view of H. Head, who was perhaps the first to identify higher integration with sensation (Head, 1918; Head *et al.*, 1920).

It is interesting to note that at the end of the nineteenth century the idea of integration as the most convenient model for explaining the obvious integrity of the organism had spread quite widely (and probably independently of Spencer) to the progressive circles of Russian public figures of the sixties.

For example, it is well known that Ogarev, an enlightened public figure of the sixties, as early as the fifties performed a number of experiments on domestic animals at his estate in the province of Pensa and was familiar with the trends in the physiology and sociology of his time. Addressing himself to Gertsen, another of Russia's progressive public figures, he writes: "Physiology is still crude, Gertsen! Science still does not take account of the intimate chain of nervous shocks under the influence of tradition and contemporary public opinion, and yet life integrates them in every growth of an organism. Because of a lack of understanding of this constant integration, neither physiology nor history have yet set up their formulas, and therefore there are only scattered observations on the one hand and tenuous theories on the other. Both sciences, which should form one unit, limp along separately" (Ogarev, *My Confession*).

This emphasizes once more that the concept of sociobiological integration as the highest level of functioning of the human organism had already entered extensively into the thinking of progressive nineteenth century figures who recognized in integration possibilities for an explanation of cerebral function on an objective scientific basis.

As we shall see below, Sherrington, in recognizing the human "self" as the highest factor of integration, essentially reached the same conclusion concerning the highest level of integration, although he understood it in psychoparallelistic terms.

It should be pointed out that the discovery of central inhibition by I. M. Sechenov and the publication of *Reflexes of the Brain*, his major work, also to a certain extent determined the actual approach to the study of integration of nervous activity on the basis of the coordination of excitation and inhibition (Sechenov, 1863b, see Bykov, 1952a, pp. 143–211). *Reflexes of the Brain* was written under conditions of a rapid growth of knowledge in natural science in Russia during the sixties. Along with other progressive ideas, the concept of integration began to penetrate into the circle of Russian public figures. At any rate, “integration” as applied to nervous activity was also widely used by those progressive figures in Russia during the sixties who were not professional physiologists.

Here we should mention the fact that Pavlov, as early as the 1880's, abandoned the shortcomings of acute experimentation and developed physiological methods suitable for the study of the entire organism under conditions as nearly natural as possible (Pavlov, 1879a, see Pavlov, 1940, pp. 41–44; Pavlov, 1879b, see Pavlov, 1940, pp. 46–54; Anokhin, 1949a, 1949d).

The conditioned reflex is, of course, an integrative expression of the organism as a whole. This is what constitutes its physiological value as a model for the study of integrated acts. At the same time we must also remember that the interpretation of the actual conditioned reflex and of the subsequent processes of unconditioned reinforcement was based on the reflex principle. Consequently, its integrative essence did not occupy the center of attention of the investigators. Therefore, the question naturally arises as to whether the conditioned reflex is something specific from the point of view of the actual laws of integration, or whether it is also subject to these universal laws but acquires some new properties as a factor of higher integration.

As mentioned above, integration, as a principle, must acquire a distinct physiological architecture with all its key mechanisms, which are characteristic only of itself and not of its components. Here we must first be concerned with whether this physiological architecture will be the same for all levels of integration, or whether it will vary depending on the complexity of these levels.

Until the end of the nineteenth century, systematic development of the idea of the integrative function of the nervous system, as a purely neurophysiological problem, did not extend beyond the boundaries of England. Sherrington, for example, strove to show by means of a number of purely physiological mechanisms how the integrative function of the nervous system (including even the cellular level) is actually brought about. He was able to gather and systematize an enormous amount of neurophysiological data which revealed new and original ideas of integrative mechanisms in the spinal cord. As it turned out, these mechanisms were of universal importance for the function of the nervous system in general.

His propositions on reciprocal inhibition at the level of the spinal cord, on allied reflex arcs, and on the final common path are well known. In fact, all these mechanisms are universal for all levels of the central nervous system. In regard to this, recall the mechanism of convergence, which was discussed in Chapter 5.

Sherrington had created a system of concepts which, for the first time, made it possible to understand how the different parts of the motor apparatus become coordinated

into a single locomotor system which then performs functions of an integrated nature.

However, to what extent did Sherrington, who unquestionably had contributed significantly to the physiology of the nervous system with his discovery of new mechanisms of integrative activity, come close to an understanding of the integration of the organism as a whole? Now that we are able to examine Sherrington's achievements in the light of subsequent advances in neurophysiology, his level of generalization in 1906 becomes clear. It was in 1906 that his famous monograph *The Integrative Action of the Nervous System* (Sherrington, 1906, 1947) was published.

Fortunately, the evaluation and true meaning of his concepts on the integrative action of the brain were clearly expressed by Sherrington himself in his foreword to the second edition of the monograph in 1947. In this foreword he holds that the ultimate and highest point of integration of an organism is, in essence, its "self," which unifies both the somatic neurophysiological basis and all the higher superstructures of mental activity which are manifested in subjective experiences.

In *The Integrative Action of the Nervous System* he presented significant data obtained in investigations conducted on the basis of his concepts of the classical reflex arc, even though he repeatedly (in the final chapter) speaks about the activity of the integrated organism. Here too, however, the guiding principles of his neurophysiological analysis are the concepts of the reflex arc.

In evaluating the sum total of Sherrington's physiological generalizations, we can now state with certainty that he provided valuable generalizations on the basis of extensive neurophysiological data dealing with complex mechanisms of coordination of individual parts of the organism. And yet, in spite of the value of these data as applied to an understanding of *particular regional mechanisms* of integration, he did not develop a theory of the integration of nervous activity of the entire organism. It would be correct to say that he discovered mechanisms of integration which could be used as a basis for the development of a theory of overall nervous integration.

The fact that Sherrington some 40 years later in the foreword to a new edition of his book regards the concepts as "artificial" suggests that he himself was not completely satisfied with the remarkable physiological data which he analyzed in his book (Sherrington, 1947, see Sherrington, 1961, pp. xv-xvi).

What, then, was the shortcoming of Sherrington's concept of the integrative function of the nervous system, if this concept is examined with regard to recent advances?

One of the most serious obstacles to the elucidation of the physiological mechanisms of integrative processes of the organism is the lack of clear concepts or generally accepted assumptions concerning just what is the physiological essence of integrated organization, what new features it acquires when it becomes integrated, and what must serve as a criterion of integrated activity.

In spite of an enormous amount of physiological data, until now the question has not yet been clearly put forth as to the location of the boundary between the mechanisms of integration and integration itself, when these individual mechanisms have already entered into coordinated interaction. The absence of a distinction between these two concepts, i.e., between the individual mechanisms of integration and the integration at the level of the organism as a whole, leaves a very serious gap.

Sherrington's monograph focuses its entire attention on the mechanisms of integration (the principle of the final common path, the allied reflex arcs, the principle of fraction, etc.). Although the original purpose of Sherrington's monograph was a search for the laws of the integrative activity of the nervous system, when he began to consider the activity of the entire organism, he left the actual physiological basis and moved into the area of purely philosophical interpretations of the complex behavior of animals and man (Sherrington, 1940, 1947, 1951).

In the physiological investigations of Sherrington as well as his many followers, in my opinion the crucial question of integration has not been asked at all. That is, does an integrated organization acquire new features as compared to the properties of those elementary processes and mechanisms which ensured its formation?

The currently prevailing physiological concept tacitly accepts that even the highest forms of organization of nervous activity do not involve anything beyond what is included in the concepts of excitation, inhibition, trace process, parabiosis*, mediator processes, relations between receptors, etc. The development of instrumental techniques and, consequently, the ever-increasing emphasis on the finer neurophysiological processes have widened this gap even more between detailed studies of neurophysiological processes and the integrated activity of the organism as a homeostatic unity.

It is interesting to note that some neurologists, in discussing the problem of the integration of nervous activity, very clearly manifest this deficiency in the evaluation of the prospects of the study of integration as a physiological phenomenon. For example, in an article reviewing modern concepts of integration, Riese (1942, pp. 308-309) writes :

Evidently, it is impossible to prove positively that each part of the whole is involved in a given manifestation of the organism. In general, we derive from a great number of observations suggesting the co-operation of all the parts of the organism the conclusion that such a co-operation exists without exception. But this logical procedure (the so-called "modus ponens") can never transform hypothesis into truth. Thus, the truth of the sentence that all parts of the organism co-operate in a given manifestation has no empirical sources; in other words, integration is not a fact which had to be stated empirically: it is a principle.

This lack of exact information concerning the concrete mechanisms of integration has led to regrettable consequences. We have proved to be reasonably well equipped in regard to the understanding of the elementary processes of the nervous system, their chemical nature, and their course of development. However, we find ourselves rather helpless when we attempt to answer the simple question: how can a frog almost instantaneously gather into some functional organization all the thousands of elementary processes that are scattered over the entire organism and execute an adaptive act such as a jump?

It follows that the problem of the study of integrative activity is equivalent to the problem of the physiological mechanisms by which any integrated system maintains

* Reference to Glossary.

its unity and executes an adaptive act for the benefit of the entire organism.

At this point I wish to briefly examine some results of our laboratory investigations which have revealed certain characteristics of physiological integration. These investigations dealt with observations on the behavior of the axolotl following extirpation of the prosencephalon and the mesencephalon.

The axolotl is an exceptionally suitable object for investigations of the integrative activity of the nervous system. During the evolutionary development of its brain, two automatic kinds of activity were formed which can serve as a model for the study of the physiological laws of integration as well as the laws of the progressive evolution of organisms. One of these clearly defined activities is *swimming*, and the other is *quadrupedal walking*. In view of the simplicity of the organization of these activities and the possibility of studying their dynamically developing interrelations, they can serve as a good model for a description of the physiological characteristics of integration.

Our investigations, aimed at an evaluation of the role of regions of the brain differing in phylogenetic age in the patterning of these two activities, have also shown the essence of the patterning of the integrative formations of the organism.

If one considers the fact that, from the evolutionary point of view, swimming is an earlier act than quadrupedal walking, it would be natural to expect that after extirpation of the prosencephalon in the axolotl the most recent integration, i.e., the act of walking, would be affected first. The actual results, however, proved to be paradoxical: extirpation of the prosencephalon eliminated swimming and the rapid lunge after food, but left walking relatively unaffected. It can readily be seen that the two post-surgical effects are not related by the principle of evolutionary age but rather by the principle of the most *rapid movements*. Thus, contrary to expectation, the extirpation of the brain affected everything that requires rapidity of action, while the act of walking, which does not require this potentiation, remained relatively unaltered.

This experiment indicates that the integrative unification of the individual mechanisms in the patterning of an integrated act may occur in such a way that each part of the nervous system makes its specific physiological contribution to this integration. Although any particular component of the nervous system does not determine the entire integration, nevertheless it provides for some fairly definite characteristic of this integration.

This principle of integration was manifested even more clearly during gradually descending sections of the mesencephalon down to and including the medulla oblongata. These sections have clearly demonstrated the interaction of different levels of the central nervous system in the shaping of such an integrated activity as swimming. Let us try to elucidate what components, i.e., individual mechanisms, are essential for the accomplishment of the effective act of swimming.

From the anterior portion of the trunk to its caudal end two waves of musculature contractions travel so as to ensure the forward swimming movements of the body. This constitutes the act of swimming. Forward movement will be possible during the propagation of the waves of muscular contractions if to each contracted muscular segment on one side of the body there will correspond an inhibition of the contralateral complex. Only under this condition can there be *undulatory* movements of the body, i.e., swimming.

Consecutive sections of the mesencephalon with a gradual approach to the medulla oblongata have revealed a number of interesting principles. First of all, the alternating delivery of coordinated series of impulses down the spinal cord was disrupted, resulting in a disturbance of the reciprocal nature of the contraction with practically no complete swimming motions occurring. With the downward extension of the sections, a level can be found at which even the rhythmicity in the delivery of the nerve impulses is eliminated so that upon provocation of swimming movements one can observe on each side of the body continuous impulses which spread along the entire spinal cord.

These observations of the propagation of swimming impulses along the spinal cord can easily be accomplished by means of the insertion of recording electrodes into various points of muscular segments and the oscillographic recording of these impulses (Fig. 6.1).

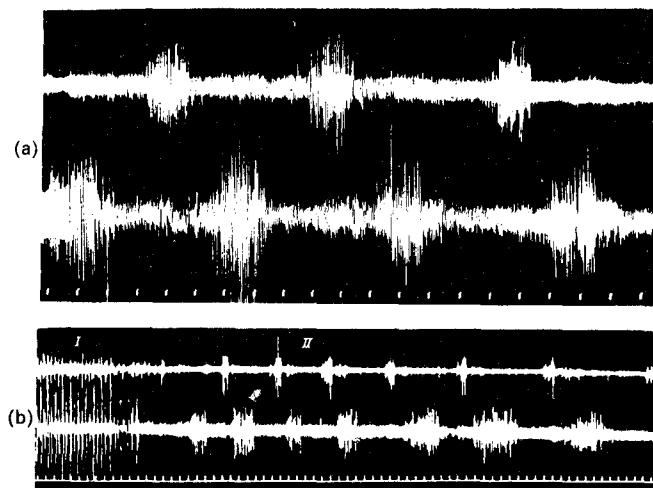


FIG. 6.1. Electromyograms of two different locomotor acts of the axolotl. The electromyograms are taken from two opposite points of the trunk in the region of attachment of the extremities. (a) record of walking. (b) the transition from swimming (I) to walking (II) is shown. In both examples, the reciprocal contractions of the recorded muscle fibers can be seen.

A considerable number of examples of whole integrative acts can be given in which the gradual dissolution of these acts reveals their highly diverse physiological composition. This was the idea that especially fascinated Jackson (1931-2) when he saw that under clinical conditions there are many examples of such a gradual dissolution of complex integrated acts in a patient. This dissolution was shown very eloquently by Luriia (1947) in his book on the disintegration of speech in man under various pathological conditions.

The experiments with the axolotls convincingly demonstrate the special construction of the integrative act. We must evidently keep in mind at least two kinds of neural elements that constitute integration. Some of them determine what could be called the architecture of the act, i.e., the selective excitation of the motoneurons at the motor

areas for the extremities and the trunk and give a specific appearance to the whole function. Other elements, on the other hand, have no relation to these architectural features of the function, but they determine the various modifications in the delivery of impulses, the unification of different impulses, and their potentiation, and, finally, the course of energy-exchange processes in the previously patterned construction of the act as a whole. We have seen an example of the latter kind of forming of the functional system in the action of the prosencephalon on the central integration of swimming.

Thus, in concluding the description of integration, we can say that a true integration involves the individual mechanisms of integration harmoniously matched in order to gain some beneficial end effect. In regard to these integrative formations, the question can be posed concerning new physiological properties. All this convinces us that those mechanisms of integration which were so thoroughly described by Sherrington are not the true mechanisms and properties of an already complete act but represent merely valuable fragments to be used by the organism at the moment of integration of complete acts.

One of the serious problems is that of how the individual mechanisms of integration are united into the integrated architecture of the adaptive act. It is quite evident that we shall not be able to answer this question unless we initially assume that all functions of such an integrated act are subordinate to the goal of achieving a definite adaptive result. That is, the beneficial end effect determines in which direction and in what combinations the individual mechanisms of the integrative activity will be utilized.

In 1935 in the book *The Problem of Center and Periphery in the Physiology of Nervous Activity*, we proposed a higher principle of the integration of individual mechanisms, calling it the principle of the "functional system." This system possesses all the features essential for integrated organization (Anokhin, 1935). This does not at all mean that these new properties of integrated organization are formed without the concrete mechanisms of nervous activity. On the contrary, they can be formed only on the basis of these individual mechanisms of integration.

However, the actual formation of a functional system from hundreds of such individual mechanisms and the order and interaction of these individual mechanisms are subject to other laws which are only characteristic of the integrated adaptive organizations of the organism and not of the components of the functional system.

At this critical point—the transition of the individual mechanisms from a separate form to an integrated form—many new problems arise for the physiologist, frequently leading to a mutual lack of understanding. Thus, I consider it essential to give a more detailed physiological description of both the actual moment of formation of the functional system and its new and specific properties.

It is natural that we must first of all direct our attention to experiments involving the compensation of disturbed functions which served as the impetus for the development of the theory of the functional system.

THE FUNCTIONAL SYSTEM AND ITS PHYSIOLOGICAL PROPERTIES

Compensatory adaptation has always been a problem of physiology and medicine. The results of the compensation were evident, but these results were never given any

theoretical physiological basis. Perhaps this partially explains the fact that the physiology of compensatory adaptations following various disturbances of the functions did not significantly influence medical practice, which has neither an established theory for the guidance of the compensatory process nor prognostic data concerning the course of compensation during a given kind of disturbance of a function, etc.

This gap in our theoretical knowledge of the compensatory process is quite understandable: nothing else in the manifestations of the organism requires such an extensive participation of all the diverse functions of the organism as does the compensation for a defective function. Also, no such involvement of the numerous functions of the organism can be understood on the basis of the reflex concept, which actually remains the dominant theoretical concept in medicine and physiology.

Being a *linear* structure, the reflex has no purpose that would *precede* the reflex action itself. Compensation does have a purpose: the ultimate normal functioning, i.e., the achievement of a specific adaptive result, toward which the compensatory process approaches by various means.

Every attempt of an animal or man to correct a defect must be immediately evaluated in terms of its result. This is the physiological essence of compensatory adaptation. The purpose of the compensatory process is to restore the disturbed function to its normal level. Thus, any subsequent stage in the compensation can ensue only when an evaluation of the preceding attempt of compensation has taken place. Meanwhile the reflex arc does not have any potentialities for evaluating the success or failure of a given stage of compensation. At the same time it is clear that without this evaluation of the stage-by-stage result, the compensatory process must immediately cease. It is therefore not surprising that the idea of cyclic interactions of center and periphery during nervous activity arose in our laboratory during the investigation of compensatory adaptations.

The experimental investigations which led to the formulation of the functional system involved heterogeneous neural anastomoses and the observation of the course of the regenerative processes. The first functional disturbances which ensued resulted from the inappropriate connection between center and periphery created by the anastomosis. For example, we anastomosed n. vagus with n. radialis in order to trace the course of restoration of the function of the vagus nerve when it is surgically provided with peripheral apparatuses (skin, striated muscles) not characteristic of the vagus.

One must visualize the physiological aspect of this anastomosis in order to understand its consequences. Cut at the middle of the neck, the vagus nerve is divided into two stumps having different physiological properties. The central stump is capable of regeneration, i.e., the growth of nerve fibers, while the peripheral stump degenerates entirely. If one now takes the central stump of the vagus nerve and sutures it to the peripheral stump of the cut radial nerve of the front leg of a dog, a highly interesting phenomenon occurs.

After the fibers of the central stump have grown through to the peripheral organs, they begin to innervate both the cutaneous receptors and the muscles of the front leg. In connection with this a number of extraordinarily "paradoxical phenomena" arise which permit us to elucidate the integrated nature of compensatory adaptation. For example, after the reinnervation of the skin and the muscles of the leg is completed,

they acquire entirely unexpected physiological properties: upon slight scratching of the skin uncontrollable coughing begins, changing to a continuous laryngeal rale during persistent stimulation.

On the other hand, if cutaneous stimulation is avoided and prolonged pressure is applied to the muscle, vomiting gradually develops. In other words, the vagal nucleus responds by reacting quite specifically according to the nature of the impulses reaching it: tactile impulses evoke coughing, kneading of the muscle evokes uncontrollable vomiting. These phenomena, which in our laboratory were named "chimerical phenomena," change with time, and the compensatory process may, after several months, bring the situation to the point that neither phenomenon can be produced by the above-described stimuli. After the inflicted disruptions, the compensation consists of a rearrangement of the neural relations in the nucleus of the vagus nerve. This rearrangement involves an enormous number of functions that are normally included in the system of the vagus nerve.

The experiment has shown that in the efferent direction we also have a decisive

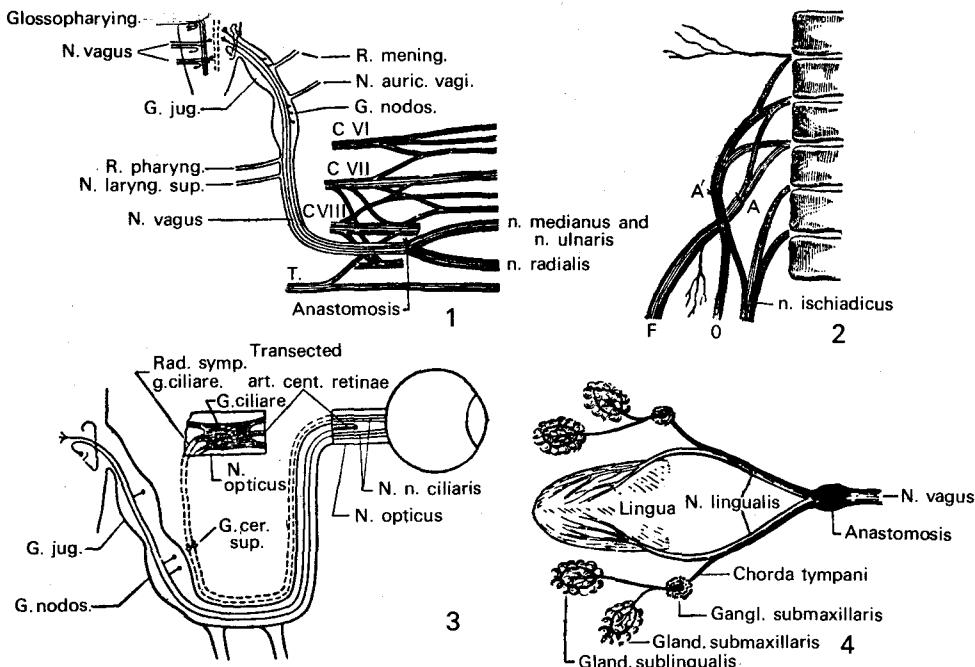


FIG. 6.2. Different forms of heterogeneous anastomoses of nerve trunks, performed for the purpose of studying central-peripheral interactions. 1, Anastomosis of the central stump of the vagus nerve with the roots of the brachial plexus that innervate the skin and muscles of the front extremity. 2, Crossed anastomosis (A, A') of n. obturatorius (O) and n. femoralis (F). 3, Diagram of anastomosis of the central stump of the vagus nerve with the peripheral stump of the n. ciliaris longus innervating the cornea. To facilitate the operation, the vagus nerve was sutured with a peripheral stump of the optic nerve, of which n. ciliaris longus is a component. 4, Diagram of anastomosis of the vagus nerve with two transected peripheral stumps of the lingual nerve.

indicator of the unusual relations between center and periphery. In the zone of innervation by the vagus nerve, i.e., at the hind leg of the dog, there occurs a rhythmic muscular contraction which corresponds to the respiratory rhythm of the animal. Detailed investigations have shown that this rhythm pertains to the efferent impulses from the vagus nerve which normally propagate along the recurrent nerve to the vocal muscles.

Thus, these anastomoses enabled us to observe two phenomena: the first of them is due to the entrance of inappropriate impulses into the central nervous system, i.e., into the vagal nucleus, while the second is of an efferent nature and is related to the emergence of efferent impulses from the vagal nucleus. We used these two phenomena as indicators for observing the subsequent rearrangement of functions in the vagal nucleus.

Since crossed anastomoses of different nerves are a very convenient model for the study of compensatory adaptation, we performed a number of different anastomoses for the purpose of studying the resulting gradual compensatory adaptations (vagus-opticus, vagus-lingualis, vagus-facialis, vagus-ventral root, and vagus-dorsal root anastomoses) (Fig. 6.2).

Special attention was given to experiments involving deafferentation and transplantation of muscles to a new functional position. These experiments demonstrated an even greater dependence of the rearrangement of locally disturbed functions on the extensive systems within which these functions normally occur. Experiments involving a splitting of the extensor muscle of the hind leg into two parts and transplantation of one of the parts to the position of the flexor (quadriceps femoris) were highly successful

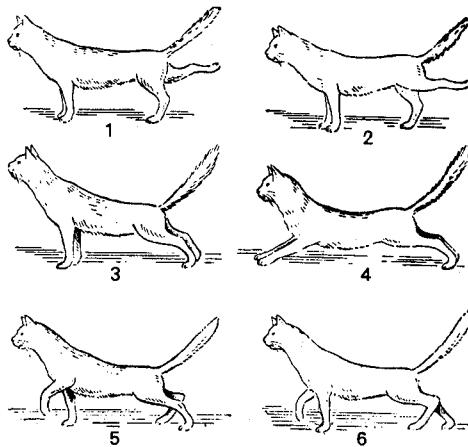


FIG. 6.3. Consecutive stages in the disturbance of the coordination of walking in a cat after transplantation of part of the extensor muscle to a flexor position. Disturbances of coordination resulting from inappropriate signalizations from the periphery can be seen.

in our laboratory. In this form of experiment the nerves remain in their former functional position. They innervate the same muscles, yet the contraction of the muscle

will be uncoordinated with the overall central integration of the locomotor act. The gradual elimination of this defect was of great interest.

Due to this operation, the muscle, receiving extensor impulses, had to move the shin in two opposite directions, which of course precluded the coordinated participation of this muscle in the integrated locomotor act. Such a disruption of functions naturally passed through a number of stages of compensatory adaptation until normal locomotion was restored. The disruptions of the locomotor functions that set in after the operation emphasize that a local disturbance inevitably becomes part of a large system. This is shown with particular clarity in sketches of the uncoordinated movements performed by a cat during different stages of compensation (Fig. 6.3).

The fact that the animal passes through several stages after such a transplantation of muscles shows that in each stage there is an evaluation of the result obtained until this chain of "positive results" has led to a complete restoration of the locomotor act. Ultimately locomotion is completely restored, and after several months the cat performs all movements with the reintegrated hind leg as easily as does a normal cat: it walks, leaps, and does not manifest any deviations like those seen in Fig. 6.3 (Laptev, 1935).

We can thus assume that the transplanted part of the extensor has begun to cooperate with the flexors, and the locomotor act has become recoordinated.

It is quite evident that such a result could be obtained only if some spinal motoneurons of the extensors corresponding to the transplanted part of the muscle reversed their functions and became excited along with the flexors (Fig. 6.4). This is the process which, referring to the vagal nucleus, we have called the process of "retraining" for a new function. However, it was unclear how this retraining was brought about. Did all flexor elements become extensor elements at all levels of the central nervous system,

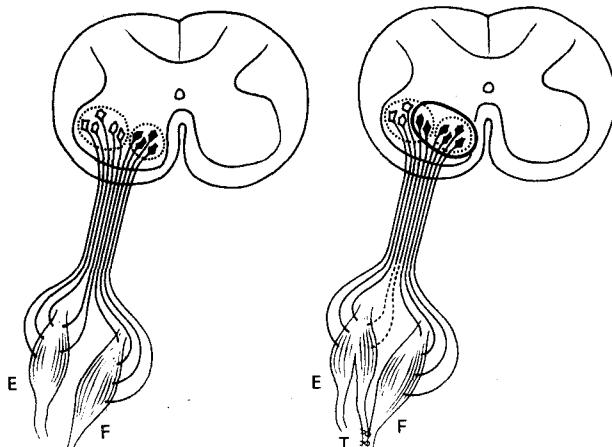


FIG. 6.4. Diagram of the transplantation of part of an extensor to a flexor position. Central interactions between those cells of the anterior horns which change their function after the operation are shown. E, extensor; F, flexor; T, transplantation.

or did the retraining occur only in the region of the spinal segments? An examination of these considerations in a special experiment produced an extraordinarily interesting result.

Cats with such a transplantation of muscles were decerebrated and checked for reciprocal inhibition according to Sherrington. It was found that the function of the transplanted muscles, just as that of muscles retaining their normal attachment, corresponds fully to their *original* function: both parts of the quadriceps, the part remaining in the normal position as well as that transplanted to the position of the flexor, developed the reactions of extensor muscles in the reflex process at the level of the spinal cord.

Thus, in the integrated locomotor act, while the transplanted muscle acted in coordination with the flexors, it also retained all of its properties as an extensor.

How can this paradoxical result be explained?

After a number of additional control tests it became clear that the rearrangement by no means occurred at the spinal level. It took place within the large system of mechanisms and processes that ensures the locomotor function as a whole. Consequently, the reaction of a part of the system (the zone of reintegration) was prompted by the coordination of the processes in the entire system.

Since such a system has a qualitatively defined adaptive effect, since all parts of the system enter into a dynamic, specially constructed functional formation, and since precisely such a system is provided with continuous feedback about the adaptive result, we have named it the "functional system" (Anokhin, 1935).

This principle has now become for us the basic principle for the explanation of all those adaptive acts which assume the characteristics of integrated acts and end in a beneficial adaptive effect. Initially it was formulated as follows:

For clarity in this question we proceed from the concept of the functional system. By functional system we mean a complex of definite physiological processes that are related to the implementation of some definite function (breathing, swallowing, locomotion, etc.). Each functional system, which to a certain degree constitutes a closed system, operates due to both the permanent connection with the peripheral organs and the constant afferentation from these organs, with the latter being especially significant. We think that each functional system has a definite complex of afferent signals which guides and corrects the implementation of this function. The individual afferent impulses in a given functional system may originate from the most diverse and often topographically widely separated organs. In the respiratory act, for example, such afferent impulses proceed from the diaphragm, the intercostal muscles, the lung, the trachea, etc., but in spite of their diverse origin, these impulses unite in the central nervous system because of the very delicate temporal relations between them.

... As soon as the impulses of the ventral horns become capable of evoking muscular contractions and of thus receiving a reverse afferent response, the establishment of a new coordinative system of excitation begins.

... Thus appears a new picture of excitation, dynamically created by the previous break and sanctioned by the vestibular impulses [Anokhin, 1935].

From these citations it can be seen that the behavior of every functional system depends very intimately on the quality and quantity of afferent impulses, both direct, i.e., those that are stimuli for the implementation of an action, and reverse afferentations, which give information concerning the results of a completed action.

Perhaps the most characteristic feature of a functional system is its individual and changing demands on afferentation. The quantity and quality of afferent impulses is the characteristic aspect of the degree of complexity and of the voluntary or automatic nature of a system. As an example of the very interesting results of this series of investigations, I shall discuss the systematic experiments of Chepeliugina (1949a, 1949b) involving section of the dorsal roots in the frog and the evaluation of the different significances of this deafferentation for different motor functional systems.

Three motor functions having qualitatively defined results were used as objects of the investigation : swimming, jumping, and turning over from the back into the normal position. In the selection of these three types of functional systems we were considering their different phylogenetic age. While swimming is the oldest function preserved in the amphibia during their development from the fishes, jumping constitutes a specific functional system which became possible only in the presence of four extremities and upon transition to a terrestrial way of life.

Experiments have shown that we cannot speak of afferentation as an unrelated function which exists independently of the functional system. The rather old experiments of Munk (1903) and Hering (1897) involving section of the dorsal roots for one hind leg will confirm this. After this operation the function of the hind legs, which participate in complex movements, is outwardly not disturbed at all. The frog is able to jump, walk, swim, and in general to perform all types of the motor functions most characteristic of it with complete coordination.

This gives the paradoxical impression that a frog does not need its dorsal roots at all, and that nature committed some kind of oversight by endowing its hind legs with tens of thousands of superfluous afferent fibers....

However, this is actually not the case. The paradoxical effect with the apparent lack of need for the afferent fibers is only a consequence of the fact that the afferent functions of a functional system change dynamically and are unequally distributed over the system in relation to the degree of its automatism. This automatism is a consequence of the fact that during jumping and other forms of movement the frog must always overcome the weight of its legs and body. Therefore, the entire functional system of jumping, for example, is stimulated from an extremely limited number of receptor formations, while jumping itself, as an integrated act formed as a result of standard discharges of the mesencephalon, no longer needs afferentation and develops as a standard integrated act.

Such a consideration can readily be checked by a control experiment we performed. If the weight of both the deafferented and the normal leg is artificially increased by attaching a small and equal load to each of them, a very impressive effect can be achieved. While the normal leg performs the jump with the attached load with just as much coordination as before, the deafferented leg, extending spastically, is unable to perform the coordinated movement of a jump.

It became clear that an intervention of reverse afferentation occurs only at that moment when the standard functional interrelations within the scope of the entire functional system are disturbed. It proved to be sufficient to perform a few alterations of the system, as in our experiment by increasing the weight of the leg, for the role of the reverse afferentations to be immediately revealed with exceptional clarity. In a normal leg, increased resistance is immediately compensated by an increase of the efferent impulses from the motoneurons of the respective segments. In this way the difficulty in swimming and jumping is unnoticeably eliminated to the observer. The deafferented leg, on the other hand, cannot send any signals about the problem at the periphery; therefore, the efferent discharges of the motoneurons, remaining at the standard level, do not increase their efficiency. This results in the leg being unable to cope with the increased load.

Of special interest is the number of afferent impulses required by the functional system in relation to the complexity of this system. For example, in order to destroy the act of swimming, one must practically destroy the entire sensory innervation in the frog, since this act is still completely coordinated even after section of all the dorsal roots of both sides of the body.

On the other hand, at the degree of deafferentation at which a frog thrown into the water very completely performs the act of swimming, it cannot perform a coordinated jump. If fewer dorsal roots are cut, a jump can still be performed. With this degree of deafferentation, however, turning from the back to the stomach cannot be accomplished. Only the preservation of an even greater number of afferent pathways permits the frog to turn from the back to the normal position.

Thus, this series of experiments quite clearly demonstrated that there is no afferentation *per se*, but there is afferentation belonging to a definite functional system, with each system requiring a different number and kind of afferent impulses in relation to its degree of automatism and its phylogenetic age.

This consideration was confirmed in the following experiment. If that degree of deafferentation is achieved at which turning over is impossible, the frog can lie on its back for a long time making unsuccessful attempts. However, pinching it with forceps in the zone of the remaining afferent innervation will intensify its attempts to turn over and cause it to resume a normal posture. Thus, in this experiment the increase in the available afferentation by means of mechanical stimulation was equivalent to the presence or appearance of some additional dorsal roots.

In these experiments perhaps the most remarkable feature is that the role of the afferent functions depends entirely on the properties and the end effect of the given functional system. As in everything which characterizes the universality of the principles of the functional system, afferentation yields to the demands of the given functional system as an integrative whole in its distribution and utilization. After numerous experiments it became evident that any approach to the explanation of complex and functionally defined forms of activity must inevitably be connected with its analysis on the basis of the principle of the functional system.

Returning to what I discussed earlier concerning the inadequacy of integration as defined by Sherrington, I must emphasize that only a physiological analysis at the level of the functional system can encompass a function of the entire organism in its inte-

grated acts without sacrificing the physiological interpretation of the individual components of this function. Moreover, only on the basis of the functional system as the unit of adaptive integration can one understand the meaning and significance of these components.

The example of the relative role of the afferent impulses as brought out in the case of the deafferentation of the hind leg of the frog emphasizes once more that the actual mechanisms of integration, which were the subject of Sherrington's interest, have no *absolute* significance: their appearance and utilization are entirely subordinate to the interests of the whole functional system, which must complete its activity in a clearly defined beneficial end effect.

In other words, the functional system, as an entity subordinate to the achievement of a definite adaptive result, may dynamically redistribute the participation of the afferent impulses, maintaining a certain constant level essential for the maintenance of its integrated nature. It is quite evident that the concrete mechanisms of integration connected with definite structural formations can change their nature and degree of involvement in the dynamic transformations of the functional system.

It follows that none of the physiological properties of any analytical component of the central nervous system may be used as a basis for understanding the integrative activity of the nervous system. Any functional system has properties specific for an integrated formation. These properties endow the system with plasticity, mobility, and to some extent an independence of the ready, rigid connections both within the central nervous system and the entire organism.

Having these general properties characterized above are the concepts of *homeostasis*, introduced by Cannon (1932), and *self-regulation*, provided by Pavlov: "Man is of course a system—roughly speaking, a machine. . . . But our system is self-regulatory in the highest degree—self-maintaining, repairing, readjusting, and even improving" (Pavlov, 1932, see Pavlov, 1963, p. 144).

However, these concepts pertaining to the integrated nature of regulation are not

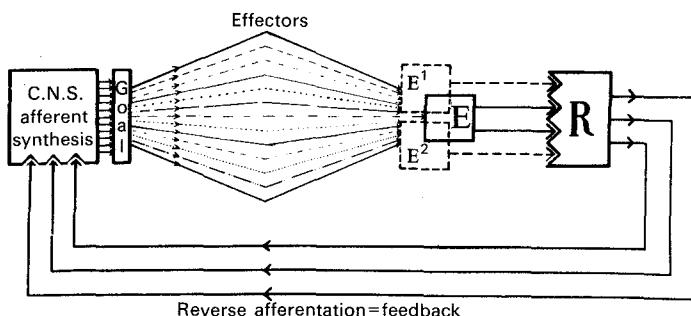


FIG. 6.5. Basic diagram of the functional system as a mechanism of self-regulation. E, beneficial end effect of the functional system. E^1 , E^2 , deviations from E due to various influences. R, receptor of the functional system precisely adapted to the characteristics of the beneficial or adaptive effect. C.N.S., the central nervous system which effects the afferent synthesis of all the information from the receptors of the system. The various lines represent the multitude of compensatory pathways along which deviations from the beneficial end effect return to normal.

apparent in their concrete principles and key mechanisms, which are only characteristic of this integrated system and not of its components. The functional system is a complex morphophysiological mechanism which ensures both the effect of homeostasis and that of self-regulation. The functional system makes use of a great variety of delicate mechanisms of integration and directs the course of all intermediate processes through the achievement of the adaptive end effect and the evaluation of its adequacy. To clarify this I refer the reader to Fig. 6.5, which depicts a universal schema of the functional system.

In this schema the beneficial end effect is the central feature since the dynamic behavior of the entire functional system will depend on the condition of this end effect and its fluctuations. Another key mechanism of the system is a receptor which in its triggering properties is exactly adapted to the physical and chemical parameters of a certain beneficial end effect. The adaptive end result of the system and its receptor are the central aspects which must be exposed when analyzing integrative formations.

It is appropriate to note that of the components of the functional system, the most conservative is the receptor, which often retains the constancy of a beneficial effect throughout life. This means that Claude Bernard's famous phrase "the constancy of the *milieu intérieur*" must be applied not to the internal environment itself, which has a tendency for considerable fluctuations, but to the receptor apparatuses, which perceive the changes in this environment and through the central nervous system connect or disconnect various supplementary mechanisms maintaining the constancy of individual components of the internal environment.

Thus, at least two categories of physiological mechanisms with very different physiological properties constitute the functional system. One is composed of mechanisms of extreme conservatism (receptor systems) and relative conservatism (the actual end effect). The other key mechanisms of the system, namely, the means for achieving the adaptive result, have a great plasticity and the capacity for mutual replacement.

For example, in the basic schema of the functional system, if we substitute the constancy of the partial pressures of CO_2 and O_2 in the blood for the adaptive end effect, it is quite evident that the most conservative components of the system will be the chemoreceptors of the reticular formation, the medulla oblongata, the sinocarotid region, and the aortic arch. The most plastic components, on the other hand, will be the mechanisms by which some change in the partial pressures of CO_2 and O_2 is brought about. These mechanisms increase or decrease both the depth and the rate of respiration and the minute volume of the blood, which itself is a resultant of the beat volume and the heart rate.

The presented universal model of the functional system is a means for studying any integrative formation which maintains or achieves some beneficial end effect in the life of the entire organism. With the substitution of the osmotic pressure of the blood or the level of the blood pressure for the end effect, the integration will operate and produce an adaptive effect on the basis of the same physiological schema (Anokhin, 1961d, 1962a).

Analysis of behavioral acts and of the conditioned reflex shows that all forms of the adaptive activity of the organism are subject to the same physiological schema and

merely acquire various supplementary mechanisms in accordance with the specific nature of the behavioral act. In spite of these supplementary mechanisms, the functional system maintains its integrity, such as the prediction of the anticipated results in the activity of a functional system. The ability to predict unachieved results in the embryo can be found even in those functional systems whose purpose it is to maintain the most elementary of the vitally important constants (see below).

Proceeding from this universality of the mechanisms of the functional system, we can say that the vital process, originally organized on the basis of self-regulatory adaptations, very long ago formed the functional system as a mechanism for the most complex integrative adaptations. We know of many such developments of evolution which, once having been captured in the process of natural selection and of use for progressive development, have proceeded to the highest stages of evolution.

To illustrate the point, deoxyribonucleic acid, for example, acquired its universal significance for both virus and man since it proved to be useful for transmitting hereditary characteristics. The membrane of the living cell, which has not changed its structure either in the sea-urchin egg or in the human cortical cell, is another example.

It is quite possible that the functional system ensuring the effect ("purposefulness") underwent an enriching development by gaining new content at each evolutionary stage while maintaining its basic architecture. I shall try to characterize the qualitatively distinctive features of the functional system before giving a detailed description of its key mechanisms.

As I have already stated, the functional system is the unit of the integrative activity of the entire organism and constitutes the tangible physiological mechanism of self-regulation and homeostasis. It implements the selective involvement and unification of structures and processes for the accomplishment of any clearly defined behavioral act or function of the organism. Hence the question arises regarding the composition of the functional system.

The *composition of the functional system* is not limited to the central nervous structures which fulfill the most delicate integrating role in its organization and impart the appropriate biological property to it. It must, however, be remembered that this integrating role is necessarily manifested in the central-peripheral relations by which the working periphery determines and implements the properties of the functional systems, which adapt the organism to the given dynamic situation by their end effect.

For example, as a biological form of adaptation to the environment, the swimming of a frog results from detailed and selective connections in the nerve centers, which determine the form of the functional system. We have seen, however, that this central integration proves to be in vain if the arrival of afferent impulses is decreased to a certain level (Chepeliugina, 1949a, 1949b).

The composition of the functional system is not determined by the topographical proximity of structures or by their affiliation with any existing *anatomical* (vegetative, somatic) unit.

It may *selectively* involve both closely and remotely located structures of the organism and also the fractional parts of any anatomically complete systems and even individual parts of some organs. The only factor determining the selectivity of these combinations

is the biological and physiological architecture of the function itself, and in individual cases even its mechanics (e.g., jumping). The only criterion of the worth of these combinations is the ultimate adaptive effect which sets in during the development of the processes in the given functional system.

Every functional system possesses regulatory properties which are inherent only in its integrated state and not in its individual components. The regulatory properties of the functional system primarily consist of rapidly rearranging its constituent processes whenever any defect in one of its parts leads to a disturbance of the beneficial end effect. As a result of such regulation, the final motoneuron can, for example, restore its normal participation in the functional system after deafferentation. This intrasystemic regulation is mainly brought about by means of a sudden redistribution of the coordinated tonic interactions of the parts of the system. Thus, if the descending integrating influence from the brain stem and medulla oblongata on a deafferented extremity is eliminated, it immediately becomes paralyzed (Chepeliugina, 1949a, 1949b; Mikhailova, 1949).

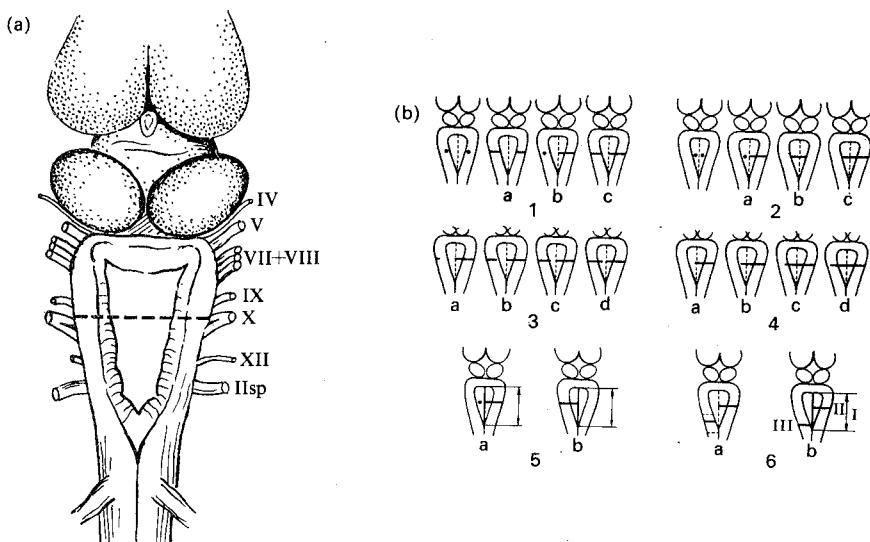


FIG. 6.6. Various levels and combinations of incisions in the medulla oblongata after which compensation in the behavior of the deafferented extremity either occurs or is destroyed.

(a) Overall diagram of the brain of the frog, on which the transection of the medulla oblongata along the middle third rhomboid fossa is indicated by a broken line. After this transection the compensation of the deafferented extremity is destroyed and it does not take part in the general locomotion.

(b) Various combinations of coagulations and incisions of the medulla oblongata with different effects on the compensation of the deafferented extremities are shown. Coagulations are indicated by black dots, incisions by solid lines. A unilateral section does not cause destruction of the function of the deafferented extremity. Of special interest is an experiment involving incision of both halves of the medulla oblongata from two sides. With sufficient distance of one section from the other, compensation proves possible (No. 6b). The results of these experiments emphasize the important role of the integrating formations of the medulla oblongata in the compensation of the functions of a deafferented extremity.

Consequently, normal functioning of the deafferented extremity is not a result of compensatory processes at the level of the spinal cord, but is rather a consequence of a higher integration in which the degree of participation of each extremity in the automated motor act is predetermined. At the same time, the loss of tone of the deafferented extremity after section of the spinal cord below the medulla oblongata emphasizes the decisive role of the mechanisms of the reticular formation in supplying energy (tonic) to the functional system as an integrated formation (Mikhailova, 1949) (Fig. 6.6).

As was shown in Chapter 2, the functional system originates in a manner specific for it, occurring by way of a number of completely characteristic stages (systemogenesis). This property of the system cannot be attributed to its components since it is truly a property of the entire organization.

The experiments with deafferentation revealed that one of the characteristic properties of the functional system is its relation to afferentation, which becomes a plastic mechanism of the system as a whole (see "reverse afferentation").

The principle which is most striking during the physiological investigation of systemic activity is the progressive elimination of afferent influences from the sum total of afferentations of the given system as soon as it changes over to stationary operation (the principle of the "narrowing of afferentation"). The end result of the "narrowing of afferentation" is always the preservation of some residual, sometimes very limited "leading afferentation." Both concepts are dynamic, and the physiology of one cannot be understood without the other.

Upon any disturbance of the leading afferent impulses or with a deviation in the end effect, "reserve afferentations," i.e., previously eliminated afferent impulses, immediately appear. As a result the functional system as a whole maintains its beneficial architecture. This demonstrates the integrative nature of the functional system.

Physiological analysis of the nature of the processes leading to intrasystemic and intersystemic regulations suggests that the central process of this unification is the activation of all the components comprising the functional system, probably as a result of the inclusion of the orienting-investigative reaction because of "discordance" in the adaptive end effect (see below).

In its physiological essence the principle of the functional system borders between the problem of the integrity of the organism in its broad sense and the analytical investigations of physiology. The concept of the functional system is absolutely essential because it provides for the formulation of new, purely practical research problems and for the accumulation of data for developing a physiological theory of the integrative activity of the entire organism.

All the enumerated physiological properties of the functional system are its distinctive features when the system acts as a whole in the adaptive activity of the entire organism. Essentially they are reduced to the ability of the functional system to plastically and dynamically rearrange its intrasystemic processes without loss of the adaptive end effects.

By what concrete mechanisms does the functional system achieve these regulatory properties, invariably maintaining the purposeful nature of the adaptation at all levels (vegetative process, conditioned reflex, and behavior in the broad sense of the term)?

Throughout many years our laboratory has been accumulating data concerning these mechanisms which are inherent in the functional system in its capacity as an integrative formation. Below I shall analyze those specific mechanisms of the functional system which provide for the universal physiological architecture of the behavioral act.

AFFERENT SYNTHESIS AS A SPECIFIC MECHANISM OF THE FUNCTIONAL SYSTEM

The concept of afferent as an essential and universal stage in the elaboration of any conditioned reflex or behavioral act developed gradually and principally on the basis of the evaluation of the *relative* role of the conditioned stimulus in the elaboration of the conditioned reaction.

For a long time in the school of Pavlov the conditioned stimulus represented something absolute and *unique* in obtaining the conditioned reaction. In any case, all changes in the conditioned reflex were directly related to the stimulus and its dynamic changes.

As it subsequently turned out, this evaluation of the conditioned stimulus is a quite natural consequence of the actual form of the experiment in which the possibility of a conditioned connection with any other conditions and factors of the experiment was eliminated. Any influence on the conditioned reflex which caused its decrease or disappearance was regarded as a result of inhibition. This persistent attribution of an absolute role to the conditioned stimulus was based mainly on the principles of the localization of functions and on physiological determinism.

If light is used as a conditioned stimulus, it is natural that it first excites some cellular complexes in the optic region of the cortex. It is also natural that the further spread of the conditioned excitation over the cortical and subcortical structures starts from here, ensuring a conditioned response specific for light.

However, this seemingly correct explanation was interpreted altogether differently due to a number of specially conceived experiments, particularly those of my collaborators Laptev (1935) and Shumilina (1965).

The aim of these experiments was to demonstrate the ability of the brain to extensively synthesize all those signals of the external world which reach the brain through various sense organs and are of diverse functional significance. It was found that impulses arising from an external stimulus by no means propagate linearly into the central nervous system, as postulated by classical reflex theory. Invariably the impulses interact with other afferent impulses which have a different functional significance. Only in relation to the synthesis of all these afferentations are conditions for the formation of purposeful action established. This interaction is enriched by new afferent impulses actively collected by means of the orienting-investigative reaction.

The significance and place of each of the external stimuli in the process of afferent synthesis can be expressed most clearly in the following general formula : the physiological significance of any external and internal stimulus lies in that it can either be of a triggering nature, i.e., be a true stimulus for the appearance of any reaction, or it may be a specific factor which prepares an integrated reaction existing in latent form.

The data show that all forms of these often highly diverse stimuli constitute an organic

unit, but each has a specific contribution to this unit. This can be concretely illustrated. The experimenter first makes a number of very routine preparations (preparing the food, sealing the funnel, closing the door, and applying the conditioned stimulus). As I have already indicated, it is customary to assume that the most important and decisive factor in the manifestation of the conditioned alimentary reaction is the conditioned stimulus. This is not actually the case, for if only the pouring of the meat-bread crumb mixture into the feeder is omitted from the preparatory procedure, the usual conditioned stimulus, which had always been effective, is now unable to evoke the conditioned secretory effect. Why did this depreciation of the conditioned stimulus occur, since the stimuli enumerated above comprise merely a complex of situational stimuli and any one alone does not ordinarily evoke salivary secretion?

It is quite evident that the conditioned end effect is not solely the result of the action of the conditioned stimulus. The impulses from the conditioned stimulus synthetically unite with those impulses triggered by the preceding stimuli. The latter do not actually evoke the conditioned reaction, but they do determine its form and intensity. Some years ago we named this latent system of impulses prepared by the various preceding stimuli "pretriggering integration." By this we mean a system capable of forming a reaction as soon as the appropriate triggering stimulus has been applied (Anokhin, 1949a). Many experiments may be cited in which there occurs a similar transfer of the ability to elaborate a conditioned reaction from the stimulus to the environmental setting.

The first serious limitation of the absolute importance of the conditioned stimulus resulted from the study of the phenomenon of dynamic stereotypy (Pavlov, 1933a, see Pavlov, 1963, pp. 98–101). As is known, this experiment demonstrated that with prolonged application of any particular sequence of conditioned stimuli, the determining role in the elaboration of the conditioned reaction shifts to this dynamic stereotype. After sufficiently long application of the given stereotypic sequence of the conditioned stimuli, all the specific effects characteristic of each of the stimuli in the stereotype can be produced by any conditioned stimulus. In other words, light may be substituted for a bell to obtain a conditioned reflex characteristic of a bell, etc. Any randomly chosen conditioned stimulus will produce that conditioned effect which always occurred at this point of the stereotype in response to another stimulus.

Thus, a highly paradoxical physiological situation develops. Light, the actual conditioned stimulus, is presented. It acts on the cells of the optic cortex. However, a conditioned response is produced which had always been evoked from the auditory region of the cortex. Since this seeming infringement of physiological determinism had previously not been noticed and analyzed, dynamic stereotypy had not been used to question the established opinion on the absolute importance of the conditioned stimulus.

Meanwhile, it was brought out quite distinctly in experiments involving dynamic stereotypy that there are at least two independent parameters in the conditioned stimulus and that the conditioned stimulus is part of some large system of relations which, under certain conditions, can be of primary importance in determining the intensity of the conditioned reaction.

It is indeed quite evident that in the conditioned stimulus we must distinguish its triggering function, i.e., the impetus for initiating a reaction, and its qualitative aspect, i.e., its intensity. The triggering parameter in the test conditioned stimulus is preserved in the dynamic stereotype, but the nature of the reaction is determined by a location belonging to some other stimulus which had been used for some time in the dynamic stereotype.

This analysis of the structure of the dynamic stereotype does not, however, explain how a conditioned stimulus applied to the visual cortex is able to produce a conditioned reaction which ordinarily originates in the auditory cortex.

The nature of dynamic stereotypy was detected by recording cortical biocurrents in man. If the above-described experiment is performed in man with simultaneous recording of the biocurrents from various sections of the brain, it will be seen that before the impulses from the next stimulus arrive at the recording site in the cerebral cortex, there develops excitation which in its nature corresponds to, but anticipates, the reaction to the future stimulus (A. D. Simonenko, see Anokhin, 1957a) (see Fig. 1.2, a).

This diversity of the afferent impulses synthesized before the establishment of a behavioral act was demonstrated even more convincingly by Laptev (1949c). He paired the same stimulus (a bell) with two different unconditioned stimuli: the bell applied in the morning was reinforced with food, while the bell applied in the evening was reinforced with electric shock. As a result of these experiments, a situation arose in which the same stimulus (a bell) produced strictly different effects depending on the time of presentation. In the morning, saliva was secreted in response to the bell's presentation, and the animal manifested an alimentary reaction, while in the evening it withdrew its paw in response to the bell, i.e., it exhibited a distinct defense reaction. Here we have a complex synthesis of the triggering excitation (the bell), the environmental conditions, and the time when the experiment is performed, with time creating the dominance of pretriggering integration.

It is clear that in these cases the qualitative aspect of the conditioned stimulus became completely meaningless, since its signal value for a secretory or electrical effect is determined by a synthetic formation related to the nature of previously stabilized excitations. Here, too, as in the case of the dynamic stereotype, the end effect is a result of the integration of different kinds of afferent impulses: the triggering excitation and the pretriggering integration created earlier.

There can hardly be any doubt that the changes of these different afferent informations constitute a complex synthetic process which, as we shall see below, involves all parts of the brain. This conclusion becomes even more significant when we consider that each of these afferent informations functionally interacting with others is physiologically distinct and has a specific role in the establishment of the whole functional system of a behavioral act. How does this process of afferent synthesis develop? What parts of the brain are involved and what are the properties of each component of this afferent synthesis?

Since the moment of perception of all these afferent influences cannot be determined from the point of view of a linear propagation of impulses, we must look for some

physiological structure providing for this synthesis.

As I have previously shown, there cannot be a simple linear propagation of excitation and inhibition in the integrative process, uniting qualitatively diverse functional systems. Each mechanism of integration contributes something new which, upon combination of the fragments, is manifested in the specific physiological properties of this fragment (Anokhin, 1948a).

Returning to the process of afferent synthesis at the level of the cerebral cortex, we must note that here, too, every new level of integration encompasses some kind of unification of the preceding excitations.

This conclusion was brought out with special clarity in the systematic experiments of Shumilina (1949, pp. 561–688). By elaborating conditioned reflexes in a special situation involving bilateral feeding and the choice of direction of movement, she showed that the frontal lobes of the cerebral cortex have the capacity to retain various kinds of afferent influences in a synthetic unity.

After elaborating conditioned reflexes for differentiating the two sides of the platform in response to two different conditioned stimuli, she extirpated the frontal lobes of the cerebral cortex (Brodmann's areas 6 and 8).

In this experimental setting, the intact animal behaves calmly, sits during the intervals between conditioned stimuli in the middle of the platform, and runs to a feeder only in response to the sound of the triggering stimulus, the conditioned stimulus. This is the result of afferent synthesis, by means of which the experimental animal, like man, precisely adjusts its behavioral possibilities to a certain situation.

As a result of the frontal lobectomy, somewhat unexpected changes in the behavior of the animal took place. Although the conditioned secretory-motor responses remained essentially unaltered, the general behavior of the dog in the experimental room changed significantly. As soon as the animal was placed on the platform, it began to move continuously back and forth from one feeder to the other, performing pendulumlike movements but stopping only briefly at each feeder (Fig. 6.7). It seemed that the animal had ceased to differentiate between the qualitative characteristics of the triggering stimuli and the overall influences of the environmental setting.

Consequently, the changes in behavior that set in after frontal lobectomy result from the disintegration of this extensive complex of afferent impulses, each of which reflects one particular aspect of nervous activity.

Summarizing the presented examples, we must conclude that the significance of the disturbances of this afferent synthesis is that the stimuli from the setting, whose effect was usually delayed until the appearance of the triggering conditioned stimulus, become themselves triggering stimuli after frontal lobectomy. This explains why the animal, after this operation, as a rule performs pendulumlike movements, i.e., approaches in turn the right and the left feeder, as soon as he is placed on the platform.

It might have been assumed that the pendulumlike movements are a form of "motor unrest." It is, however, easy to prove that this explanation does not apply here and that all these movements result from the disturbance of the synthesis of the heterogeneous afferent influences which are specific for the active choice of one side of the platform.

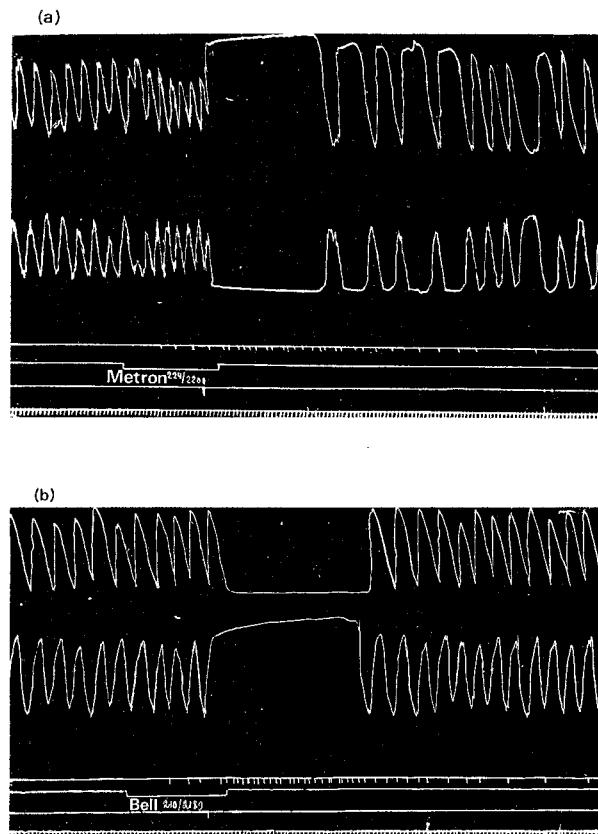


FIG. 6.7. Curve of continuous pendulumlike movement of dog in a bilateral stand after extirpation of the frontal lobes of the cerebral cortex. Explanations in text. For explanation of this method of conditioning, see Fig. 15.1. First line, movement to the right; second line, movement to the left; third line, salivary secretion; fourth line, record of presentation of conditioned stimulus; fifth line, record of unconditioned stimulus; sixth line, time in seconds. Metron. 224/2200, conditioned stimulus to right feeder; Bell 210/2189, conditioned stimulus to left feeder. (a) experiment in which a metronome was used as a conditioned stimulus for the right feeder; (b) experiment in which a bell was used as a conditioned stimulus for the left feeder.

A special control experiment may be mentioned as evidence for this. If a conditioned response to the feeder on only one side of the platform is elaborated, i.e., so that the animal does not have a choice between the two opposite sides of the platform, a frontal lobectomy does not lead to the appearance of the characteristic pendulumlike movements. The animal sits in front of the feeder exactly as in the classical Pavlovian experiment. Lacking frontal lobes, this animal needs to be fed only once from the opposite feeder, and pendulumlike movements immediately occur.

It is clear that the pendulumlike movements are a specific reaction to the possibility of a choice between the two opposite sides, which in the intact animal exists as latent

pretriggering integration and becomes supraliminal after the presentation of the triggering conditioned stimulus.

The above-described data concern the ability of the cerebral cortex to synthesize numerous and functionally diverse afferent influences and only then to pattern an appropriate adaptive behavioral act. This is the true stage of afferent synthesis, in which several forms of afferent information are integrated simultaneously. Thus, we should now discuss the four forms or fragments of afferentation which comprise the stage of afferent synthesis.

Motivational excitation is an essential component of any behavioral act, for it is always the purpose of behavioral acts to create sufficiently favorable conditions for the existence of an organism. The behavioral act always satisfies some need of the organism, nutritional or spiritual. The importance of motivational excitation participating in afferent synthesis can be seen in the inability of the conditioned stimulus to evoke the conditioned reflex if the animal has eaten its fill, i.e., if it lacks ascending activating impulses from the hypothalamus which form a distinctive and always selective system at the level of the cerebral cortex (Anokhin, 1961d, 1962a; Sudakov, 1965).

Motivational excitation plays an important role in the formation of the stage of afferent synthesis, since it is difficult to conceive of any behavioral act without the appropriate motivational prerequisites. Such motivations can be created either by the nutritive and hormonal processes or by the need to perform specifically human acts, i.e., social behavior.

Proceeding from this we can assume that practically any information entering the central nervous system is compared and evaluated on the basis of the motivation dominant at the given moment. This motivation is a filter by means of which information is classified. In other words, the significance of this information for the dominant motivational excitations is continuously evaluated. Consequently, motivation as a general dominant state, in U'khtomskii's terminology, is a filter which selects what is necessary and rejects what is unnecessary or, more accurately, what is inappropriate for a given initial motivational set.

The investigations of my collaborator Sudakov (1965) have shown that the neurophysiological basis of such motivational predispositions is the ascending influence of the hypothalamic and reticular formations manifested in the selective activation of the cortical synaptic formations. This allows for the selection of current information in the interests of the dominant motivation. From this it can be seen that the active selection of appropriate information by means of the orienting-investigative reaction proceeds with maximum success only because every part of this information is confronted with the dominant excitation evoked by the given motivation. The whole process of this confrontation is, of course, not simple. In cybernetic terminology, "information scanning" must select the maximally useful information for the fulfillment of the given motivational set. When considering motivation as a component of afferent synthesis, we must remember that it has a preeminent role in the determination, guidance, and active selection of the information most essential for deciding an action and purpose and then achieving the appropriate adaptive effect.

In order to evaluate this classifying role of the initial motivation, it is quite important

to know that while the sense organs and central nervous system are potentially capable of transmitting an enormous amount of information (if it is calculated in bits), only a very minute part of it becomes involved in the synthetic process which we have called afferent synthesis. For example, Rushton writes that the fovea centralis of the human retina has approximately 30,000 nerve fibers which have the potential ability of transmitting a million bits of information in 0.1 sec. The neural structures, however, are capable of processing during this time only approximately 4 bits. Rushton attributes this extreme limitation in the processing of the information obtained at the periphery to the difference between the capacity of both the transmission lines and the coding-decoding system (Rushton, 1961, p. 171). There is no doubt that on account of difficulties of a purely structural nature the central nervous system has a considerably lower capacity than the transmission part of the analyzer. When we deal with the limitation of the excess information at the level of the cortical cells, however, the problem has a different solution. Even if the entire information perceived by the primary receptor mechanisms were able to enter into the cortex, it would have to be immediately reduced to a very low level in complete accord with the dominant motivation. It must be said that this dependence of the selection of information on its significance for the organism is intuitively sensed even by cyberneticists, whose outlook is oriented more towards engineering. For example, discussing the significance of the "frequency of occurrence" of information for its coding in the central nervous system, Barlow (1961, p. 228) writes: "... in learning and conditioning, the animal does not act upon a predetermined feature of the sensory input but has to find sensory correlates of the rewards, punishments, and unconditional stimuli it receives before it can act on them."

The *sum total of situational afferentations* is a type of afferent influence including not only the stationary environmental setting in which some behavioral act is performed, but also the series of consecutive afferent influences ultimately leading to the creation of the overall situation of the behavioral act. The sum total of these afferent impulses creates in each individual case a pretriggering integration of excitations which, though latent, can nevertheless be immediately manifested when the triggering stimulus is applied.

Triggering afferentation is physiologically significant because it times the manifestation of the latent excitations to a definite moment which is the most advantageous from the point of view of the success of the adaptation.

Utilization of memory mechanisms is vital to afferent synthesis, which would be impossible if the complex of situational and triggering stimuli were not intimately linked with stored previous experience. How does this highly intriguing, undoubtedly universal mechanism develop? In what manner does each given stimulus gain access to the larders of the memory and specifically to those of its stores which specifically meet the demands of the given situation? On the basis of these mechanisms, there is a mobilization of those fragments of past experience capable of enriching the current behavioral act and of imparting maximum accuracy to it. This constitutes one of the intimate mechanisms of afferent synthesis.

All the above-mentioned mechanisms, however, would not be capable of the

synthetic work in the processing of the information entering the brain if the insufficiently precise information were not supplemented by the continuously active process of the orienting-investigative reaction. Only when the reticular formation and the hypothalamus constantly activate the cerebral cortex does a unification of the previously separate afferent impulses and the shaping of this "decision" become possible, which in the broad sense corresponds to the demands of the overall situation and the true purposes of behavior.

THE NEUROPHYSIOLOGICAL SUBSTRATE OF AFFERENT SYNTHESIS

In the preceding section it became apparent that without analyzing afferent synthesis in regard to the overall architecture of behavioral reactions, we would be unable to formulate the "purpose of action" and "decision making," as cyberneticists designate this crucial factor in the patterning of goal-directed behavior.

From our point of view, *establishing a goal for achieving any result depends mainly upon the stage of afferent synthesis*. This enables us to scientifically explain, on a physiological basis, those concepts and processes of "purposefulness" which for a long time have been the prerogative of idealistic psychology. By the introduction of the stage of afferent synthesis, all the operations involving "spontaneous" cerebral processes were rendered unnecessary. Due to afferent synthesis, every goal for the achievement of a result, regardless of its complexity, can be interpreted purely as the result of diverse processes in which each of the four components presented above participates to a different degree.

Thus, the detailed physiological analysis of all the component mechanisms of afferent synthesis assumes special importance. With this analysis we encounter an extraordinary complexity and multiplicity of interactions of specific processes at the cellular level.

Without doubt, afferent synthesis cannot take place without an interaction of all those impulses which originate in the receptor systems, emerge at the subcortical level, and then ascend in various combinations to the cortical cells. At the cortical level, the most highly synthetic interaction of afferent ascending impulses takes place, establishing the goal for the achievement of specific results.

During the last decade we have been persistently studying this process, utilizing all the advanced methods of investigation, as I discussed in Chapter 5. The study of the interaction of afferent impulses at the synapses has now become a very timely aspect in the study of cerebral function. Such outstanding neurophysiological laboratories as those of Fessard (France), Jung (West Germany), Mountcastle (U.S.A.), Jasper (Canada), Moruzzi (Italy), and many others are devoting much attention to the mechanism of the convergence of impulses.

After the discovery of the so-called nonspecific activating effect on the cerebral cortex (Moruzzi and Magoun, 1949), it became clear that the cerebral cortex receives impulses highly diverse in nature and localization. These impulses, *frequently converging upon the same cells of the brain*, form here something *new*. This is a natural consequence of the interaction of these impulses at the molecular level.

One of the most significant advances in these investigations in recent years is the clear realization of the *amazing multiplicity of ascending impulses*, even when a simple stimulus, e.g., a flash of light, has been applied to the receptor apparatuses.

Even such a simple series of impulses, upon reaching the subcortical apparatuses, disperses very widely and excites absolutely all the known principal subcortical nuclei. Only after this dispersion and specific processing can the impulses enter the cerebral cortex both in individual specific series and in a generalized form. In other words, by means of certain synaptic formations almost every cortical cell is involved by the impulses arriving from lower levels and participates in an extensive system of excitation. Of course, at this moment the cortex is not uniformly excited. Nearly all sections of the brain and all synaptic formations of the cortex become involved in a highly individualized way. Therefore, there are very substantial reasons for assuming that the final result of these diverse ascending impulses is some kind of statistical system composed of numerous nonuniform excitations which develop in various parts of the brain.

Thus, neurophysiology was given a quite definite picture of the interaction of impulses. They do not form any particular isolated "focus of excitation," to which even recently we have given great significance in our main concepts of cortical function. It has become evident that the leading role is played not by one initial "focus of excitation," but by an extensive system of diverse excitations, which are of unequal importance and interact with each other.

Let me give an example of ascending impulses which are of a generalized nature in the cortex but come from a very localized region of the subcortex. One of my collaborators has discovered a special neural pathway over which impulses from stimulation of the sciatic nerve propagate directly from the lemniscal system into the hypothalamic region, where they are processed. These impulses then *spread in an ascending direction in a generalized manner* over the entire cerebral cortex. If we proceed from the fact that nearly all the principal subcortical structures (the reticular formation, the hypothalamus, the thalamic nuclei in general, the hippocampus, the amygdaloid nucleus, the nucleus caudatus, and many others) direct into the cerebral cortex series of impulses *which often converge upon the same cortical cells*, the marvelous diversity of the synthetic function of the cerebral cortex becomes apparent.

Even now it can be stated with certainty that the convergence of impulses upon the same neuron is the central mechanism without which afferent synthesis cannot occur, since this convergence ensures the interaction, comparison, and synthesis of all impulses in the actual cytoplasm of the nerve cells. What delicate cellular processes are the basis of this? What impulses arriving from the subcortical apparatuses enter into these interactions?

Neurophysiology is only at the beginning of the clarification of these important processes on which the understanding of afferent synthesis depends.

One can agree with Fessard (1960) that the prototype of this afferent synthesis is the homogenization of impulses in the same neuron, which receives hundreds of different series of impulses. The neuron itself "makes the decision" about sending on to the axon one single series of impulses characteristic of this neuron.

Thus, the whole problem of afferent synthesis may be reduced to the solution of several important questions:

1. In what form do what impulses reach the cortical cells?
2. How are the synaptic formations constructed?
3. Is there a selectivity for the distribution of ascending impulses, and what does it involve?
4. What are the neurochemical properties of the synaptic formations formed on the same neuron?
5. Is there an interaction of the impulses converging upon the cell in the molecular processes of the cytoplasm?
6. What processes and mechanisms determine the actual transition from the diverse processes of the afferent synthesis to the selection of definite efferent pathways for the implementation of the action? This last stage, which corresponds to decision making, will be considered separately below.

One laboratory, and especially the efforts of one person, certainly cannot completely answer these questions. The efforts of many investigators will be needed.

During the last several years, our attention was drawn to one important aspect of afferent synthesis at the level of the cerebral cortex, namely, to the *biological modality* of those ascending impulses which converge and interact at the level of the cerebral cortex. This direction of our investigations was suggested by a certain dissatisfaction with the established point of view concerning the diffuse and nonspecific activation of the cerebral cortex by the reticular formation.

Indeed, if the activation of the cortex is diffuse and nonspecific, then how does it evoke differentiated states during alimentary, nociceptive, or defense activation? And would not the cerebral function be chaotic if the cortical activation were nonspecific, i.e., if all neural elements, both alimentary and defense, were involved?

Just how does the cortex differentiate between all these states of different biological modality?

The currently popular concept of the diffuse, nonspecific activation of the cerebral cortex by the reticular formation does not provide an answer to these questions. If all the activating impulses reaching the cerebral cortex are uniformly nonspecific, then how can we close the gap to the specific diversity of behavioral acts and emotional states that fill our lives, lifting us up to the most exalted forms of joy and lowering us to painful sufferings and doubts?

We first suspected a possible difference in the ascending activations after an experiment on an animal under urethane anesthesia. This anesthetic, which suppresses the ascending *activation of wakefulness*, allows free conduction to the cortex and activation of the cortex during *nociceptive stimulation* (see Fig. 2.10). Thus, this experiment led us to the seemingly paradoxical conclusion that there are at least two types of ascending activations which, from the point of view of neurochemical specificity, have entirely different substrates (Agafonov, 1956).

Further experiments performed by my collaborators Agafonov, Shumilina, and Gaylichek have shown that the cerebral cortex by no means receives uniform impulses from lower levels. On the contrary, it is activated in a generalized way by *specific*

ascending impulses in each particular case. These impulses emerge at the level of the subcortical systems and here acquire their biological specificity, which determines the effect of the ascending activating impulses at the cortical level.

It was found that at this level a remarkable process occurs which had previously escaped the attention of investigators; only with the discovery of the specific nature of the ascending impulses did it become evident. This process is the *selective involvement* of the synaptic formations on the body of a cortical cell in accordance with the *biological modality of the ascending activating impulses*. As we shall see below, this is directly related to the problem of afferent synthesis.

It is known that on its body and dendrites each cortical cell receives several thousand different impulses arriving from thousands of other cortical cells. These mutual contributions by the synaptic formations of the cortical cells create a vast number of possible interactions. If we add to this the no less diverse subcortical ascending impulses converging upon the same cortical cells, then we can imagine the true arena for the occurrence of afferent synthesis.

It is worth visualizing what chaos would result in our activity and behavior if all these manifold connections between the nerve cells were excited in a generalized, "diffuse," and "nonspecific" way. Fortunately, this is not the case. It turned out that the spreading of the activating influences is highly selective. Just as a river spreads out during the spring floods and channels its waters first of all through various passages, depressions, and ditches, so also do the ascending activating influences selectively involve those cortical neural elements and their synapses which historically, i.e., during phylogenesis and ontogenesis, were connected with a particular biological condition.

New possibilities for understanding the elusive role of the ascending impulses in the cerebral cortex have become available.

Previous experiments in our laboratory suggested that the subcortical apparatuses of the brain, which mobilize inborn and acquired reactions of different biological nature, *have different chemical properties intimately connected with the characteristics of their metabolism*. It has become possible to speak of a specific chemistry of certain states, or at least of a "chemistry of fear" and a "chemistry of pleasure" (Shumilina, 1956, 1959; Gavlichek, 1958; Makarov, 1960).

Naturally this reasoning led us to question the chemical essence of these various ascending impulses at the level of the cerebral cortex. That is, what is the nature of their chemical substrate at the point where the essential part of the actual process of afferent synthesis occurs? Do they preserve the specificity of their subcortical chemistry or do they completely transform their molecular nature?

As can be seen, at this point the problem of afferent synthesis comes into the most intimate contact with the material of Chapter 5, which deals with the convergent coupling of the conditioned reflex. In that Chapter, I presented those experiments which emphasize the extraordinary chemical diversity of the postsynaptic membranes on the body of the same cortical nerve cell.

When we say that there is a mutual convergence of impulses upon different cortical neurons, we cannot help but admit that the final stage of this synthesis consists of molecular rearrangements of those chemical ingredients of the protoplasm which are

inevitably drawn into action by the postsynaptic reactions.

As in the evaluation of the overall nervous activity, we must discern both the structural-physiological principles and the intimate molecular nature of the processes in afferent synthesis. For example, we can appreciate the important role of the motivational factor in the classification of the afferent influences that arise at every moment during afferent synthesis. There is no doubt that the motivational factor performs the initial and rough classification of all afferent influences into what is "essential" and "nonessential" with respect to this dominant motivation. But where does this essential preparatory work for the afferent synthesis occur?

The analysis of the ascending influences from the hypothalamus to the cerebral cortex (Sudakov, 1963; Badam Khand, 1965; Turenko, 1964; Shevchenko, 1965) compels us to think that the most significant sorting out of superfluous afferentation takes place on the dendrites of the cortical cells either in the form of a suppression of all extraneous afferent impulses or in their subordination to the current motivation.

We should not fail to mention another important factor which undoubtedly plays a role in the implementation of afferent synthesis, namely, the enormous structural diversity of the cortical cellular elements (pyramidal cells of all dimensions and layers, stellate cells, cells of the granular layer, etc.). Each of these cells contributes something individual to the mechanisms of afferent synthesis, but all our arguments are still

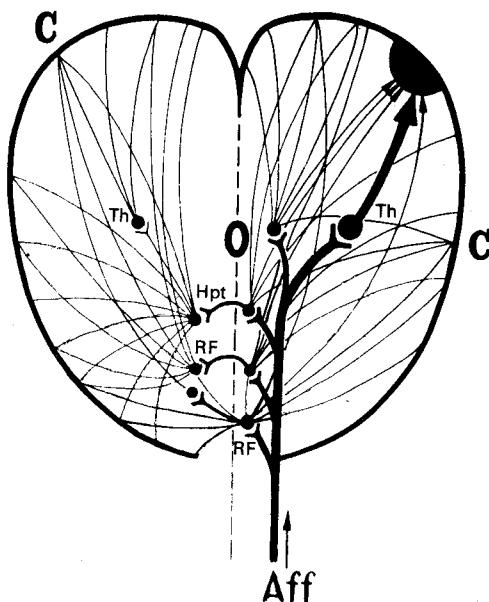


FIG. 6.8. Diagram of afferent ascending influences on the cerebral cortex. One can see the multiple processing of the information in the subcortical centers as well as the multiple convergence of ascending excitations to the same site of the cerebral cortex. From Anokhin (1964d, p. 360). Aff, afferent impulses; C, cortical cells; Hpt, hypothalamus; RF, reticular formation; Th, thalamus; heavy line, specific projection system.

oriented toward the universal role of the pyramidal elements of the third and fourth cortical layers.

We can imagine the great diversity of the connections on which afferent synthesis is based. A decisive role is unquestionably played by ascending influences, which may be either highly generalized or regionally differentiated (Fig. 6.8).

The diagram presented above, composed on the basis of our own and other data, gives a general idea of what ascends into the cortex upon simple stimulation of one afferent channel.

Intracortical connections, which unite remote regions of the brain, are also important in the implementation of afferent synthesis.

Our concepts of afferent synthesis would be incomplete if we did not take into account the important role of the orienting-investigative reaction in this mechanism. We must first consider the fact that the orienting-investigative reaction sets in on the background and by means of ascending activation coming from the reticular formation. Direct investigations of the effect of stimulation of the reticular formation on cortical discrimination show that during activating influences from the reticular formation the cortical processes occur with a greater acuity of differentiation (discrimination) between external stimuli (Lindsley, 1958) than without such stimulation of the reticular formation. In addition, an increase in the activation by the reticular formation at the moment of onset of the orienting-investigative reaction leads to a facilitated interaction of the individual parts of the cortex by means of intracortical connections. This second significance of the orienting-investigative reaction is of special interest since the main feature of afferent synthesis is the confrontation and integration of cortical processes located far apart.

The whole purpose of the orienting-investigative reaction at this stage is to confront the afferentations with the basic dominant motivation and the elements of previous experience.

Every investigator working with conditioned reflexes is familiar with the behavior of an animal when, after mobilizing in turn all its senses (primarily sight, hearing, and smell) and undoubtedly heightening their sensitivity by means of efferent influences, it suddenly exhibits behavior most appropriate for the given moment.

As we shall see below, this orienting-investigative reaction is of special importance and is the most frequent manifestation in that phase of a behavioral act in which the results obtained do not correspond with the previous decision and with the previously set goal of the behavior.

DECISION MAKING AS A KEY MECHANISM OF THE FUNCTIONAL SYSTEM

Quite remarkable in the patterning of a behavioral act is the making of a decision to perform a particular action. Recently this concept has become very popular among cyberneticists and engineers who have had to introduce it in the study and modeling of self-organizing systems (Bishop, 1960). Only a few biologists and physiologists, however, have begun to include it in physiology as an essential concept.

When I referred to afferent synthesis as an inevitable stage in which the integration of all the information entering the central nervous system takes place and to its transformation by the time of the patterning of the efferent program of impulses, it was evident that it is difficult to do without some kind of essential intermediate process. This process must be condensed to the highest degree, since it must consolidate all the qualitatively different fragments of afferent synthesis.

Decision making is a logical process of the functional system, but at the same time it is the result of specific physiological interactions which still need to be studied. To determine the place of decision making in the system of physiological knowledge while evaluating the neurophysiological basis of the behavioral act, we must analyze some characteristic features of this process.

What objective indications do we have that in the patterning of the behavioral act there is a mechanism related to the process called "decision"?

The main indication of such a mechanism is that the organism chooses one kind of behavior from many possibilities at any one time.

However, every time the organism performs a specific act, it must be appropriate to the given situation. Consequently, under any conditions there is a *choice* of a specific act and the elimination of all other possibilities. For the muscular system this process has been designated as the "elimination of superfluous degrees of freedom" (Ukhtomskii, 1945, p. 119).

What is the basis for eliminating some impulses and giving preference to a specific integral of efferent impulses with a highly selective excitation of muscular systems at the periphery?

A critical moment for choosing this efferent integral is essential for the actual selective excitation of the motoneurons. Since the moment of decision making is preceded by diverse afferentations and a comprehensive processing of these afferentations during the afferent synthesis, it would be physiological nonsense to assume that every element of the afferent synthesis is *linearly* connected with a unit of motor response. The motor act or behavioral act is critically decided at some moment of the afferent synthesis as a complete efferent integral.

The process of decision making is also a "choice" of one particular form of behavior. This choice can either come about with a considerably delayed stage of afferent synthesis with the participation of consciousness or proceed instantaneously on automatic pathways.

The problem of choice has been very thoroughly analyzed by Diamond *et al.* (1963). Very convincing evidence was presented that the choice of a particular behavioral act is inevitably coupled with the inhibition of the remaining degrees of freedom.

Upon applying the method of active choice in a specially designed bilateral platform with two feeders (see Chapter 15 and Fig. 15.1), we were repeatedly convinced that the moment of choice by the experimental animal of one feeder or the other is coupled with a very specific and often sudden "decision" to proceed to one of the two sides. For example, in some cases the animal sits in response to the conditioned stimulus for a long time in the middle of the platform. However, from the movement of its head, which turns alternately to the right and to the left with evident visual fixation on one

feeder and then on the other, we can conclude that an active collection of additional information is taking place and that the stage of afferent synthesis has not ended.

At some moment in this pronounced orienting-investigative reaction, the animal rapidly jumps up and proceeds to that feeder which is signaled by the given conditioned stimulus and waits for the issuance of the food (Anokhin and Artem'ev, 1949). A phenomenon of the same kind probably also unfolds in the central nervous system of an animal at those moments which have been designated as "ideation," or as a state of the "eureka" type (Hilgard and Marquis, 1961).

In all these cases the active selection of the maximum number of afferent parameters of the given situation by means of the orienting-investigative reaction ends in an appropriate behavioral act. This is the decisive factor in the patterning of the behavioral act at its efferent end.

The second substantial objective indication of decision making is the ratio of the very large volume of initial afferentation used in the stage of afferent synthesis to the quite definite and limited number of efferent impulses which, after decision making, are included in the patterning of the behavioral act itself. A typical model of this is offered by the neuron. Specifically, this would be the relation between the informational data at the "entrance" and at the "exit" of the neuron.

As we have seen above, Sherrington (1906, 1947) had already observed that the motoneuron constitutes a "common path" for numerous impulses, while only one impulse which is quite specific for the given neuron emerges onto the axon. Adrian (1947) emphasized the very same circumstance, calling this brief moment the "homogenization of impulses." It is therefore not surprising that at present many neurophysiologists are acknowledging the existence of decision making and thus regard the neuron as a convincing example of this critical process.

The importance and necessity of such a stage in the processing of the afferent impulses entering the central nervous system was expressed with particular clarity in one of the latest publications of Bullock (1961, p. 718) :

... we take up the question of the final stage of processing [of information] when all preceding integrations are summed to yield a simple yes or no answer.

If the integration is performed in the nervous system, then there must be, before the command enters the effectors, a final determination by some competent functional unit of whether the criterion has been met. All relevant input and central predisposition must be read and finally evaluated by a single integrator. Whatever its composition, the integrator is a unit because it is necessary and sufficient for the performance of this act.

As we have seen above, the most diverse forms of impulses can converge upon the same neuron. This presupposes that there occurs within the neuron some kind of highly complex activity of the type of afferent synthesis which is concluded by a decision at the point of generation : to send to the axon a particular configuration of discharges. Bullock considers it possible to apply the concept of decision also to a single neuron on

the same basis on which the synthesis of diverse outside information leads to the decision to pattern a particular behavioral act. In regard to this he writes (1961, p. 721) :

Every neuron is a decision-making element when it changes from a silent to an impulse-firing state. In this context only those neurons are interesting that integrate a complex input or control a large output. The capacity of a single neuron to integrate a large number of incoming impulses and to give a single-impulse answer, for example, the mediation of escape jerks by giant neurons like Mauthner's, demonstrates its suitability for a "decision" unit.

The realization of the necessity of introducing the actual fact of decision making into the structure of the integrated activity is now encompassing an ever widening circle of physiologists. Bishop, for example, in discussing the problem of self-organization, writes (1960, p. 139) : "... the higher decision-making levels are what concern us here . . ." Elsewhere he emphasizes even more clearly: "Thus any brain, however primitive and elementary, makes decisions and choices among alternatives and integrates motions into movements" (1960, p. 126).

From the formulations presented above, as well as from many other statements which I have not given here, all of which use the term "decision making," we may conclude that decision making is a critical point at which there occurs a rapid elimination of degrees of freedom and the organization of a complex of efferent impulses capable of producing a quite specific action.

We can admit in principle that if much diverse information enters some mechanism by way of numerous paths, and new and highly coded information leaves this mechanism through a quite definite path, we can always say that this mechanism is making a decision. This is the actual course of events both in the single neuron and in the whole brain during the patterning of a behavioral act. In all cases, however, the decision making is preceded by afferent synthesis; as we shall see later, it subsequently determines in many respects the development of the other stages of patterning of the behavioral act.

The rigid concept of the reflex arc did not take into consideration this critical point in the patterning of the response, even though it was noted in many investigations that the nature of the spinal reflex depends to a considerable degree on the combinations of afferent impulses reaching the motoneurons and on how the other impulses converging toward the motoneurons are distributed. In any case, afferent synthesis terminates in decision making, i.e., in the selective excitation of a complex of neurons able to pattern at the periphery one single behavioral act appropriate for the results of the given afferent synthesis.

As we have already pointed out, at any given moment the organism is potentially capable of performing an infinite number of acts. Consequently, the very fact of decision making immediately eliminates superfluous afferentation.

The universality of decision making in the functions of the organism can be seen not only from the behavioral acts, but also from purely vegetative functions. For example, the amount of air inhaled at a given moment corresponds to the organism's needs for

oxygen supply and carbon dioxide elimination. Any change in these needs is immediately met by a decrease or an increase in the air intake.

What is the cause of this delicate adjustment of the amount of air to the needs of the organism? It is quite evident that the motoneurons of the respiratory center receive a "command" which exactly reflects this need of the organism. This need, however, is complex: it includes several components which must be integrated, and only then does the motoneuron of the respiratory center receive a specific decision as to whether to take in 400 ml or 600 ml of air.

The need for such decision making in the intake of a definite amount of air at a definite rate and depth of respiration becomes especially evident when the respiratory system has a nonrespiratory purpose, for example, in singing or speaking.

Since the oxidative function of the tissues cannot be stopped during either singing or prolonged speaking, the respiratory neurons become "servants of two masters. . . ." While they must satisfy the needs of the organism for oxygen intake, they must also, during the utterance of sound, cause thoracic expansions adequately programmed for volume and rhythm. Here a very delicate afferent synthesis of all the above-described conditions takes place, and only after this is the decision made to expand the thorax to a certain volume.

If we were to reject decision making as the critical point in the development of the respiratory act, it would be very difficult to understand how the diverse requirements (CO_2 , O_2 , speech, a diseased lung, etc.) are met by the intake of a certain volume of air.

Thus, the physiological meaning of decision making in the patterning of a behavioral act lies in three highly important effects:

1. Decision making is the result of afferent synthesis accomplished by the organism on the basis of the dominant motivation.
2. Decision making eliminates superfluous afferentation, thereby promoting the formation of an integral of efferent impulses having adaptive value for the organism in a specific situation.
3. Decision making is a critical moment after which all combinations of impulses assume an executive, efferent character.

THE RESULTS OF ACTION AS AN INDEPENDENT PHYSIOLOGICAL CATEGORY

As we have seen above, immediately after decision making, an integral of efferent impulses is formed which must ensure first the peripheral action and then the achievement of the results of the action. Between all these stages of the patterning of the act itself there is an exact, i.e., equivalent, informational connection.

This means that the central integral of the efferent impulses ("program of action") corresponds most accurately to the volleys of efferent impulses traveling centrifugally to numerous peripheral organs. These organs themselves can be very remote from each other, depending directly on the biomechanics of the action.

If one regards the results of the action as a consequence of organized series of efferent

impulses, these deterministic relations can be extended further to include information about the results obtained. It seems strange that for many years the *results of an action* have never been the object of a special physiological analysis, since they are the decisive link between the reflex action and the patterning of the subsequent stages of the behavioral act.

Essentially, the reflex, the "reflex act," and "reflex action" interest only the investigator. The animal, however, is always interested in the *results* of action. In order to achieve them, very long chains of behavioral acts are performed. The results become stimuli for performing other acts until the achievement of the desired adaptation.

This seems so obvious that it could hardly contribute something new to science. And nevertheless, this was the greatest shortcoming of the reflex theory. The same reason led Descartes, the originator of the reflex theory, to dualism, and for a long time hindered the materialistic solution of the problem of *purposefulness* in behavior.

In fact, the persistent use of the reflex arc for the explanation of behavior eliminated any possibility of the utilization of the results as a driving factor in the patterning of variable behavior. Results simply had no place in the reflex scheme, and therefore their decisive role in the formation of the functional systems of the organism has remained outside the field of vision of the physiologist. This, apparently, is no accident.

Bunge (1959, pp. 226-227) discusses this problem in a way that is of great interest to us: "The confusion of cause with reason, and *that of effect with consequent* are, moreover, common in our own everyday speech" [italics—P.A.].

If this confusion of action with results holds true for philosophy, then it becomes especially significant in physiology. In fact, physiology not only has failed to make the *results of action* the subject of objective scientific analysis, but also based the entire terminology, developed during almost three hundred years, on the concept of the arclike nature of the course of adaptive reactions ("reflex arc").

The familiar concepts "scratch reflex," "cleansing reflex," "sneezing reflex," and "cough reflex" are part of this terminology. What is reflected in these terms other than that there was scratching or sneezing or that the acid-soaked paper was thrown off, etc.? In other words, all these terms only define the nature of the *action*. This is understandable: by its very nature the reflex theory could not cross this barrier and for this reason the results of action were not incorporated into the sphere of physiological investigation.

For our concept of the overall architecture of the behavioral act, the *results* of this act have become an integrated part of the whole architecture and thus were analyzed in greater detail in our laboratory. For example, we proposed the necessity of *classifying these results into various parameters*. This was believed to be essential because it was thought that the results of an action will only become a reality, permitting their scientific analysis, if in each case all those parameters defining the afferent information about the results obtained are completely encompassed. Such an understanding of the matter becomes especially essential because these parameters of the results have the ability to inform the brain about the usefulness of the action performed and constitute a *reverse afferentation*, i.e., a distinctive afferent integral, an afferent model of the results.

From this point of view, any single localization of the mechanism of the action acceptor or its identity with the dynamic stereotype is out of the question. Being a reflection of the afferent parameters of the results expected, the action acceptor always has within itself various afferent components of different sensory modalities. In some cases these may be visual and tactile parameters, and in others, auditory, tactile, and gustatory ones, etc.

This diversity of the action acceptors with respect to the composition of the afferent modalities can be fully expressed in the following: *there are as many different action acceptors as there are different results of action*. And since our everyday life is full of results of action, it is difficult to assume a single localization of the action acceptor. It is always composed of different sensory cortical representations and only the systemic integration of these components has, as was shown above, a predominant localization in the frontal lobes of the cerebral cortex. The investigations of Luria (1962) on patients in whom the frontal lobes were somehow afflicted provides convincing evidence of this.

As for the identity of the action acceptor with the dynamic stereotype, it is obvious that these mechanisms are of a completely opposite physiological nature and could have been identified with each other only through a misunderstanding. In fact, the action acceptor is, as could be seen from the preceding material, a *temporary* formation resulting from a given situation. It is always a reflection of the changing reality which is represented by afferent synthesis.

The dynamic stereotype is quite different. With special regard to the methods of its elaboration, this stereotype is *a conservative formation of the nervous system, which, once formed, asserts itself in defiance of actual events*. Concerning this, recall the example from the experiments of Simonenko (see Anokhin, 1957a) in which desynchronization of the electrical activity in the visual region set in not only in the absence of the regular visual stimulation of the dynamic stereotype, but remained specifically visual even when *an auditory stimulus was substituted for the light* (see Chapter 1).

This comparative evaluation of the two mechanisms is quite sufficient to demonstrate the profound physiological difference between them. Considering that all processes of the dynamic stereotype are based on the principle of anticipatory excitation, which is also mandatory for the action acceptor, one can conclude that the dynamic stereotype is a particular case of the universal function of the brain for predicting the future. Here the afferent synthesis has become a constant, conservative, and *internal* process of the brain itself, which is activated by some very definite signal from the external world ("narrowing of afferentation").

In referring to the physiological mechanisms forming the model of future results, I have repeatedly mentioned that the *parameters of the results obtained* are the decisive factor determining the further patterning of the behavioral act.

However, by focusing our attention on the results of action, we must then ask how the central nervous system is informed about these results.

In formulating the principle of the functional system as the unit of the integrative action of the organism, we have turned our attention to this information about the results of action (Anokhin, 1935). Out of purely physiological considerations, however, we termed this information *sanctioning or reverse afferentation*.

Thus, the cybernetic "closed circuit" with its "feedback" had been comprehensively formulated and worked out in detail in physiology long before the appearance of Wiener's first publications (1948) on cybernetics. Even then, among the mechanisms of the functional system, the reverse afferentation from the parameters of the results assumed special significance for us. On a physiological basis we could broaden the structure of the "reflex arc" and construct a physiological architecture in which all the key mechanisms are bound into a single causal system of processes.

In such a functional system the reverse afferentation, i.e., the *afferentation from the parameters of the results obtained*, terminates the entire logical model of a single behavioral act while proceeding toward the apparatus of the action acceptor.

In concluding this section I wish to briefly specify our concept of the results of action. This concept is based on the necessity of singling out the *afferent parameters of the results* because all subsequent events in the central nervous system develop according to the composition of these parameters and the coincidence with those parameters, also afferent, which had been prepared in the action acceptor.

If an *action* involves extending an arm and closing a hand, the *result* may be the picking up of an object. Immediately there develops a complex of afferent parameters which is truly an afferent model of the results (the weight of the object, its tactile properties, temperature, shape, etc.). All these parameters constitute reverse afferentation.

REVERSE AFFERENTATION

Before evaluating the role of reverse afferentation as integrated information about the results obtained, it is necessary to study afferentation more extensively.

We must remember that all the numerous energies and the infinite number of diverse factors of the external world act continuously upon the organism. These external influences on the nervous system increase considerably during the reciprocal action of the organism on the external world.

Physiologists are therefore confronted with the tasks of classifying the numerous afferent influences on the organism, basing their investigation on objective scientific laws, and indicating at the same time their place in the activity of animals and man. With the classification of afferent influences, there is obviously a need to establish criteria for such a task. These influences can, for example, be classified with respect to their *sensory modality*, which, in effect, was first accomplished in physiology. In this classification we differentiate the nature of the acting energy and the nature of the corresponding receptors. We thus have visual, auditory, tactile, gustatory, etc., afferentation. Or the afferent influences may be classified by using their position with respect to the external world as the criterion. Then we have "exteroceptive" and "interoceptive" afferentation. If the criterion of the distance of the stimulus is used, we then deal with "distant" and "contact" afferentations. The afferent influences can thus be classified according to the most diverse criteria.

It is therefore not surprising that with the ideas about the integrative forms of activity of the whole organism, there was a need to evaluate afferent influences with respect

to their significance and place in this integrated activity, i.e., according to the criterion of their role in the cyclic activity of the functional system.

It is evident that the selection of this criterion removes the significance of other criteria, e.g., of the modality of the afferent impulse or of its anatomical features. Indeed, for integrative activity an impetus is quite important for its manifestation, i.e., its triggering. Naturally, a *triggering stimulus* may be a stimulus of any modality.

This classification must systematize our opinion of the various influences on the organism and enable us to specify the place of each afferentation in the cyclic systems that ensure continuous functioning. Presently we are able to distinguish the following forms of afferent influences, which have been classified not according to the nature of the acting energy but according to their place and significance in the patterning of integrated behavioral acts of the organism:

1. Situational afferentation
2. Triggering afferentation
3. Reverse afferentation :
 - a. Movement-directing
 - b. Resultative—may be subdivided into stage-by-stage and sanctioning afferentation

Situational afferentation is the sum total of all those external factors and their influences which are relatively stable, prolonged, and always constitute an extremely intricate complex of different influences.

For example, when we sit in a concert hall, a number of special influences reach our sense organs, both from the sight of the audience and the stage and from auditory stimuli. Possessing a relative stability and duration of action, situational afferentation forms a highly complex afferent interaction in the central nervous system to prepare the specific reaction which can be adaptive only in the one setting.

This *correspondence* between the complex of the situational afferentation and the form of the reaction, which can occur only in the one setting, constitutes the characteristic aspect of situational afferentation. Its organic connection with another form of afferentation, the *triggering afferentation*, is one of the characteristics of the diverse afferent influences on the organism which determine its appropriate behavior.

Let us assume that a person becomes thirsty while he is at home. In most cases, he immediately quenches his thirst. Let us now assume that the same person became thirsty during some concert performance. The initial stimulus is physiologically the same, and yet in this setting it does not evoke the same kind of immediate action as in the home. Consequently, the specific nature of the afferent influences from the setting of the concert hall creates a complex of excitations which completely excludes the possibility of quenching the thirst at once.

Another example may be taken from clinical practice. A person has come to the out-patient clinic and is asked by the physician: "What is your complaint?" Such a question, when considered without reference to the situational afferentation occurring at the moment the question is asked, may evoke a number of answers: "I don't have enough time," "I have quarrelsome neighbors," etc. However, the original motives for going to the out-patient clinic (illness), the sight of the physician and of the whole

setting of activities in the clinic (i.e., the situational afferentation) create in advance a nervous integration for which the question "What is your complaint?" cannot be equivocal. Therefore, it is natural that normally a patient who has come to the clinic will, in answer to this question, tell the physician about his illness. In case of psychopathological disorders, the above inappropriate answers are possible.

The relation between situational afferentation and the subsequent triggering afferentation can be seen most clearly in experiments with conditioned reflexes. Let us assume that for a number of years, experiments involving conditioned alimentary reflexes were carried out on a dog in the same chamber, i.e., it was always receiving alimentary reinforcement in a definite setting. Then every feature pertaining to the given setting of the chamber will have a relation to the alimentary activity of the animal. Consequently, the entire setting—the stand, the walls, the lighting, the door, etc.—assumes an alimentary significance on the basis of the conditioned reflex principle. In spite of this "alimentary" effect of the setting, however, the animal usually does not reach the stage of conditioned salivary secretion during the intervals between conditioned stimuli; saliva ordinarily appears only at the moment of presentation of a specific conditioned stimulus, i.e., the triggering stimulus.

If, on the other hand, the animal is placed in an entirely different setting, e.g., an auditorium filled with an audience, and the same conditioned stimulus is presented, one that for several years has been reinforced with food and has always evoked conditioned secretion, we may, under these conditions, fail to observe conditioned secretion. It is known that this circumstance caused Pavlov much grief when, wishing to demonstrate conditioned reflexes in the auditorium of the Society of Russian Physicians, he did not obtain any conditioned reflex.

It is quite evident that in this case we are observing an interaction of situational and triggering afferentation and that an appropriate conditioned reflex can occur only upon a certain synthesis of the two. The distinguishing feature of situational afferentation consists in the preparation of the appropriate activity and not in the manifestation of this activity. This compels us to place this form of afferentation in a special category, since it creates the *pretriggering integration* of nervous processes (Anokhin, 1949a).

Triggering afferentation is thus the impetus, i.e., the stimulus, which leads to the external manifestation of some adaptive activity of the organism by exposing the structure of the excitation present in the central nervous system. For a rather long time in the evaluation of the reflex theory, the role of the situational afferentation, being obscured to a certain extent, had not been the object of special analysis.

In certain kinds of experiments we are able to distinguish between triggering and situational afferentation so that it is evident that these are two different forms of afferent influences on the organism. A classic example of this dissociation is the experiment with the dynamic stereotype performed in Pavlov's laboratory. As is known, the conditioned stimulus may fail to evoke its characteristic conditioned response and may give the response characteristic of another stimulus which had been applied repeatedly and stereotypically at the given place in the stereotype. For example, light may evoke the effect of a bell, and a bell the effect of light. In experiments of this kind, it is brought

out quite clearly that a conditioned response results from the situational afferentation and the triggering afferentation, and that the proportion of either may dynamically change in relation to the conditions of life.

It can be experimentally shown that this continuous organic synthesis of the two kinds of afferentation is accomplished with a definite participation of the frontal lobes of the cerebral cortex. Thus, in an animal with stabilized conditioned reflexes in the setting of a bilateral motor reaction, as described earlier in this chapter (see Shumilina, 1949, pp. 561–688), if the frontal lobes are extirpated, a very interesting phenomenon is observed. Such an animal will continuously move to the right and to the left feeder, performing pendulumlike movements on the platform. Instead of calm behavior in the intervals between conditioned stimuli, the animal exhibits a continuous reaction, as if the setting had begun to act like a triggering stimulus.

These examples reveal the importance of the influence exerted by the setting on the results of the triggering afferentation. As we shall see below, this importance becomes even greater when a new kind of afferentation, i.e., reverse afferentation, is added.

Reverse afferentation is of special interest to us at this time, since it alters our concepts concerning the mechanisms of organized behavior. As the analog of the “feedback” of cybernetics, this kind of afferentation naturally attracts great attention in physiology and medicine. A definite role of muscular afferent impulses, for example, had been suggested long ago by Charles Bell and by I. M. Sechenov (1863a).

However, these first indications, connected mainly with muscular afferentation, did not create a system of concepts about the role of the reverse afferentation depending on the results of the action. This is how one must explain the fact that the “reflex arc” continued to dominate even though it is inadequate for understanding behavioral acts on the basis of feedback information about the results of action.

The physiological role of reverse afferentation in the organization of complex activity was clearly established and formulated only in 1935 on the basis of an analysis of the physiological mechanisms of the compensation of disturbed functions, i.e., precisely on those examples in which the role of reverse afferentation is especially striking (Anokhin, 1935). At first this problem was studied only physiologically. For many years this concept had no points of contact with the field of investigation of mechanical systems, with the theory of automatic regulation. Only in recent years, in connection with the rapid growth of the feedback theory in cybernetics, has the theory of reverse afferentation in the organism begun to be confronted with this new realm of knowledge. This explains the presence of some insufficiently clear notions and differentiations of the corresponding concepts. I have in mind first of all the incorrect understanding of the role of proprioceptive, i.e., muscular, afferentation during the implementation of any behavioral act. The proprioceptive afferentation is often overestimated by foreign scientists (Cossa, 1955, p. 98; Wiener, 1948, 1950); this inaccuracy can also be found in Soviet literature at times.

What is the meaning of reverse afferentation? In any physiological process, or in a behavioral act aimed at the achievement of some adaptive result, i.e., one that is beneficial, reverse afferentation informs about these *results* of completed action, enabling the organism to evaluate the success of the action performed.

For example, on the basis of a number of objective processes of interaction of the organism and the environment, a person may intend to drink a cup of tea. He extends his arm toward the cup of tea and picks it up. Then the tactile excitation of the palm by the surface of the cup, and the thermal, weight and, finally, visual stimulation from the contact of the hand with the cup supply the information that the *result of the action corresponds to the original intention*. In the implementation of this action, however, the actual approach of the hand to the cup is continuously regulated by proprioceptive signalization which attests to the correct and appropriate distribution of the contracted muscles, to the degree of effort exerted by the hand, to the height of its position in relation to the intended aim, etc.

This form of afferentation is undoubtedly very important for the execution of the movement of the hand, but it cannot provide the central nervous system with any information about the *results* of the given action, since no position of the hand and, consequently, no proprioceptive afferentation may provide information on whether a cup or glass has been grasped. Unfortunately, this circumstance receives little consideration in the evaluation of reverse afferentation in the organism. Therefore, attempts to compare feedback in organisms and machines begin with proprioceptive signalization and sometimes end with it too.

Thus, the reverse afferentation arising during any motor act should be divided into two completely different categories : *movement-directing* and *resultative*. While the former afferentation is represented primarily by proprioceptive impulses from the muscles bringing about the movement, the latter is always complex and encompasses all the afferent signals indicating the actual result of the movement decided upon. We relate the concept of reverse afferentation to resultative afferentation, which always has an organizing influence on the patterning of the subsequent stages in behavior.

In fact, the subsequent motor acts of the organism will depend on the extent to which the reverse afferentation about the results of an action corresponds to the movement decided upon.

In the life of an organism, and especially in human life, there are no actions not resulting from preceding actions and not evoking subsequent actions. Therefore, it is natural that appropriate distinctions must be introduced into the actual concepts of reverse afferentation, depending on what type of reverse afferentation we are dealing with : whether it involves information about the results of some intermediate action or whether it provides information about the final implementation of an initial intention.

Thus, if a person who is at home resolves to make some purchase, a number of individual actions occur after the appearance of this intention : the person gets dressed, checks for money, opens the door, goes downstairs, crosses the street, opens the door to the store, selects the needed item, etc. The intention of buying something includes a number of intermediate stages which, in their sequential order, are dynamically patterned in the action acceptor. These stages could not be carried out if the person did not receive reverse afferentation about the successful completion of each of them.

For example, in putting on his overcoat he receives a definite number of afferent

signals from the completion of this action. Only after this does he begin to open the door, etc.

The whole category of resultative reverse afferentation must be subdivided into two separate types: *stage-by-stage* reverse afferentation, which corresponds to the implementation of a new goal of a behavioral act, and *sanctioning* reverse afferentation, which consolidates the most successful integration of efferent impulses and completes the logical functional behavioral act (e.g., "I am thirsty"—"I have quenched my thirst").

It is clear that the criterion for such a distribution of the reverse afferentation is the intention which is the result of afferent synthesis and which the person wants to implement at a certain time. Naturally, therefore, in relation to the scope of the tasks and to the nature of every action, we may have a greater or lesser number of stages in the implementation of an intention, and in individual cases the stage-by-stage afferentation can also be the sanctioning, or final, afferentation.

Actually, the purchase of something in a store is by no means the end of all the activity of a person, since it may be just a stage in the implementation of an even longer chain of actions, e.g., of a trip to another city. Since reverse afferentation is afferentation about the results of an action, it corresponds very closely to that information which, in automatically controlled machines, continuously arrives from the object being regulated over feedback channels.

In *The Human Use of Human Beings: Cybernetics and Society*, Wiener (1950) does not consider the physiological essence of reverse afferentation in the organism, and therefore all the analogies between phenomena in the organism and in the machine have a very schematic appearance.

THE PREDICTION AND EXAMINING OF THE RESULTS OF ACTION

The formulation of the purpose of action is a critical point in the patterning of the behavioral act. After this, there begins the formation of the intricate complex of efferent impulses which, in propagating over the working mechanisms, determine the achievement of a result that corresponds exactly to the intended purpose. It is important to emphasize that there occurs here a little-understood *transformation of the results of the afferent synthesis into a very appropriate distribution of efferent impulses over the working organs*.

In the present phase of the unfolding of the behavioral act, I shall analyze other highly important mechanisms which also form immediately after the moment of decision making. We already know that as soon as the purpose of action and the program of action are formed, immediately and simultaneously with the emergence of the impulses onto the effector mechanisms, a somewhat unusual complex of impulses is formed. Its physiological purpose is to evaluate that information which is yet to enter the central nervous system from future results of action. This is the true mechanism for the evaluation and comparison of the results with the intended purpose. We have long since had indications of the existence of this mechanism in conditioned reflex experiments. The first experiment that compelled us to think in this direction involved a change in the unconditioned reinforcement.

In a dog, conditioned reflexes were invariably reinforced with 20 g of bread crumbs for a number of years. From the standpoint of the usual concepts about the conditioned alimentary reaction, there should not be a great difference between reinforcement with bread crumbs and with meat, both being unconditioned stimuli.

The experiment, however, demonstrated that the substitution of meat for bread led to an accentuated orienting-investigative reaction and a temporary refusal to eat. Naturally, the question arose: what are the mechanisms of the activation of this orienting-investigative reaction? The conditioned stimulus was the usual one. The basic reaction of the animal (a secretory reaction and movement toward the feeder) remained the same. What, then, did the animal lack in order to react further in the usual way? What factors evoked such a vigorous orienting-investigative reaction in the animal?

An analysis of this problem has convinced us that the presentation of the conditioned stimulus contributes not only to the formation of a complex of efferent impulses, on the basis of which the entire conditioned alimentary reaction is patterned, but at the same time there is formed a complex of afferent impulses *which correspond in their parameters to the complex of characteristics and properties of the impending result*, i.e., the appearance, odor, and taste of the bread crumbs, etc. The hypothesis was advanced that, in order for the alimentary reaction of the animal to end in the usual way, it is necessary for the impulses resulting from the external characteristics of the bread crumbs to enter the central nervous system and then to correspond to the appropriate afferent complex established immediately after the appearance of the conditioned stimulus and before the start of the conditioned reaction.

However, the complex of impulses evoked by the external characteristics of meat differed from the expected complex, i.e., that complex evoked by the bread crumbs. Thus, there was a discordance between the prepared complex of afferent impulses and the actual complex which entered the central nervous system. At the time when these experiments were performed and published (Anokhin and Strezh, 1933), the idea of discordance was not currently used in physiology. Therefore, our explanation of this phenomenon followed a somewhat different course.

There were, in fact, no apparent possibilities of explaining such an effect from the appearance of the meat. For us, the only physiologically conceivable cause of this was the *inappropriateness* of the complex of afferent impulses evoked by the external characteristics of the meat. To what was the complex inappropriate?

We thus gradually arrived at the hypothesis of the presence of a special afferent mechanism which forms before the action occurs and the result appears, but has all the characteristics of these future results. We named this mechanism the *acceptor of the results of action*, i.e., a mechanism intended for the perception of information about the results obtained and for comparison of these results with the pattern of expected results which arose from the conditioned stimulus. Subsequent experiments were directed toward elucidating those concrete neurophysiological mechanisms which form the basis of the afferent system predicting the future results of the action.

Special experiments with recording of electroencephalographic changes were performed on human subjects. A system of three stimuli (siren, light, bell) was presented many times to the test subject for several hours every day. Of these three stimuli, only light produced desynchronization of the electrical activity of the cerebral cortex. This

served as the criterion of what was expected in the visual region of the cortex upon switching stimuli.

The second stage of this experiment was the substitution of a bell for the light and was carried out during and after the elaboration of the stereotype. When a bell was presented instead of the light, a quite remarkable phenomenon occurred : in spite of the absence of light, desynchronization appeared in the visual region of the cortex as if light had been presented and not a bell. How could this happen? Analysis of the electroencephalogram showed that the desynchronization had set in even a little before the bell was presented. It follows that the impulses had reached the visual region before it could be reached by the outside stimulus.

It has become evident that during the organization of a chain of stimuli connected with signaling principles, *the impulses propagate over the brain from point to point much more rapidly than the actual external stimuli sequentially appear*. The impulses anticipate the actual stimulus yet to act on the central nervous system and arrive at those regions of the cortex which they are to excite. This is how the concept of the adaptive role of the impulses which we named "anticipatory impulses" came to be.

The ability of neural substrate to organize a chain of processes resulting in anticipatory excitation is that fundamental, historically ancient basis on which both the conditioned reflex and any prediction of future phenomena develop. It has become evident that the orienting-investigative reaction of the animal to the substitution of meat for bread could similarly appear only because the impulses arising from the conditioned stimulus signalizing the consumption of bread form an afferent complex in those cortical cells where it is to appear only in the future, i.e., at the moment of presentation of the unconditioned stimulus. Meanwhile, the parameters of excitation evoked by meat have proved to not coincide with this "prepared excitation."

Since the principle of the development of anticipatory impulses is a consequence of the constitutional properties of neural tissue, it occurs wherever the necessity of a "precautionary reaction" (as Pavlov called it) arises. This principle actually "predicts" probable results of the action for a given decision and for a given purpose. At the same time the complex of impulses in which the characteristics of future results are encoded fully provides for the comparison of the results obtained with the expected results or with the sum total of the criteria of the particular situation. The mechanism of the apparatus of the action acceptor is universal, and it is doubtful whether any behavioral act, however simple, could be patterned without the preliminary formation of this apparatus.

We have attempted to study this mechanism of the prediction of future results under conditions of self-stimulation as well. Olds (1960) has developed a method by which a rat is enabled to stimulate itself by means of implanted electrodes in the hypothalamus. The experiment has shown that when the electrodes are located in a zone which forms a biologically positive state of the "pleasurable" type, the rat persistently and continuously stimulates itself, sometime pressing the lever up to fourteen thousand times per hour.

In order to reveal the presence of the action acceptor in this type of experiment, we have modified this procedure by inserting a switch into the circuit of the electrical

reinforcement. With this switch we were able to turn off the electric current at will and at a moment chosen in advance, thus eliminating the positive emotional effect of the stimulation. The results have shown that immediately after the current is turned off and the rat fails to receive the reinforcement, it begins to press the lever with increased force, trying by all means to regain the lost emotional excitation (Fig. 6.9).

Here, just as in the cases described above, we are dealing with the same principle. Any movement of the rat toward the lever and of the paw to the lever involves the formation of an action acceptor having some modified version of the future emotional state resulting from the stimulation of the brain. Having once failed to achieve this result, the rat tries to regain it by pressing the lever more frequently and more forcefully.

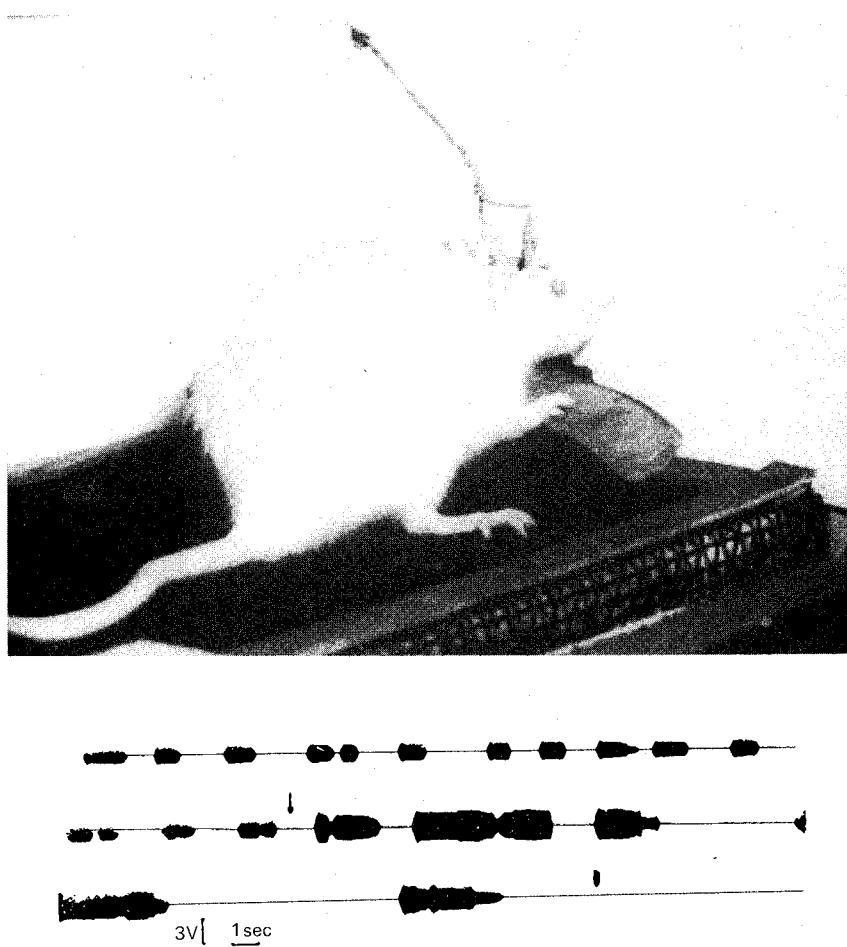


FIG. 6.9. Record of lever depressions performed by a rat under conditions of self-stimulation. The arrow indicates the point at which the stimulating current was switched off. The intensification and prolongation of the bursts of self-stimulation can be seen.

This experiment shows that at the very beginning of the elaboration of a motor act, there also invariably forms an acceptor of the results of the action. This alone can explain the fact that immediate compensatory adaptations occur if the information concerning the results does not coincide with those parameters originally encoded in the decision, the purpose, and the action acceptor. The sudden breaking of the circuit and the resulting failure of the rat to achieve a positive emotional state creates the conditions for discordance between the expected results (the positive emotional state) and the sudden absence of these results.

We were faced with the evident ability of the central nervous system to predict the results of future actions on the basis of the principle of anticipatory excitation.

We thus had to search for the more specific and delicate mechanisms responsible for this function of predicting the results and comparing the predicted parameters with the parameters of the actual results. For this purpose we chose the respiratory functional system because it offers particular advantages. It involves a considerably simplified afferent synthesis in comparison with even the simplest behavioral acts. Its physiological architecture has been well studied in a series of scientific investigations in our laboratories as well as in others. Of especial importance is that all of its components and parameters can be accurately measured quantitatively.

The special investigations of the respiratory center performed by V. A. Poliantsev, a collaborator in my laboratory, have shown that the respiratory center has the same kind of functional organization, i.e., it employs elements of the prediction of results.

It is quite evident that every efferent volley of nerve impulses leaving the respiratory center for the respiratory musculature exactly reflects the organism's need for efficiency of the respiratory system for a certain moment. As we have seen, the information concerning this need is based on all the indices of respiration (concentration of CO₂ and O₂ in the blood, afferentation from the vascular chemoreceptor regions, etc.). This constitutes the distinctive *afferent synthesis* of the respiratory functional system, determining the magnitude of the volley of efferent impulses. The magnitude of this volley is decisive for the force of contraction of the respiratory musculature and reflects the "decision" concerning the intake of air in precisely the given volume. It is always an accurate reflection of the results of the afferent synthesis.

When the lungs begin to take in air as a result of the contractions of the respiratory musculature, the alveoli consequently begin to expand, and afferent signals immediately arise from their mechanoreceptors. These signals *accurately reflect the amount of inhaled air prompted by the afferent synthesis*. The respiratory center, having sent a volley of efferent impulses to the respiratory musculature, *forms a mechanism for examining information about the future results, i.e., an acceptor of the results of the action*. This mechanism, receiving afferent impulses from the expanding lung and from the receptors of its alveoli, compares the *code of these impulses (equivalent to the volume)* with that of the *efferent command sent to the periphery*.

The quantitative characteristics of impulses at different levels of this functional system are easy to discover, so that it is possible to control the conditions of an experiment. Therefore, we performed an experiment using the same kind of *sudden replace-*

ment of the beneficial end effect as was discussed in the cases of the substitution of meat for bread crumbs and of the sudden elimination of the positive emotional stimulation (the "surprise" procedure, as it was called in my laboratory).

The experiment was conducted as follows. A special electronic device was set up on the path of propagation of the efferent impulses, i.e., on the phrenic nerve. It was the purpose of this electronic device to transform the volleys of efferent impulses of the respiratory center, *in which the need of the organism for a definite volume of air is encoded*, into the delivery of an adequate volume of air through an artificial-respiration pump. By means of this method of transformation of the natural "command" of the respiratory center, the artificial-respiration mechanism becomes *self-regulatory* in exact accordance with the organism's need for oxygen and for the elimination of carbon dioxide at any moment. In this setting the whole process of dynamic air intake is guided by the respiratory center, i.e., as under normal conditions.

Such a method of self-regulatory respiration permits the organism itself to select the regimen of respiratory activity most favorable to its oxidative processes. Naturally this can be of great practical importance in medicine.

At present, however, we are not interested in this aspect of the matter. For purposes of studying the characteristics of the action acceptor using the above-described electronic device, we were able to achieve *international discordance* between the natural command of the respiratory center sent by way of the phrenic nerve and the information about the results (amount of inhaled air) arriving in the form of equivalent volleys of impulses from the pulmonary alveoli. The discordance was effected as follows: by means of the appropriate electronic device we reduced the natural command represented by efferent impulses propagating down the phrenic nerve, so that instead of 500 ml of air, there were 300 ml actually delivered to the lung by the artificial-respiration device (Fig. 6.10).

Owing to this intervention, the respiratory center, which had dispatched (as a result of the afferent synthesis) efferent impulses capable of organizing the intake of the 500 ml of air needed, is informed by the lung that only 300 ml have been inhaled. How will the respiratory center react to this sudden discordance between the decision and its actual implementation on the periphery?

The experiment has shown that, upon being informed by the lung about the only partial carrying out of the command, the respiratory center immediately reacts to the *decrease in the impulses from the lung by a considerable increase in the efferent impulses*, which now corresponds to an intake of 700 ml rather than 500 ml of air (see Fig. 6.10).

Such a rapid and adequate reaction of the respiratory center to information from the periphery about a suddenly decreased result can occur *only if a complex (action acceptor) capable of checking the agreement of future results to the original decision is established in the respiratory center simultaneously with the dispatch of the efferent impulses to the periphery*.

Another important detail must be emphasized here: even though the control mechanism has been initially formed on the basis of efferent impulses, its control part must, however, accept and compare impulses of an entirely different nature, namely, afferent ones.

As the cyberneticists would say, the information about the results is furnished here

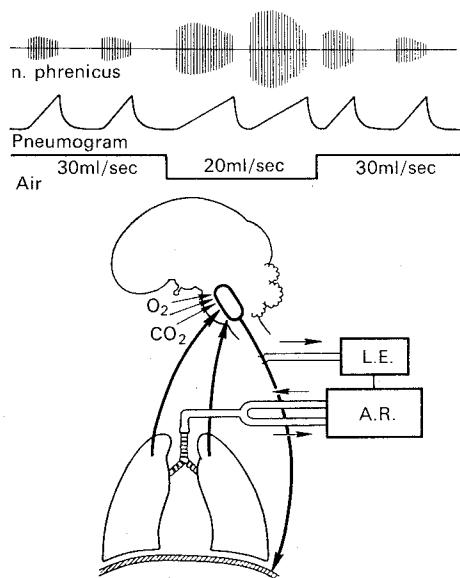


FIG. 6.10. Diagram of interruption of circulation of efferent respiratory impulses in the phrenic nerve and insertion of an electronic device transforming the respiratory volleys and triggering the artificial-respiration apparatus. The diagram shows the intensification of the volleys of the respiratory center following a "surprise" decrease of the amount of air admitted to the lung. A distinct intensification of the volleys issuing from the respiratory center can be seen. A.R., artificial-respiration apparatus; L.E., lead electrodes from the phrenic nerve and amplifier of biocurrents.

in a "different code," although, generally speaking, recoding is taking place continuously during the entire respiratory cycle (center, phrenic nerve, muscles, alveoli, afferent impulses from them, and action acceptor).

Other experiments involving the action acceptor have been performed, e.g., on man (Walter, 1964). These data indicate unequivocally that there exists some universal principle in the function of the brain which evidently applies to both behavioral and physiological acts at all levels of integration. This principle could be formulated as follows: *in all cases of the dispatch of impulses by the brain through the end neurons to the peripheral working mechanisms, simultaneously with the efferent command, some afferent model forms which is capable of anticipating the parameters of future results and of comparing this prediction at the end of the action with the parameters of the actual results.*

This principle is of special significance in complex human behavioral acts. Here the most diverse goals for behavior may be set—major and minor; nevertheless, the action acceptor, formed at the moment of decision making, subsequently determines the degree of coincidence between intention and result.

Predicting the results of action is a universal function of the brain, which prevents "mistakes" of all kinds, i.e., the implementation of actions that do not correspond to the goal set by the organism. The continuous comparison of the results of actions with the previously predicted parameters of the results is the only means for developing

harmonious behavior and avoiding errors.

Being the universal mechanism for all types of behavior and using anticipatory impulses for its patterning, the action acceptor may assume different forms, depending on external circumstances. These variants of the action acceptor, while maintaining the fundamental purpose of predicting results, may differ in their detailed mechanisms. Frequently this leads to the erroneous separation of some action acceptors into independent and seemingly new categories of adaptive activity.

Here I wish to point out the "extrapolational reflexes" reported in our literature. For example, birds (crows, chickens) may be shown food that is moving in a definite direction, and yet they see it only over a small segment. The food then disappears behind a screen and continues to move in the same direction.

The significance of the "extrapolational reflexes" is that the birds (especially crows) determine the direction of the motion of the food and *run to that end of the screen from behind which the food must appear*. Sometimes the birds run around the corner of the screen at the appropriate side and obtain the food. Thus, the essential feature of this is that, upon seeing the moving object and determining the direction of its motion, the birds "extrapolate" the object to its subsequent location of the feeder. This form of prediction is in accord with the general principle of the prediction of future results.

For the animal, several observable locations of a feeder moving in a definite direction represent the material for afferent synthesis, after which a decision about movement in a certain direction is made and the action acceptor forms with afferent parameters according to the future location of the feeder. Just as in all other cases of the operation of the action acceptor, it is here a mechanism of comparison and, consequently, predicts the possible results of the observed movement of the object (Fig. 6.11).

Another example involves the neurophysiological structure of speech. Similar analysis is needed here. We must remember that the decision to utter a sentence or to

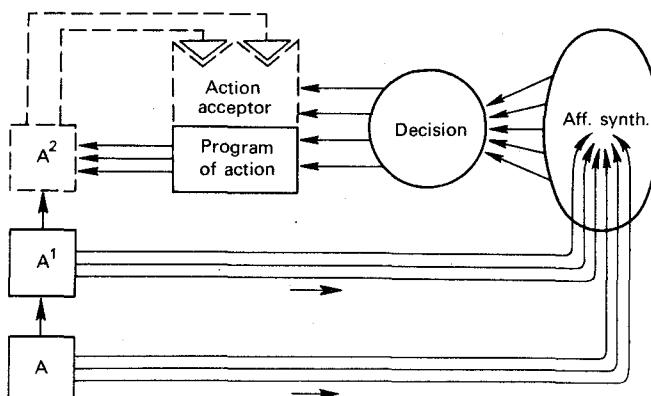


FIG. 6.11. One of the types of function of the action acceptor. The example of the movement of an animal in the direction of a hidden moving object. A, A¹, A², different locations of the moving food. The locations A and A¹ were observed by the animal and served as a basis for the afferent synthesis. The programs of action and the action acceptor were patterned according to the predicted future location of the food behind a screen. Explanations in text.

express an opinion is also formed following the stage of afferent synthesis. It is important to keep in mind that the decision to express an opinion is formed, just as in all other cases, by an action acceptor having all the afferent characteristics of the *future* sentence.

Consequently, there is not, as is usually visualized, a patterning of each word individually; an action acceptor is patterned for each sentence with a sequential arrangement of words with sometimes even anticipatory meaning, which is a reliable indication of the patterning of an action acceptor for an entire system of meaning (Fig. 6.12).

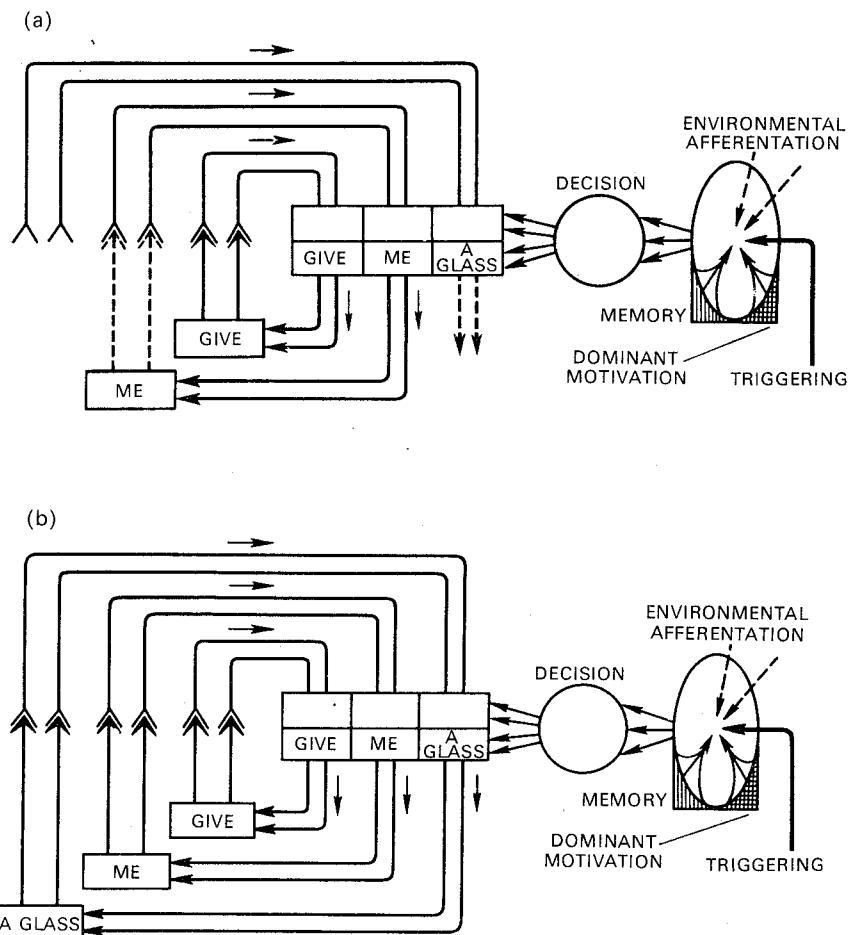


FIG. 6.12. Diagram of the formation of a sentence with participation of the action acceptor.

(a) The moment when the decision to utter the sentence arose and the action acceptor for each word of the sentence has already been patterned.

(b) The completion of the sentence is accompanied by the appearance of reverse afferentation (feedback) of an auditory nature which is stabilized in contact and in the comparison of the reverse afferentation with the parameters of the action acceptor.

The figure shows that after the decision to utter a sentence (e.g., "Hand me a glass."), the action acceptor is patterned for each phoneme. And only the subsequent pronunciation of the words of the sentence with stage-by-stage control in the form of reverse afferentation eliminates the possibility of an error in the expression of the whole idea formed during the stage of decision. One cannot conceive of any other possibility of uttering a long sentence without a displacement of words or even, on the contrary, with a variation of their arrangement but without a loss of meaning, without the formation of an action acceptor.

This becomes especially evident when the word pronounced first has a meaning that depends directly on a word pronounced later. For example, in the English sentence "It is a book," the article "a" can be used only when the *indefinite nature* of the book was known before the start of the pronunciation of the sentence.

Dozens of examples can be given which convincingly show that the prediction of the afferent parameters of each word of a future sentence is already represented by the action acceptor. The actual utterance of the sentence is examined (i.e., compared) stage by stage by the successively organized action acceptor. The necessity of the concept concerning the action acceptor is further dictated by the fact that it enables us to see in different forms of behavior those common features which radically alter our interpretation of the very mechanisms and nature of the behavioral acts in animals at different stages of evolution.

If we accept as a basic assumption that *an action acceptor, as a mechanism for examining the results of the action and comparing them with the intended goal*, is absolutely essential for all animals, many complex acts of animals will no longer appear to be paradoxical.

I wish to point here to the very interesting investigations by Pastore (1954a, 1954b, 1955) in which he demonstrated that a canary quite freely piles boxes on top of each other for the purpose of reaching food. Only with the participation of the action acceptor can such a procedure be accomplished. And yet not so long ago it was customary to assume that such goal-directed activity is the prerogative of the highest animals, namely, the anthropoid apes.

In concluding this section, I would like to note that the necessity for the above-discussed functions of the prediction of the results of action is felt already by many contemporary physiologists and especially cyberneticists.

There are already many statements by physiologists concerning the necessity for assuming such a function in the activity of the brain. Bishop writes: "As a stream of activity, however initiated, flows across the nervous system, its course must be capable of redirection by comparison of present stimulus with past experience. Similarly, the *anticipation* of the result of central activity so determined must be compared again with the records of past final results of previous similar activity" (Bishop, 1960, pp. 141-142).

We may also cite the work of Bullock (1961), who arrives at the inevitability of assuming some kind of mechanism that would be able to predict the results of a future action.

This tendency to recognize the inevitability of prediction has become particularly evident among cyberneticists. Minsky (1963), one of the closest collaborators of

Norbert Wiener, rates the theory of the action acceptor as "the central point for the understanding of the function of the brain."

An outstanding cyberneticist, Maron (1962, p. S179), writes :

But we would argue that this interpretation implies that the brain is not merely a mechanism for maintenance of homeostasis, but that it is a mechanism for anticipating the future. It must predict what outputs are appropriate and how its responses will influence future inputs. This means that the essence of brain function is prediction and that its predictions are not only for the next moment, but for more distant futures. The brain is a mechanism which constantly answers for us the key questions : "What shall I expect?", "What shall I do?" Given this characterization of brain function, any theory of brain organization which cannot account for the predictive nature of its behavior must be rejected, and no system which is unable to predict can be properly considered intelligent.

This conclusion is undoubtedly of great practical significance. As we have seen, any fractional function of the organism proves to be possible only if, at the moment of patterning of the decision and the command to act, the mechanism of prediction is immediately patterned, too. It is quite evident that machines capable of "looking into the future" at every stage of their action would be preferred to the present ones.

There are further similar indications. Maron (1962, p. S179) postulates that "the principal ingredient in these (and other) criteria of intelligent behavior is the notion of prediction." Moreover, he claims that he has designed a model consisting of neuronlike elements and capable of making predictions on the basis of the calculus of probability.

Thus, the function of predicting results is universal and is found in any activity of an organism, both in the behavior and in the regulatory processes of the body. Its further study must include a neurophysiological analysis.

A HYPOTHESIS CONCERNING THE POSSIBLE NEUROPHYSIOLOGICAL SUBSTRATE OF THE ACTION ACCEPTOR

Of further interest was the more detailed investigation of the neurophysiological nature of the mechanism for the prediction of the results of impending action. A comparison and analysis of the results of all the previous investigations of our laboratory have clearly indicated that an action acceptor has all the afferent parameters of previously obtained results. Its formation must proceed in such a way that the complex of efferent impulses, which evokes a quite specific action at the periphery, consequently determines results with specific parameters as well. Thus, the parameters of the impending results depend entirely upon the integrative characteristics of the efferent impulses.

As can be seen, the secret of the formation of the action acceptor as a mechanism for the prediction of results had to be sought both in the structure of the commanding, i.e., efferent, impulses arising after the decision to act and in the interaction of these

impulses with the processes of the formation of the action acceptor. A suitable model was needed so that it would be possible to compare in a considerably simplified form the efferent impulses (command) with the reverse impulses (feedback) signaling about the achieved results.

As could be seen from the preceding presentation, the functional system of the respiratory act was very well suited for solving the problem before us. Both the command (the impulses in the phrenic nerve) and the reverse afferentation (the impulses from the alveoli over the vagus nerve) may be said to lie close at hand, i.e., they are accessible to experimental investigation. On the basis of the temporal interrelations in the respiratory center it could be assumed that the mechanism for predicting results, *patterned at the moment of the emergence of the command impulses to the periphery, should be in a state of expectation for exactly as much time as it takes the efferent impulses to contract the diaphragm, expand the thorax, stretch the alveoli, and, finally, form the reverse afferent signalization that passes over the vagus nerve to the respiratory center.*

With 15 respirations per min, this period of time must equal approximately 1 sec. Therefore, the action acceptor must already be prepared to receive the reverse afferentation from the alveoli during at least 700–800 msec.

Several questions arise :

1. How can the afferent impulses, which are essentially an integrated model of the action, initiate the formation of the action acceptor?
2. What is the physiological state of this mechanism during the 800 msec?
3. What is the physiological nature and mechanism of the actual encounter of the impulses of this previously established apparatus with the impulses arriving later as reverse afferentation?

The actual nature of the physiological interrelations in the functional system of respiration is such that these three mechanisms are completely indispensable and must actually exist. It was, however, necessary to establish how these physiological mechanisms are implemented. At the very beginning of the work, we naturally had to accept some hypothesis that would agree with the modern advances in neurophysiology and at the same time satisfactorily explain the observed physiological interactions within the functional system. In answering the first of these questions, we first considered it to be inevitable that the formation of the action acceptor during the dispatch of the efferent impulses to the periphery can be accomplished only if *the action acceptor contains an exact copy of the command to act sent by the efferent impulses to the periphery.*

In fact, phylogenetically, the action acceptor can form only on the basis of the interaction of the efferent complex of action and the afferent projection of the results in the central nervous system. Only under this condition can a mechanism subsequently be organized, by means of which the formation (immediately after decision making) of the central complex of efferent impulses involves the projectional afferent apparatuses that correspond to the parameters of future results.

In which stage and over which structural pathway can the efferent complex present "copies" of its impulses to the action acceptor being formed?

Upon comparison of the efferent complex with the composition of the act, we concluded that the most exact correspondence between the two occurs when the

efferent impulses have already emerged onto the axons of the final pathway. These impulses, no longer influenced by changes caused by the complex processes of afferent synthesis, constitute an exact pattern of impulses equivalent to the future action and, consequently, to the future results.

Thus, we constructed a logical model of the inevitable interaction of the efferent stage and the afferent stage in the formation of the action acceptor (Fig. 6.13).

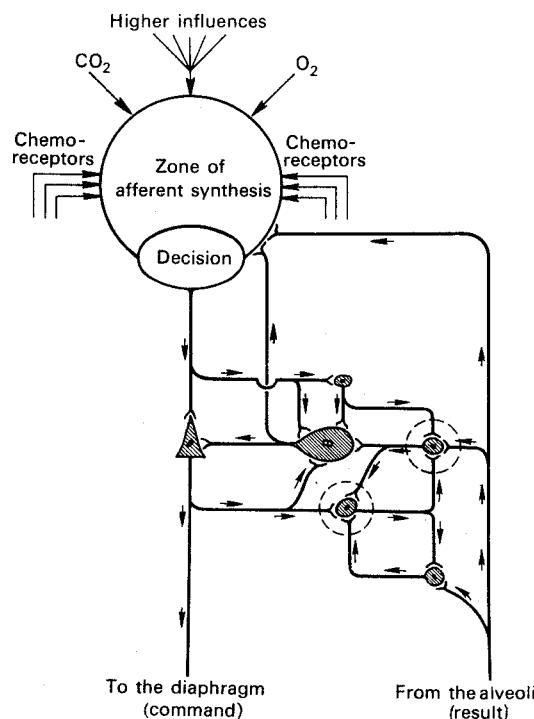


FIG. 6.13. General diagram of the spread of collateral excitations of a respiratory axon to internuncial neurons which constitute a zone connected with a Renshaw cell (at center). Depicted are the zone of afferent synthesis and the decision concerning the intake of a definite amount of air by the lungs. The diagram shows the overall relation between the impulses of command and the afferent impulses from the lung.

Are there any structural elements and physiological processes able to ensure this delivery of "copies" of the efferent impulses into the zone of formation of the action acceptor? Naturally our attention focused on the axon collaterals of the neuron, which occur with amazing consistency in all those neural formations which serve as final pathways and are located in the zone of formation of the volleys of efferent impulses.

By their very essence, these collaterals must conduct an exact copy of the basic efferent command. Consequently, the number of such collaterals in one axon can serve

as an indication of the number of copies of the efferent command sent out over these collaterals.

If we look at the depiction of the axon collaterals given in the classic publications of Ramón y Cajal, the inadequacy of the general point of view concerning the role of these recurrent collaterals becomes evident. According to this point of view, they basically perform self-inhibitory functions: the collaterals are distributed over the internuncial Renshaw cells, which in their turn are capable of inhibiting the motoneuron. By examining the distribution of these collaterals, one sees that this explanation of the role of the collaterals alone is entirely inadequate.

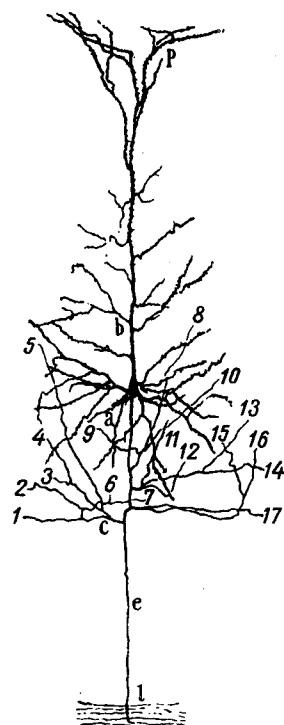


FIG. 6.14. Example of a cortical neuron. Along with the dendritic ramifications of the pyramidal cell, there are abundant ramifications from the axon. The total number of such ramifications in this preparation is 17. Explanations in text. a, basilar protoplasmic extensions; b, dendritic trunk and its branches; c, collaterals of the axis-cylinder; e, long axis-cylinder; 1, white substance. From Ramón y Cajal (1909; see Ramón y Cajal, 1952, p. 60).

In fact, in the neuron presented in Fig. 6.14, taken from Ramón y Cajal (1909, see Ramón y Cajal, 1952, p. 60), there are 17 collaterals from the axon, which are aimed in various directions. Why such an abundance of recurrent collaterals, one may ask, if just two or three inhibitory synapses can exert the necessary inhibitory effect on a neuron?

Furthermore, we cannot fail to notice the paradoxical fact revealed by a simple calculation of the temporal relations of the propagation of impulses over these collaterals. If one assumes that the collaterals from the axon are necessary for inhibiting the given axon, or even neighboring axons, the physiological significance of such a reverse inhibitory effect on the axon *at the height of its activity and even before the achievement of the end effect* is completely unclear. If the collaterals were to become involved in the generative function of the nerve cell, conditions for the chaotic arrival of impulses to the working organ could arise. Though the axon collaterals had been discussed in great detail, even before Ramón y Cajal, by Lenhossék (1895) and by a number of other investigators, their functional significance remained unclear. In addition, investigations of the collaterals in the pyramidal neurons, performed by my collaborator I. Chernyshevskaya, show that these collaterals may end at such a distance from the body of the neuron that a reverse effect of these collaterals on the same neuron is out of the question (Fig. 6.15).

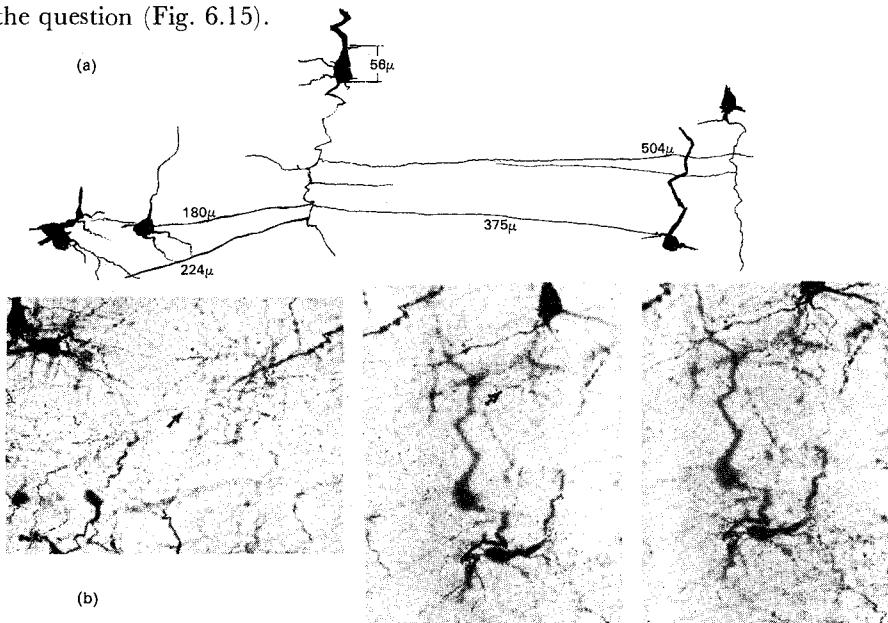


FIG. 6.15 Schematic drawing (a) and composite photomicrograph (b) of some cells in the semimotor region of the cerebral cortex. Very large axon collaterals are shown which, as indicated in the drawing, occur at such a distance from the body of the neuron that a feedback effect of these collaterals on the same neuron appears to us to be ruled out. One such axon collateral is traced by arrows on the photomicrograph.

Thus, the actual anatomical arrangement of the axon collaterals speaks against such a simplified interpretation of their physiological significance. Moreover, the observations of Lorente de Nò (1934) and those of Eccles (1964) have shown that the axon collaterals can spread not only toward their own neurons, but that they can also enter into very unusual contacts with the basket cells of the cerebral cortex (Fig. 6.16). These contacts serve as a direct indication that the abundant axon collaterals have a

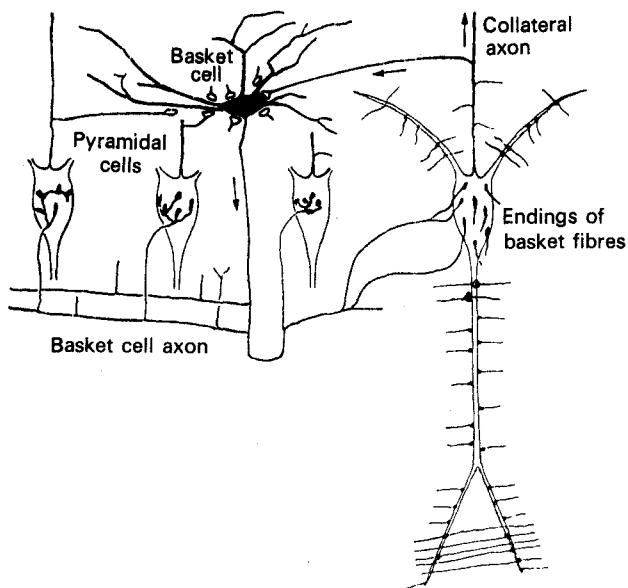


FIG. 6.16. This diagram shows that the collateral ramifications from an axon are aimed at a basket cell which distributes its excitations via axosomatic synapses to a number of other pyramidal cells of the cerebral cortex. From Lorente de Nô (1934, p. 168) and Eccles (1964, p. 212).

special but as yet unknown integrating role in the general cortical activity.

What, after all, could then be their function if one takes into consideration the indisputable fact that they are sending out an exact copy of the impulses generated by the neuron itself?

Most plausible is the assumption that these collaterals excite the complexes of satellite cells which form the peculiar formations that have been repeatedly described as closed, self-reexciting chains since the outstanding investigations of Lorente de Nô (see Fig. 4.5).

However, this hypothesis assumes that when impulses emerge from a pyramidal neuron of the cortex (or from a motoneuron of the medulla oblongata in the case of the respiratory center), they must activate other cells which naturally begin their discharges later than they started in the initiating point of this system, i.e., in the pyramidal neuron. Modern microelectrode experiments demonstrate the possibility of such delayed discharges in regions adjacent to the initially excited neurons.

While studying individual cells of the respiratory center by the microelectrode technique, von Baumgarten and Kanzow (1958) were confronted by the paradoxical fact that some cells of the respiratory center discharge after the emergence of impulses onto the descending spinal axon. From the point of view of the general dynamics of the activity of the respiratory center, such delayed volleys of impulses, appearing after several dozen milliseconds, can be explained only as being impulses arising from the axon collaterals. Von Baumgarten and Kanzow arrived at precisely this interpretation of their data, assuming that these delayed impulses are generated by the Renshaw cells.

In our laboratory, Iu. Fel'dsherov has performed special experiments, taking into consideration all the temporal relations between the cells of the respiratory center. The methodological setup of the experiment allowed the determination of the temporal relations of any single recorded cell of the respiratory center to the efferent volley having emerged from the respiratory center onto the phrenic nerve.

For this purpose, one of the electrodes was placed in a permanent location on the descending pathway conducting efferent impulses to the diaphragm, while the location of the other microelectrode continually changed, thus recording the discharges of different cells of the respiratory center. For correlation with the actual respiratory cycle, the pneumogram was recorded. Fel'dsherov has demonstrated the existence of a great variety of neural elements in the respiratory center. Many of them discharge at different intervals, starting with the emergence of efferent impulses from the medulla oblongata, and all of them have an individual pattern. The above-described observations justify the conclusion that, upon the emergence of impulses from a motoneuron of the respiratory center onto an axon over the collaterals of the same axon, the same impulses are directed to the adjacent cells and cause their excitation, which can be of varying duration.

Naturally, the frequency of impulses cannot be completely identical because of the varying rates of propagation. While in some cases several neurons are involved in the total discharge, in other cases the discharge originates from an individual neuron that has received impulses via one collateral.

Recently, Kuznetsov and Nadvodniuk (1965), while investigating the discharges of various cortical neurons during antidromic stimulation of the pyramidal tract, discovered that the discharges of the cortical neurons, during this stimulation, encompass much more extensive regions of the cerebral cortex than would be expected from the generally held assumption that the collaterals of an axon conduct impulses only to the body of the same neuron.

In connection with this, it is necessary to call attention again to the work of Lorente de Nó (1934) and Eccles (1964), who had demonstrated the propagation of impulses from the axon collaterals to the cortical basket cells and back again to the axon (see Fig. 6.16). The basket cell receives impulses from the axon collaterals of the pyramidal cells of the cerebral cortex, and at the same time its axon collaterals terminate in synapses predominantly on the body of the pyramidal neurons.

The concept that the recurrent axon collaterals are aimed via an internuncial neuron at the same axon had been considered so sound that little attention was paid to the physiological significance of the extensive propagation of collateral impulses away from the axon, even to a considerable distance from it. Meanwhile, the different temporal relations between the impulses arising at the collaterals, the length of these collaterals, and their extraordinary abundance lead us to think that such a wide dispersion of "copies" cannot be organized solely for the purpose of inhibiting the activity of the neuron. Such a concept is not very likely for the further reason that the impulses propagating along the collaterals reach the region of the internuncial neurons considerably sooner than discharges in the neuron itself cease altogether.

All the data and considerations presented above compel us to assume that the entire

ramified system of axon collaterals constitutes a special substrate which delivers models of the volleys of efferent impulses (in fact, exact copies of commands) to various zones of the cerebral cortex and to subcortical apparatuses. And since it is impossible to create a model of future results without this important component, it is most likely that the collateral impulses enter into contact with those neural elements which receive impulses from the results of the action.

The only condition for the feasibility of such an encounter is the retention, for a definite period of time, in the central nervous system of an exact copy of the pattern of impulses implementing the action up to the moment when information about the results of the action reaches the central nervous system.

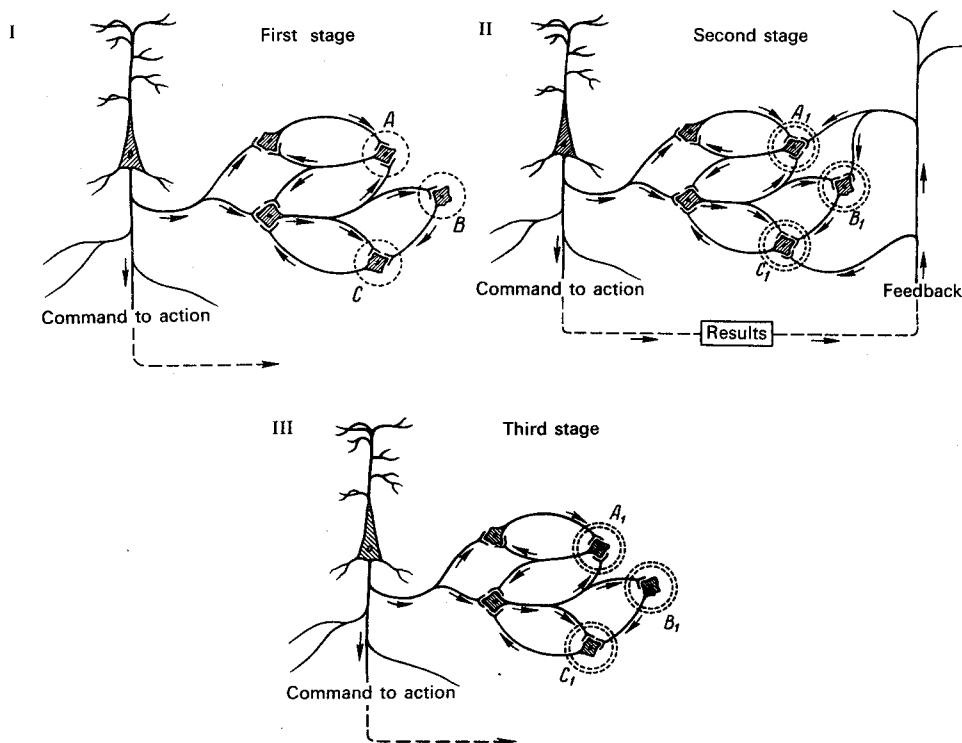


FIG. 6.17. Diagram of three stages in the patterning of the apparatus of prediction in the respiratory center. Only an efferent cell of the respiratory center has been used. The stage of afferent synthesis and the stage of decision making, which occur earlier, have been eliminated in these figures.

I. The impulse entering the axon collateral interacts with the interneuronal elements and forms several closed self-reexciting chains involving cells A, B, C. Thus, the nerve cells encircled by dotted lines remain in a state of stable excitation for some time and include a "copy" of the command to act.

II. The same neuron is shown up to the moment the results are obtained (intake of air by the lung). Signalization from the results interacts with the cells excited previously and patterns some new states A₁, B₁, and C₁.

III. By now the impulses arriving via an axon collateral are sufficient to pattern the afferent apparatus A₁B₁C₁, and when information from the results arrives now, it will interact with this newly formed afferent apparatus of prediction.

The closed, self-reexciting chains described by Lorente de Nò constitute the well-known mechanism for the short-term retention of excitation in the central nervous system. It may be assumed that the countless number of internuncial elements in the cerebral cortex constitute the substrate which for a brief period retains, in the form of dynamic circulation, the copies of the efferent impulses sent to the periphery (Fig. 6.17). These interrelations may be visualized in the diagram, which reflects the encounter of the impulses from the terminal neurons with the afferent impulses from the result of the action. It also explains the properties of the action acceptor, which is subsequently patterned on the basis of this encounter.

To clarify our concept, the figure shows three stages of the interrelation of the impulses entering the axon collateral and the impulses engendered by the results of an action.

Stage I represents a fragment of an action performed for the first time, i.e., conditions for the patterning of an action acceptor did not previously exist. The figure shows that after a few milliseconds and before the completion of the action, a number of foci of circulating impulses are created (actually, there is probably a multitude of them) in the vicinity of the efferent neuron. When an action has been performed at the periphery, the afferent information about the results of this action, upon reaching the central nervous system, interacts with these circulating impulses. As a result of this interaction, a certain complex formation is established which retains the properties of the heretofore obtained results (II). It constitutes an organic association of these impulses and now, with the subsequent patterning of an efferent complex of an act and its emergence onto the efferent pathways, the impulses entering the axon perfectly duplicate the entire complex formed earlier as a result of the integration of the efferent impulses with the impulses of the reverse afferentation. This afferent formation is, in essence, the action acceptor. It is a complete mechanism for the prediction of the results, capable of comparing the "prediction," i.e., the decision and purpose of action, with the actual results of an action (III).

The hypothesis concerning the neurophysiological bases for the patterning of the prediction of results proposed above is for us a most suitable model, on the one hand agreeing with the presently available information about the physiological properties and function of the action acceptor and, on the other hand, helping to raise new problems for study. At present this hypothesis objectively promotes the scientific explanation of so important a function of the brain as the prediction of results yet to be achieved and their subsequent comparison with the results actually accomplished. By providing for the purposeful behavior of animals and man, this function of comparison is the highest function of the integrative activity of the brain.

Now that we have analyzed the whole cycle of patterning of the behavioral act, we realize that all its key mechanisms constitute a physiological unit. We cannot *separately* examine any one of these mechanisms without understanding the entire architecture of the behavioral act and, most importantly, *the specific role of the considered mechanism in the appearance of the processes in the functional system*. Herein lies the methodological role of our study of the physiological architecture of the behavioral act, which is based on the strictly determined mechanism of the functional system (Fig. 6.18).

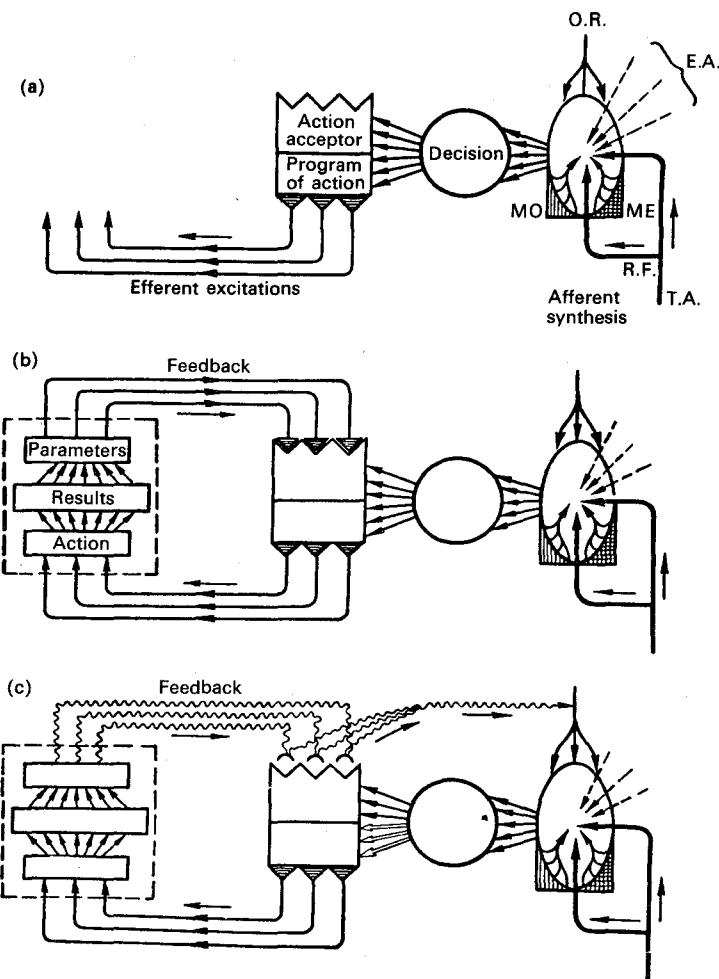


FIG. 6.18. Schematic diagram of a model of a behavioral act represented in three stages of development.

(a) For an understanding of the dynamics of nonlinear processes of the functional system, that stage is shown in which the afferent synthesis (AS) has been completed and the formation of the goal and, after that, of the action acceptor has taken place. The efferent impulses at this stage have only emerged onto the afferent peripheral pathways. At this stage, however, no useful adaptive effect has been achieved.

(b) Further development of the processes in the system in connection with which a final result corresponding to the original goal of the action was obtained. The parameters from the results of the action form a reverse afferentation (feedback) directed toward the central nervous system where it establishes contact with the action acceptor.

(c) An example of discordance between the feedback information and the action acceptor. This discordance immediately activates an orienting-investigative reaction which facilitates the formation of a new program of action. O.R., orienting reaction; E.A., environmental afferentation; T.A., triggering afferentation; R.F., collaterals of the reticular formation; MO, motivation; ME, memory; see text for explanations. The designations used in part (a) apply to parts (b) and (c) as well.

There are a number of advantages for research in the neurophysiology of the behavioral act if it is based on the physiological architecture presented above, which in this case serves as a distinctive main goal for such analytical investigations.

In fact, from the point of view of the functional system, there is no such thing as a *general afferent function* or *general afferent processes*. As we have seen, the functional system serves different purposes in the system of the behavioral act, and this substantially affects its characteristics as well as the selection of methodological conditions for its investigation.

A visual stimulus is a *triggering stimulus*, but it may also be a component of a resultative afferent integral aimed at the central nervous system *as a part of reverse afferentation*. The role of these two similar afferent volleys of impulses is entirely different. Their fate in the central nervous system proves to be even more specific.

In triggering afferentation the afferent impulses establish organic contact with the other components of the afferent synthesis, and we must turn our attention toward the mechanisms of interaction of these impulses which converge upon definite cortical and subcortical neurons.

Our evaluation of this interaction must be carried out with regard to the patterning of the next stage of the general architecture, the decision making, since the actual convergence of afferent impulses upon the neurons serves the formation of a correctly developed efferent complex of impulses ("program of action") and consequently leads to the correct effect.

Entirely different are the fate and interactions in the central nervous system awaiting the reverse afferentation about the results of an action. It enters into a kind of interrelation with the already formed afferent mechanism of prediction, which can be called a *comparison of parameters* based on some still unknown dynamic trigger. With the development of even a slight discordance, the focal point of the entire activity of the brain is shifted toward the subcortical activations and the active selection of new complexes of afferent impulses (see Fig. 6.18).

For me and my collaborators, the physiological architecture of the behavioral act presented above has for a long time been a unique "determinant" of the integrated nature of any nervous process. This approach opens endless possibilities for new experimental approaches and new interpretations of the research results thus obtained.

CHAPTER 7

Conditioned (Internal) Inhibition: Statement of the Problem and Approaches to Its Solution

THERE is no doubt that among the basic problems in Pavlov's theory of higher nervous activity, the problem of internal inhibition is of primary importance, especially in any field related to the physiology of higher nervous activity.

This idea remains in effect for the theoretical aspects of investigation and even more so for the practical application of cortical inhibition by physicians, educators, etc. For example, the numerous pathological disorders of cortical activity may exist for one reason only: the correct relations between excitation and inhibition are disturbed. The extensive field of neurotic diseases is, as we know, always regarded as a special result of the collision of the inhibitory and excitatory processes. This pertains especially to those pathological disorders caused by the formation of foci of "persistent" inhibition. At the same time, internal inhibition also plays a decisive role in the development of the most specific forms of adaptive behavior in both animals and man. Every differentiated act of behavior involves processes of internal inhibition.

In short, internal inhibition is an integrated part of any acquired activity and, together with excitation, forms the basis for the "mosaic" pattern of cortical points which characterizes the active state of the cerebral cortex. It then follows that inhibition and excitation, as two aspects of a single nervous process, determine by their balanced interaction the success of the adaptive activity.

However, in spite of the importance of the investigation of these two processes and especially of their interactions, we cannot presently claim to know even approximately the mechanisms of these interactions. Through the investigations of recent years we are able to visualize rather clearly the nature of the excitatory processes occurring in the nerve cell. In regard to inhibition, however, we are just beginning to penetrate into the cellular processes. Particular credit for this should be given to the most recent investigations of Eccles (1964). The lack of knowledge concerning the overall physiology of the inhibitory process could not fail to influence the idea that internal inhibition is a special form of individually acquired inhibition, or *conditioned inhibition* (as Pavlov called it).

This discrepancy between the importance of internal inhibition in medical problems and the level of our understanding of its mechanisms has had a marked effect on the progress of knowledge in the pathogenesis of a number of neurogenic diseases.

The lack of specific data about the physiological mechanisms of internal inhibition

and, what is especially important, the absence of definite methods of obtaining these data lead to a considerable limitation in the study of this problem. For this reason, some investigators simplify the physiological meaning of the inhibitory process, ascribing to it properties which it is incapable of possessing. Other investigators transform the relative concepts and terminology of this problem, most of which are of a *phenomenological nature*, into something absolute and certain. By doing this, they shift the concrete physiological problem of inhibition to purely speculative, verbal operations. These shortcomings in the study of internal inhibition considerably limit the success in solving other problems of higher nervous activity.

This general characterization of the problem concerning the physiological mechanisms of internal inhibition emphasizes the need for a profound and comprehensive analysis to enable the investigator to clearly see both the *answered and unanswered* questions regarding this crucial problem. These questions will be the subject of comprehensive discussion in the subsequent chapters of this book.

Such a comprehensive analysis of the overall problem of cortical inhibition would hardly be justified if it were not logically concluded by appropriate *constructive propositions*. This is all the more essential since there are as yet no clear-cut guidelines as to how or in what directions the study of cortical inhibition as a distinct physiological phenomenon is to develop.

In addition to the above, we had other reasons for a thorough analysis of the basic points of Pavlov's theory of cortical inhibition. Some of these reasons are:

1. As is known, Pavlov always regarded the problem of the interrelation of excitation and inhibition to be still unresolved. He commented on this many times, and often, with the adherence to principle that is characteristic of a great scientist, he expressed these statements very emphatically. Since there has been an attempt to dogmatize the existing state of the problem of cortical inhibition for quite a long time, I consider it most appropriate to quote at least some of Pavlov's conclusions.

For example, in a special analysis of the problem of internal inhibition, he said: "We must admit that at the present time we know altogether nothing of the real nature of internal inhibition" (Pavlov, 1923a, see Pavlov, 1967, p. 211). ". . . we do not know exactly the nature of either of these [excitatory and inhibitory] processes. We have only hypotheses concerning them, which have not led to definite results" (Pavlov, 1924, see Pavlov, 1967, p. 331). "Notwithstanding the mass of pertinent material . . . the relation between excitation and inhibition remains a question as yet unsolved" (Pavlov, 1933b, see Pavlov, 1963, p. 109).

Though these citations do not completely characterize Pavlov's attitude toward the problem of cortical inhibition, it is evident that he regarded it to be still unclarified in many respects and thus called upon his students and collaborators to make every effort to solve it. Naturally, at the present time any attempt to develop a working hypothesis on the mechanisms of the interaction of excitation and inhibition in the cerebral cortex is most necessary and justified. It is essential that this hypothesis utilize the very abundant data of Pavlov and his students, as well as the modern advances in the study of the physiology of the brain.

In recent years exceptionally important and interesting data have been obtained,

compelling us to reevaluate some as yet incomprehensible phenomena of higher nervous activity. Just what is it that remains *unsolved* in the problem of the interaction of excitation and inhibition? What did Pavlov consider to be the "accursed question" in the physiological essence of these processes? It seems beyond doubt that the interpretation of Pavlov's comments in regard to this vital problem and a precise formulation of the physiological meaning of the "accursed question" will aid us considerably in developing the most suitable working hypothesis.

2. The second reason necessitating a comprehensive analysis of the problem of cortical inhibition concerns its significance for general medical and educational practice. The extensive dissemination of the theory of higher nervous activity both in the U.S.S.R. and abroad has considerably increased the responsibility of physiologists to solve a number of problems of this theory, especially the problem of cortical inhibition. While a few years ago the problem of the interaction of excitation and inhibition could, to some extent, be considered a theoretical one, primarily the concern of physiological laboratories, this problem has now become important for clinical medicine in differential diagnosis, the characterization of the type of higher nervous activity, as a prerequisite for the choice of therapeutic action, etc. In short, the problems of cortical inhibition have become problems of *extensive and concrete practical activity*. All this imposes on us the need for accurately determining the boundary between the resolved and unresolved questions in the problem of cortical inhibition and of focusing accordingly the attention of clinicians and physiologists on the most rapid solution of the unresolved questions.

3. A number of foreign scientists skeptically regard some hypotheses of the physiology of higher nervous activity. While not denying the great significance of the conditioned reflex as a factor in the highest adaptation of animals and man to their environment, some foreign investigators do not agree with those interpretations of the mechanisms of higher nervous activity which are universally accepted in the U.S.S.R. This pertains especially to the mechanisms of internal inhibition.

Resolving and comprehensively explaining the questions related to the problem of internal inhibition will ensure further progress in this important problem. On the other hand, to move away from these questions would be to fail to provide for the creative development of one of the most crucial problems in the theory of higher nervous activity.

4. The final motivation for a detailed analysis of the problem of cortical inhibition involves the historical traditions of Russian physiology concerning this problem. Science is indebted to the Russian mind for the discovery of inhibition as a function of the central nervous system (I. M. Sechenov) and for the interpretation of the functional nature of the inhibitory process (N. E. Vvedenskii). Finally, I. P. Pavlov demonstrated for the first time that the cerebral cortex is capable of inhibitory functions of a special kind, i.e., *conditioned inhibition*.

Is there any *continuity* between the three above stages in the historical development of the problem of inhibition? Is there any direct, logical, and ideological continuity in the Russian schools of physiology in the understanding of the inhibitory process and especially its relation to the process of excitation? Do the original contributions of the Russian physiologists, who had created the *general theory* of inhibition, contribute toward the understanding of the mechanisms of "higher inhibition," i.e., the inhibition developing

in the cerebral cortex on the basis of the principle of temporary connections?

Unfortunately, at the present time we do not have a definite and adequate answer to all these questions. On the contrary, there exists such a substantial number of contradictions in the understanding of the basic mechanisms of the origin of the inhibitory process by our schools of thought that one may hardly hope for their mutual understanding without a special analysis of these contradictions. Although there were individual attempts to establish a connection between Pavlov's theory of inhibition and Vvedenskii's theory, they basically involved *protective inhibition* (Magnitskii, 1949; Ufliand, 1952; Chukichev, 1953; Durmish'ian, 1952; and others).

The problems of *conditioned inhibition*, which are presently of special interest to us, were not broached. The lack of clarity and mutual understanding in regard to these problems represents an undeniable shortcoming which is increasingly felt in research. This shortcoming is further aggravated by the fact that some investigators, having focused their attention on the coincidence and unity of a number of the propositions in this field, either intentionally or unintentionally avoid those serious contradictions which a more profound analysis reveals.

For example, it is well known that in the Pavlovian school the formula of the "struggle between inhibition and excitation" serves as the basis for understanding neurosis and conflict. This formula resulted from the acceptance of the proposition that excitation and inhibition are "fundamental" nervous processes of the cerebral cortex, i.e., each one of these processes has its own individuality and, to a certain extent, each is independent of the other.

Meanwhile, according to the Vvedenskii-Ukhtomskii theory of the origin of inhibition, excitation can never "struggle" with inhibition, since the latter is a result of excitation and immediately disappears as soon as the excitation that gave rise to it has disappeared (Vorontsov, 1953).

The question of this special status of the inhibitory process in the physiology of the nervous system has recently been clearly raised by Makarov, one of the most distinguished followers of the Vvedenskii-Ukhtomskii school. Evaluating the processes of excitation and inhibition in regard to their independence, he wrote (1957) :

Inhibition, as a characteristic physiological phenomenon, undoubtedly also has an infinite number of forms. However, the problem is whether or not inhibition possesses its own inimitable, individual intracellular pattern as does excitation. In other words, in addition to the intracellular process of excitation, is there an intracellular process of inhibition? No one has, after all, ever seen inhibitory impulses, even though each of us has stopped a beating heart by stimulating the vagus nerve. . . .

It is clear that the contradiction involves one of the most basic points of the theory of the interaction of excitation and inhibition if one considers the most recent data on the local character of inhibition. In order to recognize the importance of resolving such contradictions, one only has to realize the great number of publications prepared *without accounting for this contradiction in a crucial issue of higher nervous activity*.

The concept of excitation and inhibition as separate and *independent* processes of the

central nervous system is widely accepted by many investigators (Hilgard and Marquis, 1961; Diamond *et al.*, 1963). The "struggle between inhibition and excitation" still serves as an appropriate explanation for many investigators of behavioral acts who are satisfied with a descriptive formulation and make no attempt to reveal the profound neurophysiological nature of the phenomena in conditioned reflexes (see, for example, the *Journal of the Experimental Analysis of Behavior*).

It is difficult to assume that three brilliant investigators and naturalists who had studied the nature of the inhibitory processes at different levels of the nervous system would not have discovered *general physiological laws*. This *general aspect* constitutes the essence of Russian schools concerned with inhibition, and the further study of the problem of cortical inhibition must be based on it.

However, it must not be forgotten that the problem of the interaction of excitation and inhibition has several aspects or, as Pavlov used to say, "planes" of investigation. Moreover, the research goals of the Russian schools were by no means identical. Summarizing his lectures on the function of the cerebral cortex, Pavlov clearly differentiated between the "planes" of investigation in the field of higher nervous activity in relation to the demands for a *definite sequence* in the formulation of questions for further research.

In view of both the fundamental importance of Pavlov's overall initial goals in working out the problems of higher nervous activity and their leading role in the formulation of the tasks of further investigations, I shall cite in full what he said in regard to this. Beginning his twenty-second lecture on the physiology of higher nervous activity, Pavlov said (Pavlov, 1927, see Pavlov, 1960, pp. 377-378) :

A scientific investigation of biological phenomena can be conducted along several different lines each of which would treat the problem from a different point of view. For instance, one may have in view the purely physico-chemical aspect, analysing the elements of life by the methods of physics and chemistry. Again, keeping in view the fact of evolution of living matter one can try to elucidate the functions of complex biological structures by studying the functions of individual cells and of elementary organisms. Finally, one can make an attempt to elucidate the activities of complex structures in their fullest range directly, seeking for rigid laws governing this activity, or, in other words, trying to define all those conditions which determine the form this activity takes at every instant and in all its variations. The line of inquiry which has been adopted in the present investigation obviously belongs to the third point of view. In this research we were not concerned with the ultimate nature of excitation and inhibition as such. We took them as two fundamental properties, the two most important manifestations of activity, of the living nervous elements. *Nor was it our aim to interpret the activity of the hemispheres in terms of elementary functions of the nervous system, as has been done, for example, in the physiology of the nerve fibres. We intentionally neglected also the controversial problem of the actual localization of these two fundamental processes, and did not attempt to assign them to either of the two elements of the nervous structure, namely, the nerve cell and the synaptic junction or fibrillary connection between two individual nerve cells. The acceptance of the more general conception of the two processes of inhibition and*

excitation as the basic functions of the nervous cellular structures was sufficient for the purposes of our research, the study of conditioned reflexes being of the nature of a general investigation of the functions of the cellular structures of the cortex... [italics—P.A.]

Thus, having opened an entirely new field of investigation, Pavlov set for himself a task of a general nature—the study of the “principles of the activity” of the cerebral cortex: the principle of the strength of the signal, the principle of the temporary connection, etc., and how they are manifested in the dynamics of excitation and inhibition.

True, Pavlov very often went beyond the confines of the plane of investigation he had set for himself, as he often discussed both the nature of the basic cortical nervous processes and their relation to the processes of the nervous system in general. This is understandable. The investigations of the last years of his life increasingly evoked the necessity of answering the questions: what is inhibition, and what is its origin and physicochemical nature?

Still, the most important direction taken by Pavlov's investigations consisted of a highly detailed systematization and physiological explanation of the basic “principles of the activity” of the cerebral cortex. In recent years, however, especially during the last fifteen years, the situation in neurophysiology has considerably changed. Contributions have been made by new discoveries (e.g., the physiological role of the reticular formation and hypothalamus) and methods of investigation, thus enabling the investigator to penetrate not only into the life of the individual nerve cell, but even, as we have seen, into the essence of its molecular processes (see Chapter 5). Certainly, these advances are related to the progress concerning conditioned reflexes and will expand our ideas on the “general principles” specific for conditioned reflexes. On this line of study it is quite indispensable and legitimate to attempt a gradual transition from the study of the “principles of the activity” to the study of the *nature of the interaction of excitation and inhibition* as it had been formulated by Pavlov.

The above statement by Pavlov is quite beneficial to this task. Rather than a study of the process of inhibition per se, detached from the basic principles of higher nervous activity established by Pavlov, it demands a study *in direct relation to these principles and then proceeding on the basis of them*. Only under this condition can one be assured of the value of a detailed physiological analysis of complex behavioral forms; in the former case this analysis can become a trivial operation that fails to contribute to the overall growth of Pavlov's work.

Such attempts have already been made. Some of the most interesting are the monographs by Eccles (1953, 1964) and by Konorski (1948, 1950). These constructive endeavors undoubtedly provide us with a basis for conceptualizing excitation and inhibition at the ultimate point of analysis, the synaptic level. However, they do not close the gap between the thoroughly investigated “general principles” of the conditioned reflex and these analytical neurophysiological phenomena. Each type of concept develops independently and relies on its own reasoning.

It is clear that there is a lack of *intermediary mechanisms* and a universal model that would assist in assigning the analytical details according to specific mechanisms of the “general principle.” An attempt of this kind was made at the end of the preceding

chapter, and it is now helping us to determine the *nature of a detail under study*, e.g., of a synapse, in relation to its position in the general architecture of the behavioral act. Without such transitional concepts, any views on the role of the synapse have no positive application to the actual problems of higher nervous activity.

For example, in the publications cited above one will not find an answer to the central question of internal inhibition: why does the *nonreinforcement with food* of the conditioned stimulus evoke inhibition in the cerebral cortex? Without answering this fundamental question, which ties together the general principles of the activity of the cerebral cortex with its most intimate physiological mechanisms, we cannot hope for a satisfactory solution of cortical inhibition.

Research in the physiology of higher nervous activity has its distinguishing features. On the one hand, there are accurately determined *general principles of nervous activity* which are the basis for the integrated behavioral acts of animals and man. On the other hand, there is the intricate work of unraveling the most delicate nervous processes which occur within ten-thousandths of a second in time and occupy hundredths of a micron in space.

It is therefore not surprising that the temptation may arise to combine these fields of investigation to clarify the higher principles on the basis of exact and detailed causal connections manifested, for example, in the appearance of electrical phenomena or in physicochemical rearrangements.

These endeavors, however, are fraught with hidden dangers for the investigator. The further he digresses in his analysis from the previously found *general "principles of the activity,"* the greater is the danger that the truth will be lost in physicochemical and synaptic speculations.

Upon testing many approaches to the problem of cortical inhibition as a special form of the inhibitory process, we have come to the final conviction that the most reliable and most rapid way to solve this problem begins with the *general principles of higher nervous activity* as they were formulated by Pavlov.

Until it is sufficiently established what cortical inhibition is in regard to its *origin* and *overall physiological mechanisms*, it will be difficult to direct even the most delicate methods of modern electrophysiological and chemical investigation toward anything substantial.

In the first chapters of this book I attempted to overcome this emerging separation of the physiological interpretation of the inner mechanisms from the basic principles of higher nervous activity, even though this is only the initial step in this direction. In view of what has been said, it is essential to begin the discussion of the problem of cortical, or conditioned, inhibition with those questions which Pavlov regarded as *most important and unresolved*.

Before analyzing the fundamental physiological features of cortical inhibition, we had to determine the *crux of the analysis*. As is known, the concepts of "excitation" and "inhibition" had been taken by Pavlov from the general physiology of the nervous system, where they had been initially used and rather well defined. However, the *conditions for the appearance* of these processes in the cerebral cortex, i.e., of the *phenomena* of conditioned excitation and conditioned inhibition, depend upon the characteristics of the behavior of the integrated organism.

Pavlov (1935a, see Pavlov, 1963, p. 173) characterizes the distinctive properties of specifically cortical, or conditioned, inhibition as follows:

... we have had to deal with the special inhibition of the cerebral hemispheres, or *cortical inhibition*. It originates under definite conditions in places where it had not previously existed, it fluctuates in intensity, it disappears if conditions are changed. In all this it differs from the more or less constant and stable inhibition of the lower segments of the central nervous system and has, therefore, been called internal to distinguish it from the latter (external). However, it would have been more correct to call it "elaborated conditioned inhibition."

Presently there is no doubt that, regardless of the levels at which the inhibitory process enters, it is of the same physicochemical nature, namely, hyperpolarizational. Here too, the investigator is confronted by two particular facts: the extraordinary variety of integrated acts of behavior, each determined by the incorporation of an inhibitory process, and the microchemical processes occurring in the elements of neural tissue, which, in spite of the complexity of a given behavioral act and its biological significance, are accomplished by the universal process of hyperpolarization.

How should the investigator proceed in order to avoid confusing various forms of inhibition as they are manifested in the integrated behavior of the animal? If the assumed identity of the physicochemical nature of all types of inhibition is correct, then I believe that the most successful analysis will be the one based on the most certain concepts on the nature of inhibition.

In view of all these considerations, we thought it most suitable to use as a guide that concept which originated in the work of Sechenov, was developed in the laboratories of Vvedenskii and Ukhtomskii, and has been recently well illustrated by the latest microelectrode investigations (Eccles, 1964; Jasper, 1963; Jung *et al.*, 1963). As is shown by experience, the point of view of the Russian schools of thought completely agrees with all the accumulated data on the physiology of higher nervous activity. True, as the further presentation will show, some data on higher nervous activity will require a new interpretation, and some will have to be related to the concept of the nature of inhibition.

When considering the characteristics of conditioned inhibition, we should first ask: to what extent is it permissible to compare the theory of inhibition which had developed in some schools of physiology on the basis of the study of *lower nervous activity* with the theory of cortical inhibition as a special form of inhibition which appears during the lifetime of an individual as a process of *higher nervous activity*?

There is every reason for such a comparison, since for all types of inhibition we must recognize a "common nature," as was done by Pavlov.

During the evolution of animals and the increasing complexity of their interaction with the external world, excitation and inhibition, as the primary manifestations of specialized neural tissue, evidently did not undergo substantial changes in their intimate nature. This can be concluded on the basis of a simple evaluation of the motor functions of the most primitive and most ancient amphibian known to present-day

paleontology. It existed during the Lower Carboniferous period of the Paleozoic era. This animal (*Eogyrinus*) already possessed all the mechanisms of quadripedal gait, similar to the modern axolotl, since the skeletal features of its locomotor system and, consequently, also the combinations of muscular groups, differed little from the latter. On the basis of this it can be claimed that it possessed all the features of spinal coordination with reciprocal interrelations, with rhythmic discharges in the nerve cells, and with "unconditioned inhibition" as we understand it for present-day animals. And this animal had lived *more than 250 million years ago!*

Thus, the evolutionary process determined long ago the principal features in the nature of excitation and inhibition as processes of coordination in adaptive behavior. The further changes and improvements of the relations of the animal to the external world depended almost exclusively upon an increasing *structural* complexity of the nervous system and its functions. The number of connections of the animals with the external world increased, the velocity of the explosive excitatory reactions increased, the inhibitory process was gradually perfected, the number of possible interactions of individual excitatory and inhibitory points was multiplied, the propagation of impulses over multilateral neural connections became more complex, the ability to associate stimuli acting simultaneously upon the organism developed still further, etc.

However, the physicochemical characteristics of the excitatory process and the mechanisms of its appearance in the neural structures of even the highest order essentially remained the same. As before, excitation is rhythmic signalization developed on the basis of single cycles of impulses.

The same can be said about the process of inhibition. Upon making its appearance during evolution as a result of the perfection of the interactions of different functions of animals, as a factor of the limitation and fractionation of excitation and the elaboration of differentiated relations of the animal to the external world, its chemical nature, even in the highest parts of the central nervous system, could not be substantially changed.

Here it is appropriate to note that point of view which maintains that excitation appeared in evolution *initially*, and inhibition appeared on its basis *secondarily*. The investigators of this point of view differ only in some features of secondary importance. Some of them claim that inhibition appeared in the evolutionary process as a result of the effect of supramaximal stimuli, i.e., essentially in the capacity of protective or supramarginal*inhibition (Asratian, 1953). Others, on the contrary, hold that it appeared as the "most primitive form of inhibition" as a result of inductive relations, where "apparently, we can speak of a stage of development of organisms, when only excitability is manifested. We know nothing about inhibition at this level, and it is probably not manifested either . . ." (Biriukov, 1955).

Without touching upon the question of the nature of the earliest inhibition, we must point out that one can hardly accept the existence of an animal which at some period of evolution would possess only excitation. As soon as there appeared in primitive organisms the possibility of having several *incompatible* functions or even chemical processes, inhibition inevitably and immediately had to appear. Actually, it takes place

* Reference to Glossary.

even in elementary metabolic processes in the form of "inhibition by the end product." This, then, is the prototype of inhibition in its highest manifestation utilized by evolution in adaptive activity. The need for refining this hypothesis will become clearly evident from the subsequent presentation.

In view of all the above considerations, one can assert both the possibility and the necessity of a general physiological analysis of the conditions for the appearance of cortical inhibition and of its relation to excitation. Here we encounter some decisive questions requiring a correct answer for a successful analysis of the whole problem of cortical inhibition:

1. What neural mechanisms are *common* to cortical inhibition as a process of higher nervous activity and to the inhibitory process characteristic of the lower parts of the nervous system?
2. What in these common mechanisms can be taken as a *starting point* for establishing an organic connection between the Pavlovian concepts of higher nervous activity (especially conditioned inhibition) and the concepts of the general physiology of the nervous process?

These questions are of utmost importance. Their correct formulation unquestionably determines the success of the whole analysis of the nature of cortical inhibition. From my point of view, many attempts at understanding the physiological nature of cortical inhibition proved unsuccessful precisely because the purpose of the analysis had not been correctly formulated.

There is no doubt that of all the possible common mechanisms, our interest must first be in those contributing to a disclosure of the specific features of cortical inhibition, allowing it to become the mechanism of adaptation to the changing environmental conditions, and serving to eliminate a number of contradictions in the data on the physiology of inhibition.

Of further importance is the condition that the investigation to reveal these mechanisms should not start with such delicate processes as, for example, the synaptic mechanism, ionic processes, mediators, etc., which might draw us away from that "plane of investigation" in which Pavlov developed the theory of higher nervous activity. The study of these delicate mechanisms would lack the necessary degree of reliability and, naturally, would not be able to reveal more intimately the already investigated interaction of excitation and inhibition.

Certainly it should not be thought that it is altogether useless to investigate humoral factors and synaptic mechanisms as applied to the problems of higher nervous activity. It is known how beneficial were the investigations of the collaborators of Pavlov's laboratory on bromine, hormones (castration), etc. We shall undoubtedly be able to gain some useful information concerning the most delicate mechanisms of higher nervous activity by means of substances with precisely known points of action.

In the solution of the basic problems concerning the origin of internal inhibition, *the synaptic mechanism must be the final stage of the physiological analysis and neither the starting point nor a standard for understanding inhibitory conditioned reflexes as acts of the integrated organism*. Our knowledge about the physiology of the synaptic mechanisms justifies this.

In our everyday work we call these "general principles" of higher nervous activity

architectural laws, meaning those characteristics of the integrative act presented in Chapter 6. It is important that any anatomical and even molecular investigation correspond to an exact location in this general architecture. This functional role of a process determines its meaning, the direction of its analysis, and the interpretation of the data obtained. Such investigative tactics further stabilize and direct any assumption about the most delicate elementary processes of higher nervous activity.

This is the reason why, in spite of many attempts to explain the problem at the synaptic level (Eccles, 1953; Konorski, 1948; Gastaut *et al.*, 1957a, 1957b), they were unable to contribute anything substantial toward answering the central question of the entire problem of internal inhibition: *why does nonreinforcement of the conditioned stimulus transform the initial process of conditioned excitation into a process of conditioned inhibition?*

This is the *paramount* question in the problem of cortical inhibition.

Many years of work and thinking have brought up problems whose solutions might constitute a *common basis* for the analysis of the inhibitory process. They are as follows:

1. The physiological mechanisms of the *origin* of internal inhibition.
2. The *localization* of internal inhibition.
3. The physiological mechanisms of the *irradiation* of internal inhibition.

Without a deeper physiological analysis of these three problems it is hardly possible to develop any clear concept of the mechanisms of internal inhibition.

Before analyzing cortical inhibition in the light of the above problems, it is essential for us to determine their role in the overall theory of inhibition developed by both Russian (Sechenov, Vvedenskii, and Ukhtomskii) and foreign investigators (Sherrington, Eccles, Jasper, Fessard, and others).

CHAPTER 8

The Concepts of Sechenov, Vvedenskii, and Ukhтомskii Concerning the Origin of Inhibition in the Central Nervous System

THE discovery of inhibition in the central nervous system represents an important contribution of Russian physiology. By defining all the conditions under which inhibition originates, as conceived by Sechenov and Vvedenskii, it will also be easier to understand those physiological peculiarities which specifically characterize cortical inhibition as proposed by Pavlov.

The *origin* of inhibition is the critical moment when in the cellular elements of the cerebral cortex there appears for the first time, on the basis of a preceding excitation, an inhibitory process which does not allow the development of fully defined reactions and is consequently in direct opposition to the active state of the nerve cell, i.e., excitation.

What factors evoke the appearance of this process? How is its origin causally related to the process of excitation? These questions have never been posed in such a way. By answering them we should better be able to understand the role of inhibition in the patterning of complex acts of higher nervous activity.

Sechenov was the first to raise the question concerning the mechanism of *origin* of an inhibitory effect in the central nervous system. He confronted this problem when he began a detailed experimental study of his discovery of the inhibition of spinal reflexes which occurs when salt crystals are applied to the thalamus of a frog.

Sechenov's discovery of "inhibitory centers" was as popular as his explanation of the physiological mechanisms of the inhibitory action of these centers was unpopular. He met a fate common to many investigators in the development of scientific thought. In his explanation of the origin of inhibition, Sechenov was far ahead of the physiology of the nervous system in his time, causing undeserved oblivion for his concept of inhibition as a whole.

In spite of the abundant literature in the Soviet Union about Sechenov, this exceptionally important question is strangely ignored by his biographers and the many authors of articles about him. For some reason the emphasis on this question in *From Descartes to Pavlov* (Anokhin, 1945b) remained unnoticed. I shall attempt to bring out the true meaning of Sechenov's ideas concerning this question and show that they have a direct bearing on the problem of cortical inhibition.

As a result of many ingenious variations of his experiments, Sechenov concluded the following:

... the depression of reflexes upon stimulation of the thalamus corresponds to an excitatory state of the mechanism contained within them, ... in other words, these mechanisms inhibit the reflexes. The paths of propagation for this type of reflex inhibition along the spinal cord lie in the anterior parts of the latter [italics—P.A.] [Sechenov and Pashutin, 1865, see Bykov, 1952c, p. 116].

Thus, in the opinion of Sechenov, inhibition of reflex activity invariably originates after preliminary excitation of some thalamic mechanisms to which salt is applied. Consequently, this primary excitation alone can further lead to a final inhibitory effect occurring as a cessation of the activity of motor elements in the anterior horns of the spinal cord.

Sechenov objects to the assumption that in his experiments inhibition originates as the result of overexcitation and that it develops directly at the point of application of the salt crystal, that is, in the thalamus. For support he points to the observation that, upon application of the salt crystal to the thalamus, there appear signs of excitation beyond the limits of the region stimulated by the crystal. The presence of such excitation must undoubtedly indicate that in the thalamus only the process of excitation can initially develop, and it is this excitation which irradiates in the central nervous system before an inhibition of any motor effect appears. In regard to this he wrote: "Depression of reflexes is the result of excitation and not of overexcitation of some kind of nervous mechanisms [italics—P.A.]. This is demonstrated by the fact that the effect develops in the first moments of application of a stimulus, before movements appear. Moreover, if crystals are applied to the cut surface of the thalamus, then the effect also encompasses a diastolic stoppage of the heart, giving evidence of excitation of the medulla oblongata" (Sechenov, 1891, see Bykov, 1952c, p. 25).

From these statements by Sechenov and from the significance of his control experiments and their explanations, it clearly follows that the inhibition of such a positive activity of the organism as spinal reflexes is the result of the propagation of excitation developing in response to direct stimulation of the thalamus.

Seeking the explanation of the mechanisms of activity of the "inhibitory centers" and attempting to demonstrate the correctness of the above conclusions, Sechenov conducted experiments involving stimulation of a sensory nerve. These experiments led him to conclude that the inhibitory effect, caused by stimulating a sensory nerve, on any given activity of the central nervous system is also caused by a preliminary excitation of a number of mechanisms which comprise the reflex act.

His view on inhibition as a reflex act is expressed with particular clarity in his introduction to *Physiology of the Nervous System* (Sechenov, 1866). This monograph appeared later than his initial ideas on inhibition and therefore is of great interest.

In establishing a classification of reflexes according to their effects, Sechenov (see Bykov, 1952b, pp. 11–12) gives special attention to two types, characterizing them in this manner:

1. The beginning of the act is a sensory stimulation; its end is the activity of the functioning organs. . . . This type of nervous phenomenon is the largest group and

represents the *reflex type*, or a *reflected phenomenon* in the broad sense of the term.

2. The beginning of the act is a sensory stimulation; *the end is inhibition of movement*. This type of nervous phenomenon does not differ at all in origin from the former; the only difference is that here *the end of the act is not the activation of motor organs but rather of special mechanisms which repress movements*. Consequently, the phenomena which belong here according to their origin also belong to the reflex type and are called *reflected repressions of movements* [italics in 2nd paragraph—P.A.].

Demonstrating the reflex nature of all inhibitory effects, Sechenov finds a complete analogy to them in the inhibitory effect of the vagus nerve on the heart as a prototype of any inhibition. He proceeds from the premise that the inhibition of cardiac function under natural conditions can occur only when *the center of the vagus nerve is excited and when impulses from that center go to the periphery along the vagus nerve*. According to Sechenov, the inhibition originates in the cardiac nerve ganglion. Similarly, he believes that as the result of stimulation of a sensory nerve, as well as the result of applying a salt crystal to the thalamus, the primary impulses achieve their *inhibitory effect* in the spinal cord.

Summarizing the experiments of Sechenov aimed at explaining the physiological mechanisms of the inhibitory effect of the central nervous system, we can say that he believes the basic mechanisms in the activity of "inhibitory centers" are primarily represented by the mechanism of the development of excitation which, propagating along the central nervous system secondarily, leads to the appearance of the inhibitory process. This means that the localization of the inhibitory centers in the diencephalon does not at all coincide with the place of origin of the inhibitory process itself, and, of most importance, the inhibitory center "operates" at a considerable distance by means of *excitatory mechanisms*.

A thorough analysis of all of Sechenov's experiments and of his examples discloses that they are concerned with two types of excitation. One evokes the initial activity (spinal reflex, cardiac function), whereas the other usually appears under special influences (application of salt crystal, stimulation of a sensory nerve). The result of an interaction of the first and second excitation is inhibition, the cessation of the initial activity.

It would, of course, be incorrect to maintain that in the works of Sechenov there is a completely developed theory that the meeting of two excitatory phenomena is necessary for the appearance of inhibition. However, the experimental findings and conclusions of Sechenov are such that there can be no doubt about the originality of his direction in interpreting the inhibitory mechanism. And this justifies the opinion that the genesis of the theory of the origin of inhibition as the result of the encounter of excitations must be dated from the works of Sechenov.

Sechenov's reasoning concerning the origin and localization of the inhibitory process has never been seriously discussed in physiological literature, and this has often led to an incorrect estimate of his position in regard to this question. This incorrect evaluation was so widespread that even such an outstanding authority on the problem of inhibition as Ukhtomskii made a disappointing omission in his evaluation of the physiological sense in Sechenov's point of view. Since Ukhtomskii's opinion has been reflected in

Russian literature and might lead to a misconception concerning Sechenov's views about the origin of the inhibitory process in the central nervous system, I shall further discuss this misconception.

In his monograph *Parabiosis and the Dominant*, Ukhtomskii (1927, see Bykov, 1952c, p. 300) writes:

Sechenov believed that in the central nervous system there are special inhibitory centers with a specific topographical localization. This was, of course, not an "explanation" of the mechanism of inhibition. The idea that inhibition must be the result of a collision of excitations in the centers was first expressed by Goltz.

Unfortunately, the same point of view concerning Sechenov's concept of inhibition was prevalent even among Pavlov's students. This, of course, diminishes the true appreciation of Sechenov's remarkable data which help to solve the problem of the mechanism of the origin of inhibition in the central nervous system. He is usually credited only with the *discovery* of inhibition. Yet this is hardly the main part of his ideas concerning central inhibition.

In order to disprove this misconception it would have been sufficient to use the excerpts of Sechenov's works cited above. However, the priority of Sechenov in this major problem dealing with the theory of central inhibition is so important that I feel it is necessary to cite his own statements on this topic. Concluding the description of his experiments on inhibitory mechanisms in the central nervous system (Sechenov, 1863a, see Bykov, 1952c, p. 51), Sechenov wrote:

On the basis of the observation that the centers which inhibit the reflexes are . . . stimulated to activity by means of stimulation of the sensory nerve, one may conclude that the inhibitory apparatus, like the motor apparatus (motor nerve and its muscle), is under constant mild tonic stimulation. The one does not contradict the other, if one but assumes that motor excitation is somewhat stronger than inhibitory excitation [italics—P.A.].

It follows that Sechenov considered the presence of activity as a victory of a stronger "motor excitation" and that, conversely, the presence of an inhibitory effect is the dynamic result of such a collision of two excitations in the central nervous system when the "inhibitory excitation" is victorious. Thus, in both types of effects, positive as well as inhibitory, we are dealing with a collision of two excitations.

The fact that, according to Sechenov, the second of the colliding excitations is supplied by special "inhibitory centers" or "inhibitory apparatuses" does not basically change his concepts regarding the origin of inhibition per se.

If one takes into account that Sechenov published his experimental material and the resulting theoretical considerations as early as 1863 (Sechenov, 1863a) and that Goltz treated this question purely speculatively as late as 1869, then world priority for this important and progressive concept about the mechanisms of the origin of inhibition in the central nervous system without doubt belongs to Sechenov.

In view of what has been said, the opinion prevalent among some scientists (e.g.,

Hilgard and Marquis, 1940, 1961) that Sechenov's theory about "inhibitory centers" is only of historical interest should be considered unfounded. The theory of Sechenov about inhibition has not lost its pertinence and scientific value. On the contrary, now that we have the problem of physiologically characterizing the interaction of excitation and inhibition in the cerebral cortex, the theory of Sechenov about inhibition must take a central place in all working hypotheses concerning this problem.

In the investigations of Ukhtomskii and his students this idea acquired a more concrete physiological expression due to which, as we shall see, it will be possible to proceed immediately to the analysis of the mechanisms of the origin of cortical inhibition.

Ukhtomskii (1934, see Bykov, 1952b, pp. 521-522) clearly expressed the idea of the origin of inhibition in one of his papers:

Inhibition demands more complex and strictly defined conditions for its immediate realization. This is a process which is developed later and at greater cost than a simple excitatory discharge. . . . Inhibition is a rapid blocking of excitation. This means that the activity and excitation which must be rapidly inhibited are already present, and only with a new rapid activity and rapid impulses is it possible to achieve the inhibitory effect on time. In other words, *inhibition is invariably the result of an encounter of the inhibited with the inhibitory excitations, i.e., their presence is invariably assumed in that substrate where the process of inhibition results from their interaction* [italics—P.A.]

Ukhtomskii expressed this point of view even more clearly in his article "From the History of the Theory of Nervous Inhibition." He not only defines his own attitude towards the problem under discussion but he states a fundamental postulate regarding the presence of two competing excitatory phenomena in all cases of the appearance of inhibition. For example, Ukhtomskii said (1937, see Bykov, 1952b, p. 537):

Considering inhibition as a derivative and modification of excitation poses for the investigator the following problem: whenever he observes an inhibition of an excitatory process which has just occurred, it is necessary to assume and to seek in the organism the appearance of another source of excitation which would send inhibitory influences to the process under observation.

He believed that this inhibitory influence is possible only when the "inhibitory excitation" is already an "incipient stimulation."

As shown by these quotations, Ukhtomskii's view concerning the mechanism of the origin of the inhibitory process is already developed in some detail and a hitherto unknown mechanism is pointed out. However, *in its essence* his view coincides completely with those expressed by Sechenov. Let us recall that for Sechenov the action of the "inhibitory centers" on the excitation in progress was also effected by the inclusion of "excitatory mechanisms," *that is, by means of the rapid dispatch of excitatory impulses to that point in the nervous system where the inhibition of the current activity is to occur*. Consequently, at this most decisive point in the theory of inhibition, the opinions of the two greatest

Russian schools of physiology, those of Sechenov and Vvedenskii-Ukhtomskii, coincide to a considerable degree.

In this short survey I do not intend to give a detailed description of the *inhibition theory of Vvedenskii-Ukhtomskii*, since it is quite well known in Russian and foreign literature. It is important, however, to fully expound their idea concerning the moment and the conditions of the *appearance* of the inhibitory process.

In summing up the theories of the Russian schools of physiology on the origin of inhibition in the central nervous system, we may express these concepts in the following three statements :

1. *Inhibition arises as a result of the developing system of reflex excitatory impulses* (Sechenov). In the nervous centers it always arises as a result of an "encounter" of two excitatory impulses. The immediate cause of its origin is the action of stronger "inhibitory excitations" on other weaker "excitations to be inhibited" (Vvedenskii, Ukhtomskii).

2. *Inhibition is localized* not in the afferent zone of the reflex arc but on the further *paths of patterning a complete reaction*. It is only here that the encounter of "inhibitory excitations" with "excitations to be inhibited" can occur, as a result of which there is a repression of some activity of the organism (Sechenov, Ukhtomskii).

3. *Inhibition does not irradiate* as an independent process of a distant action. From the initial point of stimulation there irradiates only the process of "inhibitory excitation" which, being stronger, thus causes inhibition in the *zone of the reaction being inhibited*.

It should be added that the rather recent discovery of efferent control over afferent pathways by means of inhibiting certain afferent impulses does not contradict these postulates. The stronger centrally integrated excitation interferes, by means of its efferent pathways, with the already occurring excitation at the first stages of its arrival in the central nervous system. For example, Hernández-Péón *et al.* (1956) and others have shown that even in the region of the primary sensory nuclei (e.g., n. cochlearis) the orienting reaction can block the afferent impulses. Undoubtedly this mechanism promotes the implementation of the most successful afferent synthesis and, as we have seen, contributes to the *active selection* of more adequate afferentation.

The general function of such inhibition remains, however, in force : the stronger "inhibitory excitation" blocks the extraneous and weaker "excitation to be inhibited." It is quite possible that this form of inhibition is brought about by means of presynaptic hyperpolarization. Judging by the latest data of Eccles (1964), the intervention of the process of hyperpolarization occurs in very diverse structural mechanisms of the nervous system.

CHAPTER 9

Inhibition as a Function of the Organism as a Whole

In the preceding material I have shown that the main idea of the Russian schools of physiology in explaining the origin of inhibition in the central nervous system is the *encounter of two excitations*. Such an approach naturally does not enable us to decide on the nature of the actual process of inhibition, but it does clearly indicate in which interactions this process becomes integrated and, consequently, determines the pattern of the behavioral act.

Since I intend to characterize first of all the integrative role of inhibition, I will present and analyze examples of the origin of inhibition, i.e., the elimination of some activity resulting from the encounter and interaction of two excitations. Inasmuch as this encounter is necessary for the appearance of inhibition, it is clear that inhibition must disappear if for some reason one of the excitations in the encounter ceases.

Vvedenskii says that inhibition is a process "*... which is evoked by arriving impulses and which therefore disappears immediately with the elimination of these impulses ...*" (Vvedenskii, 1901, see Bykov, 1952b, p. 401). Thus, inhibition is always dependent upon competing excitations. It arises and persists as long as the excitations which gave rise to it continue.

Applying this to the natural conditions of behavior of animals and man, we must first note that this "encounter of excitations" is not an isolated and local occurrence. It invariably comprises the physiological basis of a *conflict* between any two specific activities of the organism which, as a rule, encompass most of the organism's functions and differ in the origin and composition of the working components.

It is appropriate to recall that, in our opinion, the actual historical necessity of the appearance of inhibition was caused by the necessity of the successive involvement of specific activities of the organism that have a clearly delineated adaptive effect.

As mentioned above, the origin of inhibition involves the inhibitory action of one excitation on another. This action can occur at any level of the central nervous system. If this relationship of excitations is considered from a purely physiological point of view, then its one characteristic feature can be established: in nearly all cases it involves a *remote influence* of one excitation on another, that is, the effect brought about at a distance along conducting elements of the central nervous system. This takes place, as we have seen, in the case of the "Sechenov inhibition" as well as in the case of inhibition of the secretory effect by motor excitatory impulses of an orienting reaction, and particularly in all cases of cortical inhibition of any subcortical activity.

Thus, the investigator who deals with the question of the inhibitory effect of one

excitation upon another must invariably show the nature of the nervous process by means of which this effect propagates along the neural elements. To show the mechanism of this inhibitory action in all similar cases means to determine exactly the moment of the appearance of the inhibition and blocking of the "excitation to be inhibited," and at the same time to define the moment of emergence of "inhibitory excitations" onto the end neurons and the peripheral apparatuses.

In connection with this I should mention one of the most popular concepts in physiology which is often introduced without any reason. I have in mind the concept of the struggle for the final common path, made popular by Sherrington as one of the principles of "integrative action of the nervous system." Here we must distinguish between two entirely different concepts in order to understand physiological integration: the idea of the "final path" and the idea of the "struggle for the final path." While the first concept corresponds fully to a definite and very important physiological principle which is the result of the architectural properties of the central nervous system, the second is to a considerable extent the result of artificial experimental conditions and only rarely occurs in natural behavior.

After Sherrington gave a universal significance to this principle in *The Integrative Action of the Nervous System* (1906, 1947), many investigators refer the physiological mechanism of the encounter of two excitations to this category of phenomena.

Since in further discussion of the problem of cortical inhibition we will often deal with the question of the "final path," in order to avoid misunderstandings in its interpretation it is necessary to clearly define the above concepts and give them a thorough physiological evaluation. Though the "final path" has been discussed elsewhere (Anokhin, 1946, 1949c), I have never related it to the appearance of inhibition in the central nervous system.

What is the "final path" in its physiological and morphological sense?

It is most convenient to examine this question in the same example which served as the basis for the development of the concept of "the struggle for the final path," that is, with regard to the *motoneuron* of the anterior horns of the spinal cord. This neuron has a characteristic feature which is also inherent in varying degrees in other end neurons: it receives impulses from a number of variously located neural centers. On this neuron converge neurons from the vestibular center, the red nucleus, the medulla oblongata, the spinal centers, the motor analyzer of the cortex (the pyramidal tract), and also the sensory neurons of the corresponding segments of the spinal cord, etc. (Fig. 9.1).

This structural peculiarity of the motoneuron of the spinal cord leads to exceedingly important physiological consequences which only very recently have been properly appreciated in the physiology of the nervous system.

Actually, the nerve fibers converging upon the end neuron bring to it, as was recently shown, impulses which *differ considerably in their parameters*. For example, along the vestibulo-spinal tract and some others travel the "fastest" impulses, the rate of propagation of which reaches 165 m/sec (Lloyd, 1941). The same neuron receives impulses having a propagation rate of not more than 86 m/sec along the pyramidal tract and along sensory neurons of the corresponding segments. Also converging here

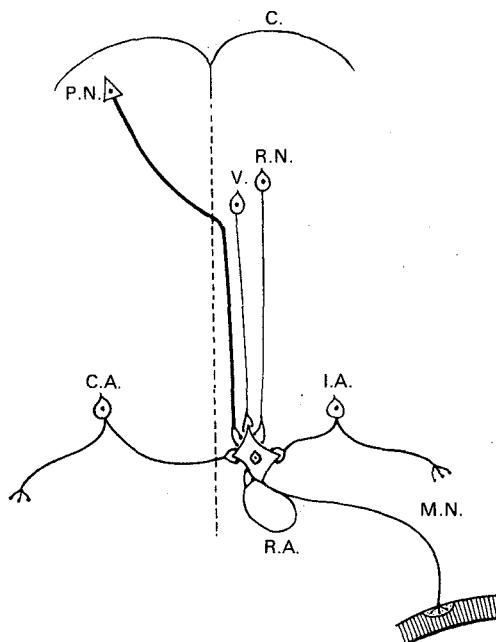


FIG. 9.1. Diagram of multiple control of a single motor neuron of the spinal cord from the higher levels of the central nervous system. C., cerebral cortex; P.N., pyramidal neuron; V., vestibular neuron; R.N., neuron of the red nucleus; I.A., ipsilateral afferentation; C.A., contralateral afferentation; M.N., motor neuron; R.A., return axon ending in synaptic formations on the body of its own motor neuron.

are the branches of some neurons of the autonomic nervous system which are in the pyramidal tract where the propagation rate does not exceed 22 m/sec; thus, there is a striking diversity of impulses *directed to the dendrites of the very same nerve cell*.

These impulses differ, of course, not only in their propagation rate but also in time of appearance, amplitude, length of individual volleys of impulses, etc. Therefore, all these impulses, different in their parameters, enter one anterior horn cell of the spinal cord which performs the most important function of *transforming all the diverse impulses into one single and homogeneous volley of impulses which travels along the motor axons to the periphery, namely, the muscle*.

What is the mechanism of transformation by the cell body of the diverse impulses into one single volley of impulses which is characteristic of the axon of the motoneuron? This question, which opens a new field of investigation, as yet remains unanswered.

In summarizing the general principles of nervous activity, Adrian (1947) called the above-described process the "homogenization" of impulses, but he does not provide an explanation of the mechanism of "homogenization" itself.

Gesell (1939) in his "electronic theory of the function of the body of the nerve cell" came close to this mechanism. However, his theory also has a number of irresolvable contradictions. Thus, the problems of the mechanism of unifying all impulses converg-

ing upon the body of the nerve cell became a tempting subject for persevering and varied investigations in our laboratory.

I cannot elucidate this problem in detail here since this would only be distracting. I have already examined it in Chapter 5, and it is of present interest only in so far as it helps to answer the question: do the above-mentioned impulses ever enter into a conflict at the end neuron?

A study of the characteristics of the motoneuron shows that the idea of a "conflict" is the result of erroneously applying data from experiments conducted under artificial conditions to the normal functioning of the central nervous system. All impulses which control the motoneuron of the spinal cord always arrive in relationships which characterize the degree of participation of each impulse in the determination of the corresponding movement of the animal and determine the degree of excitation of that neuron.

But where is the problem solved concerning the degree of participation of each impulse in the activation of the motoneuron? This question is undoubtedly solved by the integrative function of the higher nervous formations, including the cortex, and the motoneuron *passively* receives the already formed incoming volley of impulses and transforms them into impulses specific for the motor axon.

We can examine an appropriate example which will help to more clearly illustrate this.

Let us assume that a dog walking quietly along feels the bite of a flea in the region of its ear. As we know, the dog must in this case have a characteristic scratching reaction which is effected by means of the hind leg on the corresponding side. However, since the dog is walking, the hind leg and its motoneurons are occupied in accomplishing the function of walking. Will the impulse which determines the forward movement of the animal now enter into a "conflict at the end neurons" with the impulse which must determine the scratching reaction?

Of course there is no such conflict, as the following changes actually occur: the afferent stimuli which arose from the bite of the flea inhibit, at the higher levels of the central nervous system, that activity which determined the act of walking, and from here then the "ready combinations of excitations and inhibitions" specific for the act of scratching are directed to the motor field of the corresponding extremity. This is why there is no conflict of excitations for the final path in the anterior horns of the spinal cord.

If, however, as in the experiment of Sherrington, one creates artificial conditions of simultaneous stimulation of two sensory nerves of the extremity which converge with their branches at the same motoneurons of the anterior horns of the spinal cord, then under these conditions there can indeed be a conflict of excitations for the final path. This phenomenon may, of course, serve as a model for the analysis of certain physiological properties of the nerve cell. Such an analysis will be useful only if we remember that in the natural activity of the entire brain, a conflict of excitations at the motoneuron rarely occurs. In the activity of the organism in most cases there is a conflict of two integrated activities of the organism not for one "final path," but for the right to emerge onto the final paths which, for the activities in conflict, may even be completely different.

Indeed, what "final common path" can there be, for instance, in an orienting-investigative reaction which is basically a motor reaction and in a secretory reaction which develops in response to a conditioned stimulus? Actually, the conflict arises between these two reactions, usually ending with an inhibition of the conditioned secretory effect. Just such a relationship of impulses has been observed in the case of external inhibition, as was described more than once in Pavlov's laboratory.

As I now begin to elucidate the intimate mechanisms of the encounter of two systems of excitations which invariably ends in the inhibition of one of them, we must remember that in the organism as a whole it is always a matter of the conflict of two specific activities of the organism for the right to emerge onto the final paths. These paths are not at all common; on the contrary, in most cases *they are different and specific for each of the activities in conflict*.

The distinction between our thesis and Sherrington's concerning the conflict for the final path is quite obvious: the encounter, and consequently the conflict of excitations under natural conditions, occurs before the emergence of the excitations onto the final paths. The conflict does not occur on the motoneurons of the spinal cord but on the higher levels of integration where the participation of any final paths is determined directly by the *composition of the functioning components* of the activities in conflict.

In other words, the sum total of external and internal stimuli (the afferent synthesis) determines the main event: *which integrative activity of the organism is to be patterned at a given moment*. The participation of one or the other motor component follows from this automatically.

This form of interaction in the central nervous system is characteristic of the organism as a whole. *On this basis*, therefore, I will discuss the possible final mechanisms of the suppression of one of the impulses in the encounter.

In light of the characteristics of interaction of the *integrated activities* of the organism, one also cannot fully accept the figurative idea about the function of inhibition which Ukhtomskii proposed in one of his articles. In regard to this he wrote (1937, see Bykov, 1952b, p. 533):

Quite briefly one can describe this mechanism thus: while the nervous pathway is occupied with conducting the current volleys of impulses it cannot be used for the acceptance and passage of the subsequent nervous impulse and proves to be practically closed for the latter. The railway from Bologoi to Moscow is, in effect, closed for trains coming from Rybinsk, while the tracks are letting through the trains from Leningrad.

We have seen that coordinated inhibition in the *integrated organism* unfolds somewhat differently: during the patterning of a stronger activity of the organism it excludes the possibility of patterning any other integrated activity, even though the latter were to use, for the emergence of the impulse onto functioning apparatuses, very distant paths which have *no common relay stations* with the dominant activity.

If we utilize the picture "from the field of railroad communications" used by Ukhtomskii, then, as I understand it, we should say: *while the train is going from Leningrad*

to Moscow, the possibility of the assembling, and consequently the arrival in Moscow, of other trains, regardless of where they began to be assembled, is completely excluded. In other words, the train going from Leningrad to Moscow blocks for other trains not only the track on which it travels but, due to an *inhibitory side effect*, it excludes the very possibility of the assembling and arrival in Moscow of trains on any other tracks.

It seems that this figurative presentation more fully reflects the principle of the patterning of activities of the integrated organism and more correctly characterizes those mechanisms of interaction of individual activities which prevent chaos in the behavior of the animal.

In connection with the characteristics of the integrated activity of the organism described above, it is necessary to comment on some terminology to facilitate the understanding of our point of view in the further analysis of the problem of inhibition.

Taking as a basic principle the "encounter of impulses" as a necessary condition for the appearance of inhibition in the central nervous system, we must nevertheless note some inaccuracy in this expression. It correctly reflects *the moment itself of the appearance of inhibition*, but does not completely correspond to the concrete conditions of this "encounter" in the integrated activity of the organism; in short, it does not reflect the actual architecture of meeting impulses and consequently hinders further analysis.

The expression "encounter of impulses" defines the general content of the mechanism but does not define the character and number of meeting impulses. The "encounter of impulses" suggests an analytic experiment in which the experimenter, using stimuli, can at will evoke two impulses which conflict with each other. Yet the characteristic feature of the integrated activity of the organism *under natural conditions* is the fact that this activity as a rule includes a number of functioning components on the periphery. These components may appear as somatic as well as vegetative activities, but they are always manifested in precise mutual coordination. For example, the orienting-investigative reaction of an animal has somatic components in the form of the contraction of neck muscles (turning of the head), the contraction of eye muscles (the setup of the visual analyzer), etc. But if one also investigates the respiratory, cardiac, and other vegetative components of the orienting-investigative reaction, it will be seen that they also participate in this reaction in *full coordination with the somatic components*.

The most remarkable feature of this coordination of peripheral functioning components is that they develop in precise temporal interrelations. The contraction of the eye muscles cannot occur later than the contraction of the neck muscles and the turning of the head in the direction of the stimulus, for in that case the biological sense of the whole reaction would be lost.

In the same manner, the respiratory component of the orienting-investigative reaction, as shown by investigations of my collaborators (Balakin, 1935; Polezhaev, 1953; Shumilina, 1956; Sanginov, 1957), always assumes a characteristic form (a heightened inspiratory tonus) and develops in a definite time relationship with the somatic components of the orienting-investigative reaction (Kas'ianov, 1950a, 1950b). Consequently, *the delicate and precise coordination of impulses of functional components in the periphery which constitute an integrated act, corresponds to the delicate and precise coordination of*

impulses in the central nervous system.

This thesis acquires special significance because each of the functioning components is provided with its own characteristic excitation which develops in its own centers. Thus, the central integration of impulses for any integrated behavioral act is organized in precise *temporal* and *spatial* coordination, and each functioning apparatus becomes active exactly at the moment when needed according to the construction of the given act.

To make this important point in the integrative activity of the organism still more understandable, an example will be analyzed here.

Suppose that in response to a conditioned stimulus the animal must go to the feeder, which is a certain distance away. Let us visualize the sum total of those functioning apparatuses which must be activated for the accomplishment of the alimentary reaction. The animal must first move towards the feeder. This movement involves great complexity of central correlations. As experiments of Shumilina, Kas'ianov, Koriakin, and other collaborators have shown, for a coordinated and localized movement to occur, it is first necessary for generalized impulses to emerge simultaneously onto all segments of the spinal cord. These impulses are not chaotic; they produce a redistribution, moreover, which corresponds exactly to that equilibrium of the body which is *necessary for the impending movement of the extremities*. Only several tenths of a second after this generalized excitation do the impulses which produce the local movements arrive at the motoneurons of the spinal cord.

This process of a double exit of impulses onto the motor fields of the spinal cord begins with a single complex of impulses in the central nervous system. Only later, due to their different propagation rates, do they separate in time, thus determining their necessary mutual correspondence at the periphery. This is the *motor component* of the conditioned alimentary reaction. There then follows the emergence of impulses to the secretory apparatus. This can occur simultaneously or after the motor impulses, but in the central nervous system they originate in precise temporal coordination with the motor impulses. Occurring simultaneously are changes in the respiratory and cardiovascular activity, a change in the intestinal tonus, a redistribution of impulses in the endocrine glands, etc.

If one takes into account that all these impulses have different qualitative characteristics in the sense of propagation rate and difference in length of path from the place of origin to the corresponding functioning apparatus, then it becomes clear how complex the central integration of these impulses must be in order that each may reach the functioning apparatus precisely at the moment required for the realization of the adaptation of the animal under the given circumstances.

Therefore, one cannot fail to be impressed by the great accuracy of the functioning of the central nervous system which instantly organizes all these impulses and all the corresponding effectors into a unified whole. We frequently speak about the "organism as a whole," but rarely do we attempt to analyze the complex physiological organization which even a comparatively simple adaptive act possesses.

We will leave for now the questions of whether all the components of an integrated reaction are needed to the same degree as we assess this reaction of an animal, and

which of them are the "principal" ones. Special attention will be given to this question in the appropriate place.

Thus, corresponding to each integrated activity of the organism (for example, conditioned alimentary reaction or orienting-investigative reaction) there is in the central nervous system not one homogeneous excitation, but a *system consisting of various but completely integrated excitations*. It is easy to see that in our universal architecture of the behavioral act (see Chapter 6) this efferent integral corresponds to the "program of action," i.e., to that key mechanism which forms as soon as the stage of afferent synthesis ends and the decision to perform an action with all its fractional parts has been reached.

Of course, if one considers the precision necessary for the performance of a specific act, the organization of volleys of efferent impulses may appear unattainable since it is so complex. It includes not only all the stages of the action, but also all the features of the vegetative components which characterize the future results of the action undertaken. The experiments of Shidlovskii (1963, 1964), performed in our laboratory for the purpose of evaluating the vegetative components of the conditioned reflex, give particular support to what has been said.

Consequently, if we apply the expression "encounter of impulses" from the physiological vocabulary to the natural conditions of the organism's activity, then it is quite obvious that we must speak of the *encounter of two systems of impulses* at the level of their central integration, as a result of which the specific picture of participation in reactions by active components changes completely.

Indeed, if the orienting-investigative reaction as "extraneous activity" "inhibits our conditioned reflex," then from the physiological point of view it is impossible to assume that the orienting-investigative reaction inhibits only the secretory component which we are presently considering, while the *integrated alimentary reaction of the animal with all its other specific components remains in its original form*. Experiments have shown that the orienting-investigative reaction always inhibits the alimentary reaction as an integrated activity of the organism.

This not only means that the "motor reaction has inhibited secretion," but also that the respiratory component, which was earlier characteristic of the alimentary reaction, has now become characteristic of the orienting-investigative reaction, with the cardiac component undergoing the same change, etc.

Direct study of pneumograms of experimental animals convinces us that it is just such kinds of changes which occur in all components of a reaction subjected to inhibition.

All these considerations compel us to speak henceforth not of an encounter of two homogeneous volleys of impulses *but of an encounter of two systems of impulses, each corresponding to some integrated activity of the organism and to its specific result*. We make this terminological change not only because the idea of a "system of impulses" reflects more accurately the actual relationships formed in the cortex and subcortex during the formation of an integrated reaction of the animal, but also because a number of new questions are put before the investigator, such as: what mechanism causes a complete inhibition of some components of an integrated reaction, and only a trans-

formation of others? Does this transformation of the individual components of the inhibited reaction occur on the end neurons or somewhere higher? Finally, where is the total integration of the entire inhibitory integrated activity determined? Actually, the concept of the "system of impulses" corresponds completely to the concept of the *functional system*, discussed in Chapter 6, as a system that ends in a specific adaptive effect in the interest of the organism as a whole.

Consequently, when we speak of an "encounter" of two systems of impulses at the integrative level, we are speaking of the interaction of two fully delineated *activities* of the organism as a whole.

It is hardly necessary to emphasize the appropriateness of these investigations in order to finally arrive at a better understanding of the problem of cortical inhibition as a mechanism which regulates the adaptive reactions of the organism as a whole.

CHAPTER 10

Current Concepts Concerning the Nature of Inhibition

AFTER what has been said about the actual architecture of the interrelations of competing excitations in the central nervous system, we can now proceed to the analysis of those *intimate physiological mechanisms* which might explain the appearance of the process of inhibition.

Returning to the original question concerning the nature of inhibition, we must point out that it is quite possible that we will encounter different kinds of inhibitory influences. In their evaluation we must first recognize that in all cases of inhibition of an integrated activity, there is a spatial interrelation of two systems of excitation. In relation to this we should ask how spatially separated neural structures are able to influence each other.

Two such forms of spatial interaction are known in neurophysiology: phasic-impulse and electrotonic, or, in the terminology of Makarov (1947), "fused tonic." Thus far, no other forms of spatial interaction in the nervous system have been determined.

Let us analyze in more detail the first form of remote effect, which is accomplished by means of the dispatch of volleys of impulses differing in frequency and configuration. This effect had been studied most extensively as long ago as the end of the last century by Vvedenskii. Ukhtomskii and his students later continued the study. Vvedenskii discovered one principle of the effect of excitatory impulses, the great importance of which is becoming known to physiologists only in recent years (Forbes *et al.*, 1949; Monnier, 1936; Lorente de Nò, 1947; and others).

The basic aspects of Vvedenskii's concept of pessimal inhibition are well known both in the Soviet Union and abroad. Therefore, I shall recall briefly only that material which considerably facilitates the understanding of the nature of the inhibitory process.

Vvedenskii based the interaction of the excitable structures on the "law of relative lability," which he had formulated and experimentally proved. According to this law, every excitable structure can respond to excitatory impulses only as long as the protoplasmic properties of this structure can reproduce the frequency and strength of these impulses. As soon as the frequency and strength of the nerve impulses reach the limit of the capacity to reproduce a given high rhythm of impulses, the excitable system at first "transforms" the arriving impulses, producing one discharge for every two nerve impulses reaching it. With an increase in the frequency the system altogether ceases to react, lapsing into a state of pessimal inhibition.

The actual limiting frequency of impulses which a given excitable structure is still

capable of reproducing without transformation is assumed to be the *measure of lability*.

As is shown by experimental data of the Vvedenskii-Ukhtomskii school, the excitable structures of the organism differ considerably from each other in their limits of lability. For example, the lability of the neuromuscular synapse is, according to the data of Erlanger and Gasser (1937), 100–150 impulses/sec, while the lability of individual nerve trunks, especially of the phrenic nerve, is 1000 or more impulses/sec.

From the Vvedenskii-Ukhtomskii point of view, the brain is an organ possessing an extraordinary variety of labilities. Each nerve cell is, in this sense, an individual structure having its own limit of reproducibility of the frequency of impulses. In addition, this lability may vary within very wide limits, depending on the initial state of the excitable structure. For example, by subjecting a nerve cell to the action of an anesthetic, the pessimal inhibition in it arises at lower stimulation frequencies. This means that the lability of the nerve cell in the given state will be considerably lower than in the normal state.

The data in Chapter 5 on the extreme diversity of the physicochemical and functional properties of the synaptic formations on the same cell lead us to think that this diversity is in harmony with the diversity of their lability. It is quite possible that, independently of the specific nature of the cytoplasmic process evoked by these diverse synapses, each of the latter has its own level of lability, i.e., of the ability to reproduce, without a transformation, its own maximal frequency of impulses.

It should be pointed out that, while investigating the ability of the cortical cells to develop conditioned excitation, Pavlov encountered the phenomenon of the *limit of efficiency* of these cells, upon which their excitation is transformed into inhibition, this being designated "supramarginal inhibition." Naturally, from the physiological point of view there is obviously a relation between the "limit of efficiency" and the "level of lability": the limit of efficiency of a cortical cell always depends upon the level of its lability. Nevertheless, one should not identify the concept of "lability" with that of the "limit of efficiency." A nerve cell with a very high lability may have a very low limit of efficiency, and vice versa.

The concept of lability is based on the overall ability of a nerve cell to reproduce without transformation a definite number of impulses in a *unit of time*—per sec. For the concept of lability it is irrelevant for how long and to what extent a cell with a given lability is able to maintain an *integrated activity* of the organism in cooperation and interaction with a vast number of other nerve cells. Meanwhile, the limit of efficiency of a cortical cell is determined by its ability to maintain and ensure some integrated activity of the organism in the interaction with other elements.

Unfortunately, the concept of the "limit of efficiency" does not have as clear a *quantitative definition* as does the concept of "lability." In its essence, the limit of efficiency of a cortical cell always depends to some extent on the efficiency of the entire system of neural connections providing for a conditioned reflex activity.

Returning to the idea of the origin of inhibition as the result of "pessimal inhibition," and taking into consideration the great diversity of labilities in the cells of the central nervous system, we must emphasize that under these conditions the *frequency of nerve impulses* becomes a universal tool for selective excitation, inhibition, the alternate

involvement of certain systems of the organism, etc. Expanding upon the idea of Vvedenskii and Ukhtomskii concerning the significance of the frequency factor in the intercentral relationships, we can say that if there were cells capable of producing an especially high frequency of nerve impulses in the central nervous system, they would thus be able to widely influence the functions of other nerve cells or any functional combinations of them. In some cases they would be able to send out a high frequency of impulses and inhibit the activity of other cells, while in other cases they would stimulate the cells to positive activity by sending out impulses of optimum frequency.

In connection with this I would like to point out one of Vvedenskii's brilliant fore-sights. Continuing the chain of logical arguments on the significance of the factor of the strength and frequency of the impulses in the inception of the inhibitory process, Vvedenskii (1901) admits the possibility that in individual cases the appearance of the inhibitory effect can be considerably facilitated *by the formation of special structures at the point of contact between individual neurons*. Vvedenskii wrote (1901, see Bykov, 1952b, p. 406) :

It is possible to assume for any nerve fiber the same dual relations as were indicated above for the motor fiber in relation to the end plate: *in one combination of frequency and strength—an excitatory effect, in another combination—an inhibitory effect.* . . . The difference in effects could be caused, on the one hand, by the properties of the terminal apparatus, and, on the other hand, by the *type of termination* of the nerve fiber in that apparatus which it is to affect [italics--P.A.].

Thus Vvedenskii had a very definite opinion about the possible mechanisms of the remote inhibitory effect of the excitation of some neural structures on others. While analyzing the characteristics of the pericellular formations on the Purkinje cells of the cerebellar cortex, he exclaimed: "What excellent conditions for producing inhibitory effects!" (Vvedenskii, 1901, see Bykov, 1952b, p. 406).

It is remarkable that in these statements the discovery of the unique structure of the end apparatuses on individual neurons which was made by Lorente de Nó (1939) had been predicted many years in advance. As is known, this investigator, being both a morphologist and an electrophysiologist, demonstrated by direct experiments that certain motoneurons have a considerable number of small internuncial neurons which provide for a considerable *multiplication* of the impulses reaching the motoneurons (Fig. 10.1).

From this figure it is evident that each individual nerve impulse, upon approaching a motoneuron and entering into the special ramifications of its internuncial neurons, ultimately creates a successive stimulation of the dendritic part of the motoneuron by at least ten impulses. It is easy to imagine what an enormous frequency of impulses can actually arise in a motoneuron if natural tetanic series of nerve impulses will arrive over the main axon.

Thus, the predictions of Vvedenskii have been confirmed in morphological investigations. Due to the presence of such a terminal apparatus some neurons can lapse into a state of pessimal inhibition even at a low frequency of impulses *arriving* at the internuncial system.

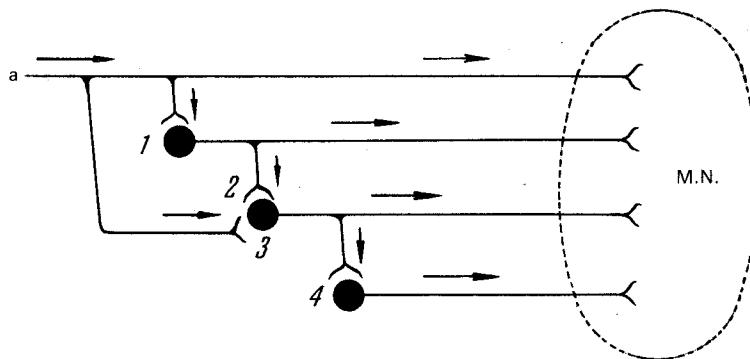


FIG. 10.1. Example of supplementary mechanism at a motor neuron (M.N.), leading to multiplication of nerve impulses. Diagram of the links of the main impulse-supplying axon (a) and of its branches leading to additional synaptic changeovers (1, 2, 3, 4).

At present it is important to note that the variable frequency of the nerve impulses and the special structures that cause an increase of this frequency can become one of the tools of the inhibitory influences in the complex dynamics of the intracentral interactions (see Fig. 10.1).

In view of the fact that these ideas of Vvedenskii are becoming increasingly popular in the explanation of the complex interactions in the central nervous system, I feel it is essential to present evidence from the latest published data that in a number of cases it is precisely the *frequency of nerve impulses* which determines the distribution of excitatory and inhibitory influences over the central nervous system, depending on the frequencies of impulses received from the working periphery.

The clearest example of this universal principle are old experimental data of Vvedenskii which were not fully understood in his time but have now been completely elucidated. What I have in mind are his data concerning different effects on the respiratory system caused by the varying frequencies of electrical stimulation of the central stump of the vagus nerve. As Vvedenskii showed (1889, see Bykov, 1952d, pp. 845–853), stimulation with a frequency of 10 to 70 per sec leads to cessation of the respiratory movements at the height of inspiration. A further increase in the frequency of the impulses leads to a cessation of breathing at the depth of expiration.

This effect was subsequently confirmed by a number of both Russian and foreign investigators, although the latter never referred to the publications of the Russian investigators (Vvedenskii, 1889, see Bykov, 1952d, pp. 845–853; Avtonomov, 1889; Schulgin, 1909–10; Mikhailov, 1914; Merkulov and Kiselev, 1933; Smirnov, 1936; Melik-Megrabov, 1936). These investigators have focused their attention on one specific question: is the inhibitory effect on the respiratory center (evoked by vagal stimulation) implemented by way of special inhibitory nerve fibers, or do the inhibitory and excitatory influences proceed toward the respiratory center by way of the same fibers with the final effect depending on the special organization of the end station?

Vvedenskii, who was the first to demonstrate the significance of the *frequency of the*

excitatory stimuli in the unique effects at the respiratory center, adhered to the latter opinion, i.e., that *excitatory and inhibitory influences are conducted to the respiratory center over the same fibers of the vagus nerve, with the inhibitory effect arising as a result of the characteristic of the structure of the central apparatuses.* This constituted his later "conjectures" concerning the inhibitory effect of excitatory impulses on the central structures. Vvedenskii (1889, see Bykov, 1952d, pp. 852-853) concludes his concept concerning the unity of the excitatory and inhibitory influences on the respiratory center with the remarkable words: "If further support could subsequently be found for this explanation and if it could be further developed, this view would help to bring much unity into the interpretation of the most diverse functions of the organism."

Below I shall endeavor to show that the establishment of this *unity* is the next task in the study of the intercentral relationships.

In neurophysiological literature increasing support is being given to the position that the decisive factor in the intercentral relationships is the frequency of the nerve impulses exciting a neural complex. These views are appearing on the basis of the most recent experimental data gathered by means of improved oscillographic equipment (to be discussed in more detail below).

Now it is important to understand why the clear data of Vvedenskii concerning the decisive significance of the *frequency of the stimuli* for the nature of the central response were not extensively developed and essentially did not exert a determining influence on neurophysiological thinking, and also why his results, as is often the case in the history of the development of scientific concepts, have fallen into the category of "forgotten facts."

This question can now be given a quite definite answer. First of all it should be pointed out that the attention of the investigators was directed toward a specific question: do special "inhibitory fibers" exist? In addition, upon discovering the well-defined reactions of the respiratory center to artificial stimulation of the vagus nerve by electrical stimuli differing in frequency, Vvedenskii could not then ask the question which would seemingly follow from his investigations: what is the equivalent of these artificial stimuli in the natural respiratory cycle?

Since these questions had not been raised at that time, Vvedenskii's data remained incomprehensible; they remained outside the logic of the natural regulation of the respiratory act on the basis of afferent impulses from the pulmonary alveoli and were therefore not considered by neurophysiological investigators.

Only after more than 30 years, with the refinement of oscillographic procedures for the investigation of nervous processes, did the actual value of Vvedenskii's experimental findings become apparent. These findings notably revealed the universal significance of the frequency of the impulses in the perpetual coordinative activity of the central nervous system.

Refined oscillographic procedures were first used by Adrian in 1933. He showed that throughout the entire inspiration, i.e., the filling of the alveoli with air, volleys of nerve impulses pass over the pulmonary branches of the vagus nerve into the central nervous system. These results were confirmed or further developed in the investigations of Keller and Loeser (1929), Partridge (1933), Rice (1938), Wyss (1954), Gesell (1940),

and others. All these investigators obtained almost identical results, showing that during inspiration the afferent impulses in the vagus nerve gradually increase from zero to a frequency of 80–100/sec. During various artificial measures, such as the forced inflation of the lungs, this frequency can be increased up to 250 impulses/sec.

Upon closer examination of the experiments cited above, one remarkable circumstance stands out: the minimum frequency of the natural afferent impulses that appear at the beginning of inspiration in the vagus nerve equals 1–30 impulses/sec, i.e., precisely that frequency which *completely coincides with the frequency of the artificial stimulation of the vagus nerve that stops breathing during inspiration*. At the same time, the maximum frequency of afferent impulses at the height of inspiration equals 80–150 impulses/sec, i.e., precisely that frequency which upon artificial stimulation of the vagus nerve *corresponds to the critical frequency of expiration*.

A comparison of these data leaves no doubt that Vvedenskii discovered in his experiments a highly important principle in the coordination of the respiratory act: its phases depend entirely on the unequal frequency-threshold characteristics of the inspiratory and the expiratory centers.

At first sight, the different relation of the inspiratory and expiratory parts of the respiratory center to the frequency of the afferent impulses would seem to depend on their unequal lability, as established by Vvedenskii. A more detailed analysis of this selective sensitivity shows, however, that its mechanism is considerably more complex.

In the experiments of my collaborator Fantalova (1949), the simultaneous oscillographic recording of the *emergence* of impulses from the inspiratory and the expiratory parts of the respiratory center onto the peripheral motor systems was performed on the background of continuous stimulation of the central stump of the vagus nerve by a low (30) and a high (135) frequency of stimuli. As was shown by the results, at a low frequency of stimulation the emergence of nerve impulses over the phrenic nerve is considerably increased, and, at the same time, the emergence of impulses from the expiratory center to the obliquus abdominis muscle is completely inhibited (Fig. 10.2).

By means of a composite curve one can demonstrate those characteristics in the interrelation of the excitation of both parts of the respiratory center which were discovered in the work of Fantalova.

On the above diagram the intensity of the excitatory effect of the current on inspiration and expiration (ordinates) is plotted against frequencies of impulses evoking inspiration and expiration (abscissae). The diagram shows that the inspiratory and expiratory centers differ in their properties considerably from the normal neuromotor reaction, these differences being clearly opposite.

The inspiratory part of the respiratory center has the ability to become excited to a maximum very rapidly and then to lapse very rapidly into pessimal inhibition at a comparatively low frequency of impulses. The expiratory part of the center, on the other hand, has completely opposite characteristics: it is not excited at all or is even inhibited by infrequent impulses and begins to become active only when the alveoli have become sufficiently expanded and the frequency of the afferent impulses traveling over the vagus nerve is becoming maximal. Undoubtedly, these characteristics of the two parts of the respiratory center are constitutional, i.e., they are genetically determined.

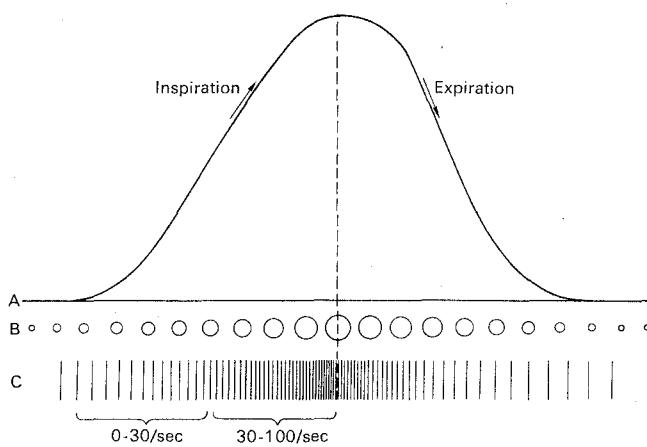


FIG. 10.2. Comprehensive diagram explaining the significance of the frequency of impulses from the afferent mechanisms of the pulmonary alveoli. (a) single respiratory cycle; (b) change of volume of an alveolus in accordance with the increasing expansion of the thoracic cavity; (c) frequency of the afferent nerve impulses arising in the receptors upon expansion. For explanations see text.

Both parts of the respiratory center are selectively excitable, which is in accordance with the natural afferent impulses arising in the interreceptors of the pulmonary alveoli and changing throughout inspiration and expiration.

As a consequence of these characteristics, very favorable self-regulatory relations occur during respiration. During *inspiration*, the impulses arising in the alveolar receptors *excite the inspiratory center and do not excite the expiratory center*. At the height of inspiration the increased frequency of impulses inhibits the inspiratory center and begins to excite the expiratory center. This is certainly an appropriate involvement of the frequency factor into the coordination of the central-peripheral interrelations.

In connection with these physiological characteristics of the coordination in the function of the respiratory center, two important questions arise:

1. By what physiological and structural means does the central nervous system attain the low threshold of excitability for the inspiratory center, and, especially important, *how is the very low threshold of the pessimum of frequency established in it?*
2. By what means does the central nervous system completely prevent the excitation of the expiratory center when those frequencies of impulses occur which both excite the inspiratory center and bring it into the state of pessimal inhibition?

Special attention should be given to this second question. One only needs to assume that the cells of the expiratory center possess the physiological characteristics of excitability of ordinary nerve cells, and the impossibility of the respiratory act will become evident. With such an assumption *expiration would start at the beginning of inspiration*, i.e., any possibility for the lungs to take in air would be eliminated.

Further investigations must disclose the harmonious relations between the develop-

ment of the respiratory function during phylogenesis and the adjustment of the coordinated interrelations in the central nervous system to its demands.

For the present it is important for us merely to establish, on the basis of the example analyzed above, that the frequency of the nerve impulses can determine both the moment of excitation and the moment of inhibition of nervous activity. The physiology of the nervous system already gives sufficient evidence that the frequency of the nerve impulses plays such a role in central interactions.

By way of example we may point to the role of the frequency of the nerve impulses arising in the fibers of the depressor nerve upon increasing the blood pressure in the aortic arch. The higher the blood pressure and, consequently, the more frequent the impulses in the nerve fibers of the depressor nerve, the more inhibited is the tonus of the vasoconstrictive center until the peripheral blood vessels have become dilated. What makes this effect of the frequency of the afferent impulses of the depressor nerve all the more interesting is that with its increase the center of the vagus nerve becomes increasingly *excited*, and hence *the same frequency* of nerve impulses conducted over the fibers of the depressor nerve has a different effect on the cells of the vasoconstrictive center and on the center of the vagus nerve.

The physiological significance of this phenomenon is clear: by two different means acting simultaneously the organism lowers an excessively elevated blood pressure. At the same time, however, it is clear that the principal operating factor in this purposeful reaction of the organism is the frequency of the nerve impulses.

The neurophysiological literature of recent years gives increasing support to the proposition we have developed above. For example, Ashkenaz (1939) has shown that one can obtain diametrically opposite effects on the blood vessels and the blood pressure by using different frequencies of stimulation of the peripheral nerves.

Upon analyzing the relation of the *frequency* of the impulses to trans-synaptic propagation, Bernhard and Granit (1942, p. 390) concluded the following: "From the theoretical point of view, the interest centers around the relation of these results to possible mechanisms of inhibition."

Even more interesting are the experimental data of Forbes *et al.* (1949) and their point of view regarding the inhibition of some cortical processes. They have shown that the so-called secondary discharge, which arises in the cerebral cortex upon stimulation of a sensory nerve, *may be inhibited by increasing the frequency of stimulation*. They ascribe this inhibitory effect to the direct action of a sufficiently high frequency of stimulation and relate it to the blocking of impulses in accordance with the "Vvedenskii effect."

In research on the cerebellum, Moruzzi (1949) showed that the selective control by the cerebellum of the nuclei of the brain stem, which are responsible for decerebrate rigidity, occurs by means of impulses of varying frequency. For example, stimulation of the cerebellum by stimuli of low frequency (2–30/sec) intensifies decerebrate rigidity, while stimuli of high frequency (50–300/sec) inhibit decerebrate rigidity. Thus, the control of the motor nuclei occurs within approximately the same frequency range as we have seen in the example of the selective relation of the different parts of the respiratory center to different frequencies of the afferent impulses.

Similar effects of different frequencies were also demonstrated on other reflex acts. Wyss and Rivkine (1950) demonstrated that stimulating the carotid sinus nerve by stimuli of different frequencies yields different reflex responses.

The delicate influence of frequency on intercentral relationships becomes evident from the work of Ead *et al.* (1952). These investigators developed a method of *pulsatory* perfusion of the sinocarotid region and have shown that the inhibitory effect on the vasomotor center by impulses from pressoreceptors is directly proportional to the *frequency of the impulses* in each individual volley. At the same time, a *considerably greater absolute number* of impulses from pressoreceptors, generated at a lesser frequency and during continuous stimulation, does not produce such inhibition of the vasomotor center. An outstanding example of the effect of frequency!

The same group of examples includes the investigations of the dependence of extensor reflexes (e.g., the knee-jerk reflex) on the frequency of the afferent stimuli (Maling, 1946).

I have hardly presented all the recent data on the significance of the frequency of nerve impulses in the processes of intracentral coordination. However, what has been presented is quite sufficient to make it apparent that physiologists outside of the Soviet Union are increasingly recognizing one of the most important postulates of the Vvedenskii-Ukhtomskii school: the universal role of pessimal inhibition in the coordination of the intercentral relationships.

From an evaluation of the material presented on the significance of the frequency of nerve impulses in the coordination of intercentral interactions, we may formulate the following proposition: *in all those cases in which the necessity arises in the central nervous system of eliminating one integrated activity by another integrated activity, i.e., when there is an encounter of two systems of excitation, the most likely immediate mechanism of the inhibition of one of them is the strength and frequency of the nerve impulses of the stronger nervous activity.*

In connection with what has been said above, the question arises: is pessimal inhibition *alone* the "tool" for inhibiting an integrated activity not needed at a given moment, and is the frequency of the impulses always, i.e., in all forms of intercentral interactions, the principal mechanism of inhibition?

Within the past few years several new concepts have arisen in regard to the possibilities of the organism to eliminate unnecessary and inappropriate activities. There are evidently several ways of inhibiting an interfering effect, and these are directly related to the nature of the activity, the degree of its automatism, and the phylogenetic development of the given species of animal. It is very likely that in individual cases, in which the relations do not change for thousands of years, one of those mechanisms of synaptic inhibition is elaborated which have recently been discovered by Magoun, Eccles, and Lloyd.

It is known that upon stimulation of the medulla oblongata, Magoun (1963) demonstrated the existence of an inhibitory substrate which exerts an inhibitory influence on the spinal reflexes regardless of the frequency of stimulation. Similarly, Eccles (1964) established the existence of both synaptic and presynaptic hyperpolarization which may block the effect of excitation, and Lloyd demonstrated the existence of so-called "direct inhibition." These findings will be analyzed in more detail later.

Now I shall point out one more remote effect which can become operative during the process of coordination and lead to the inhibition of an activity.

Long ago the Vvedenskii-Ukhtomskii school put forth the concept that, along with the impulse signalization represented by series of individual volleys of impulses, there is still another remote effect on the neural elements in the central nervous system. This second kind of effect is "fused tonic," i.e., electrotonic, and can be continuous. Such an effect may either be aneurotonic or catelectrotonic.

With Vvedenskii's discovery of the phenomenon of perielectrotonus and the prodromal phase of parabiosis, this line of thought has been developed into a completed concept. Its basic propositions can be briefly formulated as follows:

1. Within the central nervous system, as well as on the efferent pathways, a definite electrotonic state is always maintained as a result of the activity of special apparatuses. In the latter case it determines the so-called subordinate influences of the central nervous system on the peripheral apparatuses.
2. The electrotonic effects, having a rapid rate of propagation, become intertwined also with the impulse effects, helping or hindering their implementation. Owing to the integration of the "discrete" and the fused tonic effects at the point of departure and also to the rapid rate of propagation of the fused tonic effect, the latter always turns out to be preparing for the development of the action of impulse signalization ("preexcitation").

These postulates were developed most fully by Makarov (1947). Being a fervent advocate of the binary nature of nerve impulses, Makarov provides a number of experiments confirming these propositions.

In addition, in other laboratories as well, highly convincing data were obtained which indicate that such "fused tonic influences" from the central nervous system take place. One may point to the investigations of Vorontsov (1953), Rezviakov (1937a, 1937b), and Rusinov (1952).

In our laboratory, too, data were obtained which lead to the conviction that the functional interrelations of the different parts of the motoneuron are to some extent determined by the electrotonic factor. Moreover, it was shown that with surgical intervention at the spinal cord there may arise an *acute* descending electrotonic influence on the neuromuscular synapses of the lower extremities, leading to a sharp lowering of their lability (Maiorchik, 1944). Thus, the participation of an electrotonic component in intercentral interactions is becoming increasingly probable.

In my opinion some investigators digress considerably from the actual situation when, in explaining the development of inhibition, they shift the emphasis to the electrotonic component, thereby underrating the delicate and universal mechanism of impulse signalization.

It should also be noted that an overestimation of the correspondence between the state of the excitable substrate and the nature of the signals received by it during the development of inhibition necessarily leads to the loss of one of the most important characteristics of central inhibition which Ukhtomskii (1927, see Bykov, 1952c) emphasized with special insistence, namely, the "deliberateness" and "urgency" of inhibition.

It remains unclear what special mechanisms produce and send the fused tonic signalization to the place where the activity unnecessary for the given moment is eliminated *independently of impulse signalization*. Thus, this working hypothesis confronts us with even more questions than there were before.

The concept of the origin of the inhibitory process based on electrotonic influences, while being grounded on correct premises, does not enable us to understand the deliberate nature of central inhibition, which is always directed and in most cases very precisely localized.

For the central nervous system any coordinative inhibition is always in a certain sense an *act of violence*, for by means of it one activity is suppressed and another activity is released, the latter being stronger for a given moment, or, more accurately, for the given external situation acting upon the organism as evaluated by afferent synthesis.

As we have seen, the natural role of inhibition in the nervous system consists of its appearance at that time when the necessity for the elimination of any fully defined activity of the integrated organism arises. This elimination frequently involves some *individual component* of a complete reaction as in the case of voluntary inhibition. This indicates that the inhibitory process cannot be strictly localized and differentiated. The manifold activity of the cerebral cortex of higher animals and especially man provides us with an infinite number of examples of such selective and strictly defined inhibition.

Therefore, I consider all those theories of the *origin* of inhibition inadequate which regard inhibition as a diffuse process, predominantly the effect of some electrotonic field. Into this category of concepts falls first of all the "neuropilic theory" of I.S. Beritashvili (Beritov, 1947). In this morphologically and physiologically well-reasoned theory there are certain features which make the theory plausible for a number of *general* inhibitory states. It is difficult, however, to explain by means of it "higher inhibition," which is of most interest to us.

True, Beritov and Roitbak (1955a) developed an essentially new concept about the inhibitory effect of the slow potentials arising in the dendrites. It seems to me that this theory is not merely a terminological improvement of the former theory, as the authors say it is. Both in its physiological essence and its structural physiological correlations, their new theory is an *entirely different concept*, being similar to the "neuropilic theory only in so far as positive electrotonic potentials figure as the causative factor in both cases.

Just what is the "dendritic theory" of Beritashvili and Roitbak?

Generalizing somewhat, this is the essence of the theory: (1) any excitation reaching the *dendrites* of a nerve cell evokes a slow potential of anelectrotonic nature, which then exerts an inhibitory influence on the "neighboring" neurons; (2) any excitation reaching the body of a cell exerts an excitatory effect on it and, evidently, on other cellular complexes connected with it. A general inhibition of the spinal cord, for example, during the implementation of the flexor reflex, should then be accomplished by the ramifications of the stimulated afferent neurons on the dendrites of all the internuncial neurons not implementing the flexor reflex. Those neurons which are carrying out the flexor act must naturally receive excitation through the synapses *on the body of the cell*.

A detailed analysis of the "dendritic theory" of central inhibition is absolutely essential, but this problem must be treated separately. Here we are interested in one question: to what extent can this theory be utilized for explaining the concrete forms of inhibition occurring in the integrated activity of an animal?

The "dendritic theory" of inhibition is, without doubt, interesting. It makes greater use of the modern advances of neurophysiology than do other theories. Its most vulnerable point is, however, that its basic acting principle is the anelectrotonic state, which does not permit a further spread of discrete, i.e., impulse, excitation.

The authors in part argue their point of view on the basis of local strychnine poisoning of the cerebral cortex. They claim that "the spasm-inducing discharges . . . are limited to the stimulated or poisoned section. They do not spread beyond this section. Around a section the electrical activity greatly decreases" (Beritov and Roitbak, 1955b). This argument in favor of the inhibitory effect of the section poisoned with strychnine on the neighboring neurons needs clarification. It is known that the application of a piece of paper moistened with strychnine to any section of the cortex leads to an excitatory effect of the poisoned area on other sections of the cortex, the effect being highly selective and distributed over the entire cortex. Such discharges can also be observed at various points of the subcortical apparatus. In essence, the approach in the study of the intracortical connections which has been designated "neuronography" is based on this principle of the selective distribution of strychnine excitation over the cerebral cortex (Bailey *et al.*, 1950).

Especially interesting in this respect are the experiments of my collaborator Shelikhov (1959). Upon obtaining generalized strychnine discharges over the cortex, he froze the section where the paper moistened with strychnine had been applied. In spite of this, the strychnine discharges continued as before. Such a systemic spread of excitation is closer to the natural interactions in the cortical activity than the focal diffuse decreases of excitability or electrical activity.

These considerations can also be fully applied to rhythmic stimulation of different points of the cerebral cortex. Is it possible to conceive of a natural function of the brain in which some section of the brain would be excited by electric current of a potential up to 40 V *without a natural afferent action*?

It seems that the temporary inhibition of "neighboring" regions obtained in this case can hardly be related to the highly selective and always *systemic* activity of the cortical neural elements. All the data presented, original and interesting as they are, must be used for explaining the mechanism of the origin of coordinative inhibition in the central nervous system.

The authors also came upon a number of obstacles when they attempted to correlate the change in the electrical phenomena in the cerebral cortex with the presence of an inhibitory process in the cortical cells. At the present level of our understanding of cortical potentials it is necessary to correlate their change with the presence of *coordinative* inhibition, which is often very delicately and dispersively distributed over the individual synapses. Diffuse inhibition, which is connected with traumatic, toxic, and other effects on the brain, is, of course, a different matter. It undoubtedly must be reflected in the electrical activity of the cerebral cortex. However, it has to be proved

that this diffuse inhibition can be identical with coordinative inhibition. It is therefore not likely that this electrical manifestation will help us to understand the nature of coordinative inhibition.

It should be noted that, due to the artificial conditions of the stimulation of the cerebral cortex with electric current, the investigators came to the conclusion concerning the absence of pessimal inhibition in the cortex.

Quite different are the results when the afferent pathways are stimulated, i.e., when the impulses naturally arrive in the cortex. Under these conditions, as was shown by Forbes *et al.* (1949), "Vvedenskii inhibition" can be demonstrated.

Summarizing all the comments presented above concerning the dendritic theory of inhibition as published by Beritashvili and Roitbek, we must say that this theory, without doubt, deals with the question more profoundly than do other theories. With this theory as a basis, it is necessary to explain the fractional, selective, and remote inhibitory influences that are widespread in the activity of higher animals and especially man. At present it is well known that all forms of activity of the brain consist of a *local, discrete* component and a *generalized* activity accompanying it which are essentially caused by the reticular formation of the thalamus and brain stem. The development of these generalized forms is undoubtedly related to a change in the electrotonic state. The authors must demonstrate the possibility of an anelectrotonic inhibitory effect, which is diffuse, as the universal mechanism of central coordinative inhibition. This inhibition must in its highest form ensure the selectivity and precision of the excitation on which the adaptive reactions of animals are based.

Undoubtedly, the electrotonic component of excitation and, consequently, its participation in the formation of inhibition cannot be ignored. The origin of an inhibitory process in the encounter of two excitations can be considerably facilitated if anelectrotonus spreads to the area of the "encounter." Apparently the extent of participation of each of the two components will be determined here by the sum total of the conditions: the localization of the inhibition, the nature of the interaction of the two systems of excitation, etc. However, in all cases of active inhibition of any quite specific integrated activity of the organism, having just as definite a set of working components, *the decisive part is undoubtedly played by the discrete impulses sent to the point of inhibition in a definite rhythm and with a definite frequency.*

Of course, in the central nervous system these interrelations are, as we have seen, always developed on a background and with the aid of fused tonic signalization. The outcome of the struggle between the two systems of excitation and the shaping of the reaction as a whole, however, will depend on the discrete impulses, which determine the accuracy and limits of activities to be inhibited as well as the one that is to take place at the given moment.

In this sense, a highly important role can be played by "general inhibition," the systematic study of which is the unquestionable merit of Beritashvili's school. I shall attempt to give a brief account of these concepts which have recently acquired greater precision and clearer functional correlations (Beritashvili, 1966).

As I have repeatedly mentioned, inhibition must be regarded as the tool for the liberation of the organism from excess degrees of freedom that are potentially at its

disposal at any given moment.

What is the physiological meaning of this? How does the organism eliminate millions of possible movements in order to perform one single, precisely coordinated movement?

It has already been stated above that the movement must be implemented by means of very discrete and exactly localized processes of excitation and inhibition. This selectivity probably extends down to the individual synaptic formations. Here "general inhibition" could only disrupt the delicate distinctions between the individual synaptic processes, distinctions which, as we have seen, may coexist on the membrane of the same neuron (see Chapter 5).

But what about the instantaneous elimination of millions of possibilities of action? It is quite likely that "general inhibition" effects this function. At any rate, Beritashvili himself ascribes a related role to "general inhibition" during the patterning of behavioral activity. For example, in one of his latest publications (1966) he writes:

General inhibition is an integral part of every reflex or behavioral reaction, causing the integrity of central nervous activity: along with the excitation of certain neural complexes, which are adapting the organism to the environmental changes acting upon it, a decrease in the excitability of the entire remaining nervous system takes place.

As a result of this, the processes of excitation become localized in certain neuronal loops, and a simultaneous excitation of other neuronal loops in response to other environmental influences becomes impossible.

If we disregard some statements made in accordance with the traditions of analytical neurophysiology, this point of view correctly outlines the *coordinative role* of general inhibition.

The question must involve not simply the elimination of "other neuronal loops," but the elimination of activities widely using these neuronal loops.

In fact, the latest data concerning the convergence of impulses upon the same neuron lead us to believe that, owing to the selective involvement of its synapses, the same neuron is able to participate in dozens of activities. This consideration, however, can be applied to every neuron. Consequently, to inhibit *entire neurons* would mean to completely destroy the activity needed for the given moment.

It is quite evident that general inhibition acts upon some more universal levers, upon more integrated areas. At any rate, general inhibition is certainly one of the components of that highly important, yet still in many respects mysterious process, which has been called decision making. It is at this moment that the opening of the pathways for the required activity prompted by the afferent synthesis and the instantaneous *general inhibition* of all remaining potentially possible activities of the organism occurs.

The highly interesting and important investigations of "general inhibition" systematically pursued by Beritashvili and his school have considerably facilitated the search for the exact mechanisms of this link in the overall architecture of the behavioral act.

CHAPTER 11

The Nature of the Interaction of Two Excitations in the Central Nervous System

EVALUATING all known data, we can definitely conclude that there are several forms of inhibition of inappropriate activity of the organism. These forms of inhibition are used in different situations and have different adaptive effects and different expenditures of energy.

For example, if a shot rings out near the window while you are occupied with something at your desk, your entire previous activity is immediately inhibited, and activity connected with the analysis of the outside situation is initiated. It is quite evident that this inhibition "doesn't cost us anything." It arises with a minimum expenditure of the energy resources of our brain. If, however, we are upset by some unpleasant situation and for some reason are unable to react in the appropriate manner, there also occurs an inhibition of some reaction. And yet this inhibition is effected with enormous difficulties for the nervous system, often overcome only after a lengthy, emotionally strenuous struggle.

It is clear that in these two cases the same architectural mechanism of inhibition cannot be utilized, even though in their ultimate physicochemical nature they may be identical.

The solution of this problem is to be sought by proceeding from the *spatial and temporal relationships of nerve impulses*. To some degree we must try to clarify the question as to how and where the "inhibitory impulses," being rhythmical in nature, come in contact with similar rhythms of the current "inhibited excitations."

It is necessary to first evaluate one of the most central phenomena of excitation, *depolarization*. There is no single form of a spreading excitation not related to a change in the polarizing properties of a given excitable system. The whole complex picture of the chemical processes which appear in an individual discharge of excitation causes a spreading excitation only if this chemical constellation leads to a *sudden* change in a stable "ionic asymmetry."

The overwhelming majority of contemporary physiologists agree that in the origin of the process of a propagating excitation, this ionic stage is absolutely necessary. Data continue to accumulate in regard to the chemical characteristics of excitation; they convince us that the early ideas on the so-called membrane theory of the origin of excitation are generally untenable.

Until recently, in accordance with the membrane theory, it was held that the ratio

of K ions and Na ions within the nerve fiber to those outside is maintained by means of the selective permeability of the membrane with respect to these ions when the nerve is in a state of rest.

The application of the method of tagged atoms (K^{42} and Na^{44}) has shown, however, that even when the nerve is in a state of rest, K and Na are continually being exchanged through the neural membrane. In spite of this exchange, the corresponding initial gradient for K and Na or, as it is customarily called, the "ionic asymmetry," is constantly maintained at the same level (Keynes, 1951a, 1951b; Keynes and Lewis, 1951).

This finding is the best demonstration that the problem lies not only in the "selective permeability" of the axon membrane, but primarily in the specific metabolic processes which maintain a definite gradient of the Na and K ions. Table 11.1 is a tabulation of these concentrations for the axons of different animals.

TABLE 11.1. MOVEMENT OF IONS THROUGH A RESTING MEMBRANE
AFTER HODGKIN (1951, p. 364) AND KEYNES (1951b).

Tissue	Ion	Concentration in mm per kg of water		Movement in $\mu\mu$ mol cm^{-2} (per impulse)	
		Outside	Inside	Inwards	Outwards
Sepia axon	K+	9.7	272	17	58
	Na+	458	110	61	31
Carcinus axon	K+	11.3	255	19	22

The relationships between ions on the outside and inside change so fast and within such wide limits that investigators necessarily assumed the presence of a special pumping apparatus in the axons which creates the required concentration gradient for Na and K ions and quickly restores the disturbed proportions (Hodgkin and Huxley, 1952a, 1952b; Huxley and Stämpfli, 1951a, 1951b; Eccles, 1957).

It is interesting to note that these mechanisms are not destroyed when the nerve is in a state of anoxia. This is a clear indication that the work of these "pumping" mechanisms is achieved by means of high-energy phosphates (Keynes, 1951a, 1951b). It was demonstrated that the speed with which the redistribution of ions occurs and the quantitative relationships which create the most favorable conditions for the explosive character of impulses are continuously maintained by metabolic processes of the axoplasm and axon membranes. Thus, polarization of a resting nerve proved to be a physiologically maintained process.

For the problem under discussion it is important that the physiological role of the initial polarization of the neural elements was demonstrated. It was shown that this is an absolutely essential prerequisite for the origin via depolarization of any form of propagating excitation. If we now proceed to the problem concerning the nature of the inhibition by means of which one system of excitation suppresses another, then we can express two fully substantiated propositions :

1. It seems improbable that there would be any excitation of neural elements without some degree of depolarization of their surface membranes.

2. Therefore, any "inhibition of excitation" can be considered effective only when the possibility of a sudden *depolarization* of the neural elements under inhibition is entirely prevented.

From these propositions it is clear that any suppression of an unnecessary system of excitation must proceed via the creation of conditions under which functioning is impossible for all those metabolic systems which, *by the release of acetylcholine and by sudden depolarization*, create conditions for the development of a propagating excitation.

Three such conditions may exist, each having its own physiological manifestation. These are as follows: (a) stable polarization; (b) stable depolarization; (c) stable hyperpolarization.

It is clear that if the propagating impulse meets one of these three conditions at any of the relay points on its path, it will then invariably be blocked. This leads to the removal on the periphery of some manifested effect: the *phenomenon of inhibition* will be present.

It should be emphasized that, in working with the idea of depolarization, we do not wish to remove the physical aspect in the development of an excitation from all the various metabolic processes of which the excitation is composed. Depolarization is of interest to us only because any development of excitation is invariably connected with the process of depolarization. We of course remember, however, that polarization as well as depolarization is only the final expression of the metabolic constellation on which these two phenomena are based.

Continuing this line of reasoning, we must ask: which of the three above-named possible conditions exists when one system of *inhibitory* excitation (for example, the orienting-investigative reaction) suppresses another system of excitation which in this case is a system of inhibited excitation (for example, an alimentary reaction)?

Unfortunately, the question concerning the relationship of two integrated activities of the organism, especially with regard to their collision which ends in the inhibition of one of them, has not as yet been solved physiologically. Usually in such cases it was merely stated that an *inhibition* of one of them had occurred. However, it is not clear what kind of process in its final physicochemical nature arises at the boundaries of two systems of excitation. This question has not been systematically examined.

Evidently, we must explain not inhibition *per se*, but the inhibition of activities by means of a stronger activity. The concept of the origin of inhibition as the result of the *encounter* of two excitations was originated by Russian physiologists and is at present widely accepted by Russian schools of physiology. In view of this, we shall attempt to answer the above question, utilizing data which apply in general to the characteristics of excitation and inhibition. These data have been obtained primarily from the study of simple preparations and from the study of reciprocal inhibition in segments of the spinal cord. This is why, at various times and in various cases of suppression of function, the most diverse terms and concepts have appeared. To a certain degree they undoubtedly reflect the actual diversity of natural processes in the neural tissue, but to a greater degree they indicate the absence of serious attempts to synthesize the various concepts on the basis of one crucial requirement: *to explain suppression of one integrated activity of the organism by stronger excitations of another activity which always occurs under the*

natural conditions of life. In this connection I should mention one attempt to put order into the whole varied and contradictory terminology which has developed during the study of the problem of inhibition. Vasil'ev (1957, p. 105) cited the existing concepts of inhibition as follows:

Types of suppression	Types of inhibition
1. As a result of stimulation (a) accommodation (b) adaptation	1. Inhibition connected with the passage of a nerve impulse (a) refractory state (b) subnormal state
2. Suppression evoked by agents causing alteration (a) electropositive (b) electronegative	2. Inhibition which depends on the strength and frequency of nerve impulses (a) pessimal (b) vagal
3. Suppression connected with the presence of a focus of excitation (a) perielectrotonic phenomena (b) concomitant parabiotic phenomena.	3. Inhibition connected with the presence of nervous activity (a) dominant (b) inductive

This attempt to systematize the terminology of inhibitory states is, as far as we know, the first in physiological literature. It is therefore natural that it should have some defects. First of all, it has no *single principle* of classification. Indeed, under "types of inhibition," conditions are listed which in the general outline appear to be independent. In their physiological essence, however, they represent only different stages in a gradual analysis of a complex nervous phenomenon.

For example, what is "inhibition caused by a dominant"? This is an *inhibitory action of a dominant activity on some other activity*. But this inhibitory action can be brought about by means of pessimal inhibition, by perielectrotonic action, or, finally, by the creation of foci of subnormality. Thus these "types of suppression" and "types of inhibition" are essentially not a kind of independent form of classification, but represent individual facets of complex forms of nervous activity, including their physicochemical nature. This once more emphasizes that in classifying inhibitions it is most valid to proceed by way of gradual simplification of the problem, beginning with the natural forms of the integrated nervous activity.

In spite of some defects, the classification by Vasil'ev helps us to see the perspective for further analysis of the nature of the inhibitory process or, to be more exact, the nature of the *inhibition of nervous activity not needed at a given moment*.

We shall attempt to see how these inhibitions could be achieved by means of the

processes which are found in Vasil'ev's classification.

The overwhelming majority of these processes can be reduced to a common denominator, namely, to the *change in polarizability of the neural elements of the inhibited system of excitations*. In other words, with all the diversity of initial "types of suppression" and "types of inhibition," they can actually inhibit a current excitation only by creating in the inhibited elements one of three states of polarization (stable polarization, stable depolarization, and hyperpolarization).

Comparison of the electrical phenomena in various stages of the development of parabiotic inhibition shows that inhibition, as an *absence of the response to stimulation*, can take place under two opposite conditions: electronegativity and electropositivity (Vvedenskii, Vasil'ev, Verigo, and others). This alone would suggest that the absence of any external functional effect on the periphery can be achieved by two different states of polarization of the corresponding neural structures in the central nervous system.

Belitskii (1954), one of the representatives of the Vvedenskii-Ukhtomskii school, in developing the concept of the so-called "autoblockade" of a nerve as a result of the passage of potassium from the axoplasm into the external milieu, considers this mechanism to be the cause of parabiotic inhibition. From the point of view of the three possible polarization states, we must acknowledge that the "autoblockade" of Belitskii, *which does not permit further discharges of impulses in the given neural element, represents a typical example of a stable depolarization*.

Indeed, if one notes the duration of the action of the depolarizing factors which create a leveling of the concentration gradients for K and Na, then in case of an "autoblockade," that is, stable depolarization, we have an example of Verigo's cathodic depression. Belitskii (1954) believes that similar relationships, starting in neural elements under the influence of supramaximal or prolonged stimulation, can determine the phenomenon of protective inhibition.

We will leave the question concerning the possible origin of protective inhibition, since this is not at the moment the purpose of our analysis and demands special discussion. But we must pose the question: which form of disturbance of the polarization properties of the neural elements best satisfies the requirements of the suppression of "inhibited" excitations and the blocking of their exit to the periphery, toward the effectors?

If one imagines all possible conditions for the development of inhibitory states, then one would hardly suppose that they are achieved in the final analysis by only one kind of change in polarization characteristics. This pertains especially to the form of inhibition which Pavlov called "higher inhibition." Nevertheless, inasmuch as depolarization is a necessary condition for every excitation of neural elements, it would be natural to assume that the "inhibitory" excitation, possessing definite parameters of intensity and frequency, causes in the zone of formation of "inhibited" excitations a state of *prolonged depolarization* which would correspond to *blocking* or *inhibiting* the end effect at the periphery.

As the model form of depolarization, one may consider the processes of neuromuscular synapses which were studied by Vvedenskii as early as 1884. Recently, due to the

delicate microelectrode technique, his data have been more thoroughly studied. Using a schematic diagram of the relationships of the end-plate to the axon and to the substance of the innervated muscle, we may, on the basis of recent investigations, characterize these relationships in the following form.

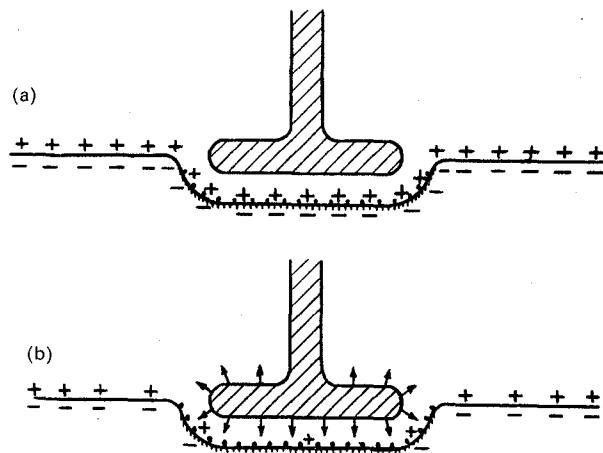


FIG. 11.1. Diagram of neuromuscular junction in two states. (a) resting polarized state; (b) state of depolarization at the moment of arrival of a nerve impulse. From Eccles (1953, p. 68).

As illustrated in Fig. 11.1, the neuromuscular synapse is represented in two consecutive states: the first, the resting state (a); the second, the state at the moment of conduction of the excitatory impulse (b). In the latter state the membrane of the muscle fiber is depolarized, which is indicated by the change in the ratio between positively and negatively charged ions. Depolarization is caused by the release of acetylcholine by the nerve ending (shown by arrows), and at a certain degree of concentration it can lead to a propagating excitation along the muscle fiber.

Electron-microscopic investigations of recent years have shown that the neuromuscular synapse has a very complex structure. The end-plate of a nerve fiber is very rich in small vesicles filled with acetylcholine (De Robertis, 1958). Here also, there are mitochondria and enzymes in large quantity. During activity, i.e., when nerve impulses reach the end-plate, the number of vesicles discharging their acetylcholine onto the postsynaptic membrane increases considerably. Thus, the postsynaptic membrane determines by its chemical composition the subsequent fate of the excitation in the molecular reactions of the cytoplasm. In this way the normal function of the synapse is effected.

From Fig. 11.1 it is clear that for the conduction of the *subsequent* excitatory impulse, the membrane of the muscle fiber must have time to be restored to its initial resting state of polarization. This restoration is the result of a special metabolic mechanism. The dots show the disposition of cholinesterase. By destroying the acetylcholine, this

enzyme prevents the prolonged persistence of the depolarized state of the membrane of the muscle fiber.

By direct injection of acetylcholine by means of a micropipet into a single end-plate, it was shown that, depending on the dosage of acetylcholine, one may obtain either a slight degree of depolarization which will not lead the substrate to an "explosive" change in ionic ratio ("local potential"), or a level which will lead to one full excitatory impulse, or a level leading to a whole series of impulses (Fig. 11.2).

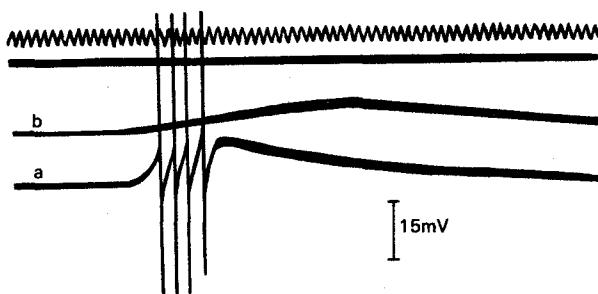


FIG. 11.2. Local application of acetylcholine (ACh) to the endplate region of a single nerve-muscle fiber preparation. Recording is done from the point of application. (a) 10^{-6} ACh sets up four propagating muscle impulses. (b) A weaker concentration of ACh produces a local negative potential only. From Kuffler (1943, p. 102).

It is evident that the acetylcholine utilized in these rhythmical impulses must soon be destroyed, since only in this way, after each quick depolarization, will there occur just as quick a restoration of the initial polarization gradient for Na and K ions.

Therefore, it is natural to assume that with increased intensity and frequency of impulses coming from the nerve endings, conditions may develop under which the mechanism of restoration of normal polarization ratios, which demands the most complex metabolic processes of an enzymatic character, will fall behind in bringing about restoration processes, and there will be a persistent depolarized state.

Thus, we may theoretically assume that during the encounter of two systems of excitations on a single morphological substrate, there may occur a stable depolarization at the contact points of these impulses. This may be the intimate mechanism of Vvedenskii's pessimal inhibition.

This supposition becomes quite probable if one considers Schiff's (1894) experiments to which Ukhtomskii gave great importance when explaining pessimal states. The essence of Schiff's experiments is as follows. If high-frequency impulses are sent to the muscle from a distant section of a nerve, then the muscle will not contract, due to the appearance of pessimal inhibition in the neuromuscular synapse. If, from electrodes situated closer to the muscle, infrequent impulses are simultaneously sent in the same direction which formerly evoked contraction of the muscle, then they also will be ineffective.

Analyzing these experiments, Ukhtomskii (1927) wrote: "The nerve not only

actively reduces the excitation of the muscle by its own impulses, but also *actively represses* that excitatory process which arises in the muscle from another source."

This remarkable model of the encounter of two impulses at one point (the neuromuscular synapse) was reproduced in our laboratory on ganglia by using the natural impulses from the receptor apparatuses of the aortic arch (Alvarez-Buylla, 1948, 1949). Thus, to a certain degree, we approached the natural conditions of an encounter of two impulses in a nerve center.

In order to describe the experiments of Alvarez-Buylla more clearly, I should first say something about the peculiarities of the anatomical relationship between the cervical sympathetic trunk and the depressor nerve. By oscillography, Alvarez-Buylla succeeded in showing that the afferent impulses of the aortic arch go from the depressor nerve along the anastomotic branch to the cervical sympathetic trunk and are then directed to the superior cervical sympathetic ganglion.

For the time being, I shall not examine the physiological significance of this anastomosis, since it will be revealed by further describing the experiments.

Electrodes placed below the connection of the anastomosis to the sympathetic trunk were used to evoke a positive background contraction of the nictitating membrane. At the moment when contraction of the nictitating membrane became stable, the blood pressure rose in the aortic arch. This led to a considerable increase in the frequency of afferent impulses. This new series of impulses, proceeding along the anastomosis into the superior cervical sympathetic ganglion, completely blocked the first impulses from the electrodes located on the sympathetic trunk, and the nictitating membrane relaxed. There was an interaction of two series of impulses on the synapses of the sympathetic ganglion, which in this case could be a model of interneuronal relationships in the central nervous system. As a result of this interaction, the series of stronger impulses blocked the propagation of impulses arriving at the ganglion from another source.

If we were to believe that this phenomenon is the result of the blocking action of prolonged depolarization created in the region of the sympathetic synapse by high-frequency stimulation from the pressoreceptors of the aortic arch, then we would have in this experiment a remarkable model of an interaction of "inhibitory" and "inhibited" impulses. It must, however, be stated that the above proposition is only a highly probable assumption concerning the role of depolarization in the origin of the inhibitory effect.

It may seem strange that, in spite of well-developed and thorough investigations on the enzymatic nature of excitation, we have to resort to theories proposed extempore, since the search for the chemical bases of excitation proceeds on a completely different level from that demanded by the interests of the physiologist in elucidating the principal physiological mechanisms. Such a mechanism may be that of the inhibition of an integrated activity to be eliminated at a particular moment. I shall try to further elucidate this disappointing disparity between neurophysiologists and biochemists who have been seeking chemical mechanisms of excitation.

As is known, an impulse consists of a series of cycles of chemical processes brought about at amazingly short intervals by the disintegration and resynthesis of the most substances (adenosine triphosphate, acetylcholine, pyruvic acid, etc.). All these meta-

bolic processes in the final analysis serve the purpose of causing *depolarization and repolarization of a neural element to occur in the shortest possible time, which determines the lability of a given excitable system* (Nachmansohn, 1959, 1961). Let us imagine that we are imposing greater demands on this broad chemical constellation, for example, by sending to it more and more frequent impulses. The complex system of chemical interrelations adjusted to each other in regard to precise time intervals begins to deteriorate and fails to ensure the most important links in the reactions. As a result, a lag is created in the rhythm of imposed stimuli, and finally there appears a complete pessimum.

A quite interesting question urgently demanding a solution from biochemistry is: due to which link does this complex system first begin to lag and finally, ceasing to respond to stimulation, cause the appearance of the inhibitory effect? Only the lack of contact between the work of neurophysiologists and neurochemists can explain the fact that this central question concerning the *origin of inhibition* has not been expressed in this way.

The question posed in this form can, however, enable us to understand the *nature* of one kind of inhibitory process. It is quite probable that upon putting some demands on the excitatory system, its chemical dynamics begins to lag due to the insufficiency of one component, while under other demands the lag is caused by another component. In order to determine the chemical composition of its constituents, the study of the chemistry of excitation must enter a new phase of development: *it must include a detailed chemical study of the strained states of the excitatory system, states which are caused by the imposition of maximum functional demands upon it.*

Only under such conditions can one come close to determining the chemical characteristics of inhibition as a result of the encounter of two impulses. However, studies now being conducted on the chemistry of excitation, in spite of their importance, as far as we know have not yet been conducted in this direction.

The nature of the central processes manifested on functional apparatuses in the phenomenon of "inhibition" may vary. This is shown by the latest investigations of Eccles (1953, 1964), who formulated the "hyperpolarization theory of inhibition." Inasmuch as this theory is becoming increasingly popular and is related to one of the three possible changes in polarization mentioned above, it is necessary to give it a more detailed critical evaluation.

The factual basis for Eccles' theory consists of recent investigations conducted by him and others on the problem of the dependence of initial polarization states of neural elements upon those concentration gradients for K and Na mentioned above. Investigating the changes of these polarization ratios during inhibition, Eccles used a fine microelectrode technique (Brock *et al.*, 1952). The aim of his work was to obtain a reciprocal state of inhibition of one of the motoneurons of the spinal cord and to measure the polarization ratios between the outer and inner surfaces of this inhibited neuron. The diameter of the recording tip of the microelectrode was 0.05μ , making it possible to introduce it into the protoplasm without destroying the integrity of the neuron. These investigations gave an interesting and to a certain degree unexpected result.

As soon as the motoneuron was subjected to an antagonistic afferent stimulus, it became markedly hyperpolarized.

It is of interest that this "hyperpolarization" did not start at once. At first, as soon as the afferent impulses came from the periphery, for a short period the usual depolarization began to develop. However, *due to the incorporation of some kind of special mechanism* (?), it quickly changed into a state of hyperpolarization. Due to its *hyperpolarized* state the motoneuron proved to be inaccessible to all the usual optimal excitatory influences, and its effect on the muscle is equivalent to inhibition.

Thus, the initial and substantiated finding in Eccles' investigations is the presence of hyperpolarization in the motoneuron at the moment of inhibition. It is on this account that Eccles' theory was called the "hyperpolarization theory of inhibition."

In view of the rapid and great accumulation of potassium and sodium ions, Eccles postulated the existence of an especially organized transmitter of these ions, a "hyperpolarizer," which would, in his opinion, help to establish the state of hyperpolarization.

However, how is one to visualize the spatial distribution of this "hyperpolarizer" over the synaptic formations of the motoneuron when it is known that the space and the membrane surface of the neuron in the synaptic area has no specific structuring? And how, in this case, will the existence of hyperpolarization, and consequently of the inhibition of a single synapse, affect the discharge activity of the hillock of the neuron?

In order to explain the ultimate mechanisms of reciprocal inhibition, Eccles had to construct a complex picture of the relationship between the nerve fiber, the synapse, and the body of the motoneuron ("postsynaptic region").

He made the following three assumptions:

1. Each of two kinds of receptor formations of the muscle has its own specific chemical characteristic which extends to the *sensory fiber itself* as well as to all its final ramifications, including the synaptic formations on the body of the neuron.
2. The same afferent fiber can have two or more end formations with different chemical characteristics, "hyperpolarizing" and "depolarizing."
3. All afferent fibers have the same chemical characteristics and release on their synaptic formations the same chemical transmitter. But the difference in their final action on the motoneuron in this case could depend on the specific chemical characteristics of the postsynaptic region which could be "hyperpolarizing" or "depolarizing."

In recent years Eccles' views regarding all three of these problems have considerably developed. They were comprehensively substantiated in his excellent monograph *The Physiology of Synapses* (Eccles, 1964), which the author regards as the culmination of his work in this field and to which I would refer you. Briefly, these results can be formulated as follows.

First of all, the concepts of the *heterogeneity* of the membrane of the nerve cell and accordingly of the possibility of having synaptic formations with different chemical properties on the body of the same nerve cell have broadened considerably. We have analyzed these new points of view in detail in Chapter 5. Thus, the actual possibility of the involvement of the same nerve cell *via different synapses* at various times has become obvious.

On the other hand, numerous data obtained in recent years increasingly support the point of view that the chemical characteristics of the trans-synaptic propagation of impulses are influenced by the postsynaptic membrane, which is thus able to bring about different functional effects in a nerve cell in response to the same initial volley of impulses. In his monograph, Eccles presents a diagram which is a good illustration of this experimentally achieved possibility.

From the structural point of view these interrelations are thus similar to those we obtained under the artificial conditions of crossed heterogeneous anastomoses (see Chapter 4). In these experiments the functional end effect also depended on the properties of the postsynaptic membrane, i.e., ultimately on the metabolic characteristics of the organ receiving the impulses.

Thus, the latest advances in neurophysiology have opened up extensive, purely structural possibilities for impulses arriving at the same nerve cell. It is most appropriate to emphasize here that these extensive structural possibilities allow almost limitless paths for the incoming impulses for the formation of always different combinations of central excitations.

These advances have made it especially apparent that for the entire organism the functional end effect is always the result of the structural interactions of the different processes of excitation and inhibition.

Still, there remains the problem which puzzles neurophysiologists : *what is the nature of the chemical processes accomplishing inhibition within a single synapse?*

In spite of the use of very delicate methods and the accumulation of a great amount of new data, the actual concept of the nature of inhibition as an "unsuccessful" explosive depolarization of the neural membrane remains unchanged. Indeed, the intracellular microelectrode recording of potentials shows that when an impulse reaches an inhibitory synapse, it first evokes an initial stage of depolarization manifested by an initial negativity. This negativity is, however, of very short duration and is immediately replaced by a more prolonged positivity, i.e., by hyperpolarization of the cell membrane. This change in polarization phenomena is what leads to the blocking of impulses at the postsynaptic membrane.

This sudden change in processes is very typical and is in accord with the discovery that in this presynaptic region *the same substance, acetylcholine, is secreted from the nerve ending in all types of synapses*. Only its reaction with the substrate of the specialized postsynaptic membranes produces a different end effect, either depolarization (excitation) or hyperpolarization (inhibition).

Any logical approach calls for the involvement of a specific factor which, upon its sudden release, interrupts the impending depolarization and transforms it into hyperpolarization, which is 10–40 mV higher than the resting potential. This still unknown factor has been called the "mediator of inhibition" or "factor of hyperpolarization." What is its ultimate nature?

The analysis of all types of inhibition in peripheral synapses of invertebrates and their comparison with the results of microelectrode studies of warm-blooded animals have led investigators to the conclusion that a certain factor *I* apparently very closely resembles the unknown hyperpolarizer in its characteristics. When applied to the

cerebral surface, it inhibits reflexes and has a definite hyperpolarizing effect on the cell membranes.

Another possibility for explaining hyperpolarizing action was suggested by the specific action of GABA. The point is that many investigators have shown that the motor nerves and nerve fibers which exert *only* an inhibitory effect on the muscles of crustaceans contain a very high amount of GABA. This has justified some investigators to state that perhaps GABA is the inhibitor which induces hyperpolarization at the postsynaptic membranes. A more thorough examination of the effect of GABA on depolarizing processes and on the state of excitation in general has led to the conclusion that in many cases GABA has an indisputable inhibitory effect similar to that of the natural inhibitory transmitter. Since the natural hyperpolarization in the postsynaptic membranes, just as the inhibitory effect itself, must be related to an increased permeability of the postsynaptic membrane, the effects of GABA on the permeability of the membrane are very impressive.

As does the natural hyperpolarizer, GABA affects this permeability rather selectively and unequivocally, increasing specifically the permeability for Cl⁻, and the action of both GABA and the natural hyperpolarizer is blocked by picrotoxin. These agents are also related by their ability to evoke inhibition in crustacean muscles.

Strychnine, which usually does not fail to eliminate inhibition in vertebrates, does not affect inhibition evoked either naturally or by means of GABA in invertebrates (Grundfest *et al.*, 1959). Completely opposite results were obtained for the action of picrotoxin.

In view of the data about the enormous amount of GABA in single, specifically inhibitory fibers in the crab, it must be admitted that all these data (except for some contradictions not yet understood) indicate the possibility of GABA participating in natural postsynaptic inhibition. This point of view requires, however, that increased amounts of GABA accumulate in the synaptic structure during the development of natural inhibition. Thus far such results have not been reported.

Another more likely substance having the role of inhibitory transmitter is acetylcholine. This may seem completely paradoxical at first, since the role of acetylcholine as a *transmitter of excitation* is well known. To realize how paradoxical this assertion is, one only has to recall the theory of the transmission of excitation developed by Nachmansohn (1959, 1961), which assigns the central role to acetylcholine. Nevertheless, many recent data rather strongly favor this point of view.

The idea that acetylcholine has a dual action is not new. Dell and Bonvallet (1956) proposed the assumption that *all types of trans-synaptic propagation of impulses are accomplished by means of acetylcholine*. Only the different nature of the receptor substances (and perhaps also the trigger structures) at the postsynaptic membranes creates different polarizing effects on the membrane which differently determine the subsequent fate of the impulses which have arrived via a given ending.

The selective and different action of the same substance, depending on its concentration, has now become quite generally accepted. It is sufficient to recall the universal biochemical principle of "inhibition by the end product" in order to visualize the numerous possibilities of the action of acetylcholine, especially since it is still active at

a concentration of 10^{-12} . What broad possibilities of a gradation of action and a selective patterning of different effects!

Perhaps the strongest argument in favor of this point of view was the discovery in the ganglia of the snail (*Aplysia*) of internuncial neurons which form an excitatory synapse with one branch of the axon and an inhibitory synapse with the other. *It is amazing that both synapses transmit impulses by means of acetylcholine!*

Although these relations were found in the snail, there is no reason to deny the existence of such a possibility in higher animals as well. It is easy to visualize what extensive possibilities this gives the central nervous system of higher animals which is composed of billions of different cells! These possibilities are undoubtedly utilized in the complex interactions of the entire brain when it implements an activity that includes all the known key mechanisms of the functional system which pattern a behavioral act. In any event, experiments have shown that acetylcholine plays the same dual role in other animals as well, evoking either depolarization or hyperpolarization, depending on its concentration and on the properties of the postsynaptic membrane (Eccles, 1964).

A review of these most reliable data concerning the nature of the inhibitory effect reveals that the localization and all the properties of the hyperpolarizer are determined by extrapolation, i.e., indirectly, by comparing its action with the action of other known chemical agents. However, in spite of the very high probability that the "transmitter" of inhibition has those properties which were determined by indirect means, the actual "transmitter" as a fully defined chemical substrate remains unknown.

Even though Eccles proceeds from reliable data obtained by extremely delicate methods, his theory of humoral "hyperpolarizers" still has a number of very substantial shortcomings. Suitable for explaining a definite form of inhibition (spinal, reciprocal), his hypothesis is based on the assumption of the *stable* inhibitory action of specific afferent fibers. Such a constitutional fixation of the hyperpolarizing action on definite synaptic formations makes it very difficult to explain all those cases in which the same action is at times inhibited and at others becomes involved in the activity of the organism.

True, everything discussed above concerning the heterogeneous formations on the membrane of the same cell admits the possibility of an influence on the same cell either by excitatory synapses or by inhibitory ones. Then in the former case the cell would participate in the active formation of some behavioral act, while in the latter case it would prevent its formation, i.e., it would promote the appearance of inhibition at the effector.

Only in this form can the concept of the humorally stable inhibitory synaptic formations be used to explain all types of inhibition which may have a temporary adaptive character. This situation is especially pronounced in the case of conditioned inhibition in which, depending on conditions of the external milieu, various inhibitory factors may come into play, the orienting-investigative reaction and others. An instant later the inhibited function may become an excited, active one.

In order to give the reader a complete idea of the present attempts to explain the origin of the inhibitory process, it is necessary to mention two more theories which are now popular in foreign literature: those of Gesell and Gasser.

Gesell's theory is based on the morphological characteristics of the neuron, discovered by means of recent histological investigations. I have in mind the structural characteristics of the so-called Mauthner cells found in some lower vertebrates. These cells have at their axon exits special structures by means of which, in the opinion of Gesell (1940), the appearance and exit of nerve impulses from the cell to the axon are regulated as well as the cessation of these impulses, i.e., the *inhibition* of neuronal activity (Fig. 11.3).

The Gesell theory considers the neuron to be an electrotonic apparatus which gives

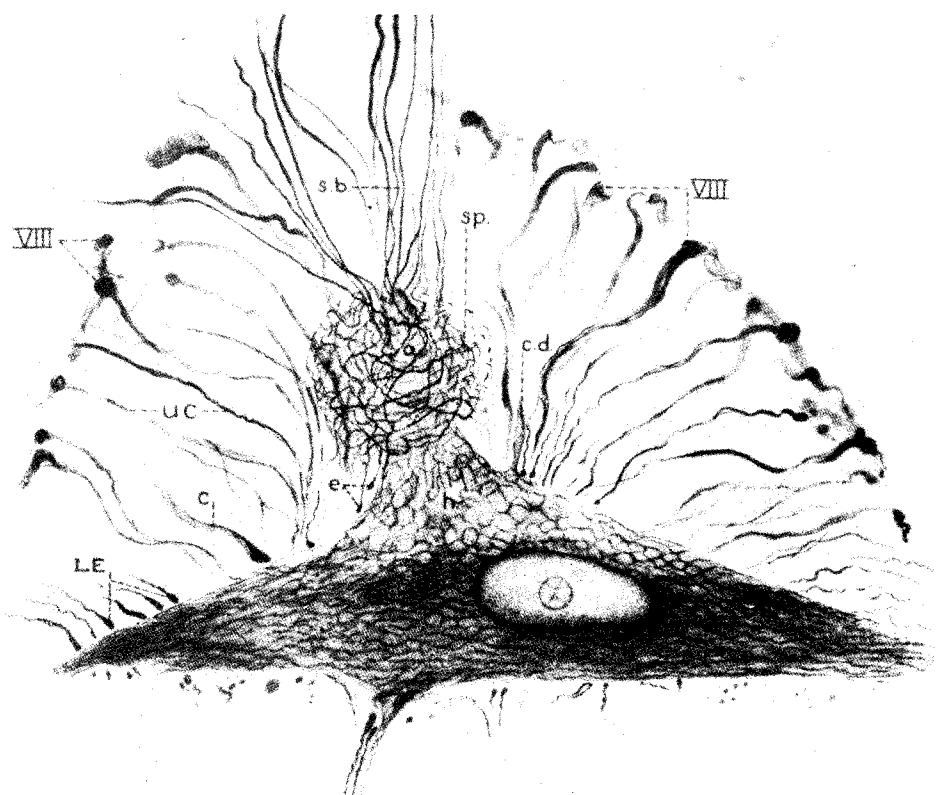


FIG. 11.3. Perikaryon of Mauthner's cell showing details of axon cap as they appear in a selective nerve fiber impregnation with activated protargol. Note irregular spiral of fine fibers forming the central core of the axon cap (sp.). These fibers enter the spiral as a bundle (s.b.) which arises in the supracommissural part of the fasciculus longitudinalis medialis, and leave the spiral to terminate on the axon hillock (h.) by means of tiny endfeet (e.). Also note the unmyelinated collaterals (UC) which arise from VIII fibers and radiate toward the axon hillock around which they terminate bluntly, or by means of endfeet. LE, large endfeet; c., myelinated club ending; a., axon; c.d., cap dendrite. From Bodian (1937; see Gesell, 1940, pp. 521 and 522).

rise to nerve impulses. The impulses arriving at the neuron and discharging on its dendrites continuously maintain the electronegativity of the dendritic part of the neuron. That part of the neuron from which the axon originates and where there are few synaptic formations proves to be positively charged. Thus, due to these functional differences between the dendrite and axon parts of the neuron, there is a potential difference between them which can be greater or smaller depending on the number of nerve impulses arriving at the dendrites.

The more intense the volleys of impulses coming to the dendrites of the neuron, the greater is the potential difference between its dendritic and axonal parts and, correspondingly, the higher is the frequency of nerve impulses emerging onto the axon. This function, the generation of nerve impulses, is, in the opinion of many investigators, fulfilled by the section of the neurocyte which lies at the point of origin of the axon. Not having Nissl granules, and therefore appearing as a clear section, it thus differs markedly from the rest of the neurocyte and received the name "hillock."

Because of these relationships between the electric potentials on the neurocyte, a cessation of nerve impulses must begin whenever the potential difference decreases.

What causes could lead to a sharp decrease in the potential difference? First of all, there may be a sharp decrease in the number of nerve impulses arriving at the neuron. We have already noted this possibility. However, there is another possibility which Gesell stresses in formulating his theory of inhibition.

Let us assume that on the background of a sufficiently productive potential difference between the dendritic and axonal parts of the neuron *increasing nerve impulses begin to arrive at the axonal part of the neuron*. In this part of the neuron an electronegativity develops. Consequently, the former potential differences may suddenly decrease, and this in turn stops the generation of nerve impulses in the hillock. Such conditions will correspond to the inhibitory state of the neuron.

Microscopic investigation has revealed the presence on the axon of Mauthner cells of some kind of peculiar structure which can be fully accepted as an apparatus for countercurrent negative impulses.

Gesell's well-developed and substantiated electrotonic theory of inhibition cannot have a universal application because the above-described axon apparatuses were not found on other neurons, especially not on the neurons of higher animals. It is true that Ramón y Cajal described recurrent axon collaterals which end either on the axon part of the same neuron or, as in the cerebral cortex, on the axon parts of adjacent neurons. In spite of these data, however, further details of the mechanism of inhibition in light of this theory remain indefinite. In particular, it is unclear what causes the excitation to arrive on the axon synapses selectively when, in response to a general behavioral situation, the necessity for inhibition has arisen. It must be noted that Gesell's electrotonic theory satisfactorily explains the phenomenon of "homogenization" of various nerve impulses by the motoneuron, which has already been mentioned.

To supplement this brief survey I shall discuss the inhibition theory of Gasser which was developed more than 30 years ago (Gasser, 1937; Erlanger and Gasser, 1937). Conceptually, this theory comes closest to the condition of the origin of inhibition in the central nervous system and does not require additional assumptions. Gasser's theory

proceeds from the established fact that there is a so-called subnormal phase which arises as a trace phenomenon after a single cycle of excitation and is characterized by decreased excitability.

This considerable decrease in excitability of the neural substrate soon (3–4 msec) after the end of a single cycle of excitation is entirely sufficient to decrease or even completely extinguish the other nerve impulse which arrived at the *same moment on the same neural substrate*.

The point of Gasser's theory is that the inhibition of a certain series of nerve impulses occurs when this series of impulses falls exactly into the phases of subnormality of another series of nerve impulses.

In special experiments Gasser showed on a nerve trunk the possibility of such an "inhibition" of a corresponding series of nerve impulses. A series of weak stimuli with a frequency of 20/sec was applied, followed by another series of impulses of the same frequency. These latter impulses were evoked by stronger stimuli and they propagated in such a way that *each impulse of the preceding series fell exactly into the phase of subnormality of the impulses of this second series*. Due to this temporal combination the first series of nerve impulses were immediately extinguished (Fig. 11.4).

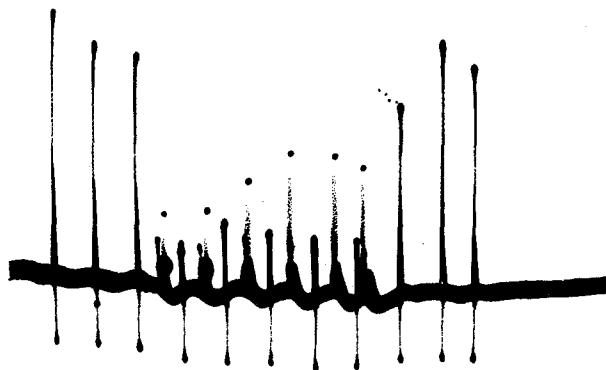


FIG. 11.4. The relationship of nerve impulses caused by two series of electrical stimuli in the same nerve. First is shown the normal series of nerve impulses caused by weak stimuli (first three impulses). Between these continuing stimuli six stronger stimuli are applied in such a way that the weaker now fall in phase with the positive after-potential resulting from the strong stimuli. A marked decrease in the initial potentials from the weak stimuli is apparent. The potentials from the strong stimuli are recorded as dots because they develop very rapidly and could not be fully recorded. From Gasser (1937, p. 189).

We are especially interested in this type of experiment because it may serve as a model for the relationship between excitations in the central nervous system. Gasser himself gives a diagram which explains, on the basis of his experiments, the appearance of reciprocal inhibition of antagonists in the spinal centers. However, the possibility of inhibiting one series of excitatory impulses by another can be utilized far beyond intraspinal relationships.

It is interesting to note that Gasser's theory is only an experimental demonstration of an old idea of the Russian physiologist Tsion (de Cyon). According to him, inhibition occurs as a result of the *interference of two series of nerve impulses*. For this reason his inhibition theory was at that time called the "theory of interferences" (Tsion, 1874, pp. 117-121).

As we shall see later, Gasser's inhibition theory most completely satisfies the conditions for the origin of pessimal inhibition in the nerve centers in the concepts of Vvedenskii and Ukhtomskii. Therefore, we shall return to it when we discuss the possible mechanisms of "higher inhibition" according to Pavlov. This theory is especially suitable to the form of inhibition discovered and developed by Eccles and has been called "presynaptic inhibition."

This form of inhibition is also brought about by means of hyperpolarization. In this case, however, it is not formed on the postsynaptic membrane but on the presynaptic portion of the nerve ending (Fig. 11.5).

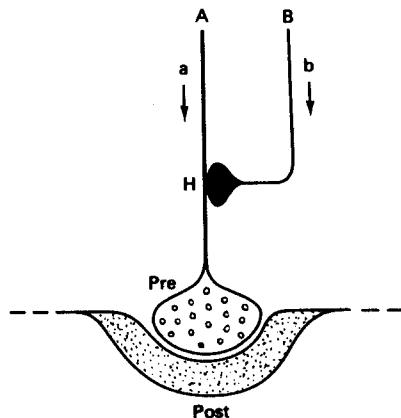


FIG. 11.5. In the usual activity of fiber (A), its presynaptic formation (Pre) and the postsynaptic membrane (Post), the nerve impulses (a) travel over the entire fiber and evoke excitation in the synapse as a whole. If, however, impulses (b) arrive during this time via fiber (B), hyperpolarization develops at point (H) and blocks the passage of the impulses to the synapse.

Owing to the fact that this peculiar "synapse" forms here in the presynaptic region on some section of the fiber a state of hyperpolarization, the impulses propagating toward the synapse are extinguished, i.e., they are blocked at this point; consequently, the result is the inhibition of the reflex effect. As can be seen, this form of inhibition is also caused by the dispatch of "inhibitory" excitation.

From the integrative and constructive point of view it seems, however, somewhat inexpedient to permit the arrival of impulses at the terminal neurons for the sole purpose of being "intercepted" almost at its point of destination.

Summarizing the present theories of inhibition, we must note that they all use as a model for their explanation of the inhibitory process the phenomenon of reciprocal or

antagonistic inhibition in the spinal centers. This is especially evident in Eccles' theory. The premise of these theories is based on the *stability and structural fixation* of the inhibitory actions inherent in this model.

On the basis of what mechanisms does the higher conditioned inhibition appear?

We shall subsequently attempt to show that the form of inhibition related to the elimination of activities of the organism which are interfering at the moment must be the central point of all our explanations. Therefore, that inhibition theory will most satisfy us which fully and convincingly explains the higher inhibition appearing under the conditions of adaptive behavior in animals.

But before we pass to this question we must analyze the *general mechanisms of the origin of conditioned inhibition*.

The material presented above regarding the existing views on the nature of inhibition now permits us to state four guiding propositions which form the basis for further analysis. These propositions are :

1. There is but one nature of the actual inhibitory process—a change in the polarization of the postsynaptic membrane, i.e., hyperpolarization.
2. Hyperpolarization always sets in as a result of *arriving impulses*, but it remains a *local process*.
3. Inhibition, as a process, never spreads over the neural substrate in the way excitation does. This means that many of our concepts, which are based on a spread of the "inhibitory process," must be brought into accord with neurophysiological data.
4. If we consider the postsynaptic membrane to be a *hyperpolarizing formation* due to its chemical properties, we must admit its active blocking effect on other depolarizing, i.e., exciting, synapses of the same nerve cell. Otherwise the role of the hyperpolarizing synapses proves to be physiologically unclear and useless for the integration of nervous processes.

CHAPTER 12

The Mechanisms of the Origin of Conditioned Inhibition

THE lack of a logical and necessary sequence in formulating the problems of investigation adds to the difficulty in solving the problem of internal inhibition. For example, the problem of *localization* of internal inhibition in the cortex is often posed for immediate investigation, while the mechanisms of the *origin* (or onset) of this type of inhibition are not utilized in order to clarify the localization of inhibition. Yet the relationship of these problems is such that no solution concerning the question of the localization of cortical inhibition can be considered adequate and convincing as long as it has not been decided by what concrete mechanisms internal inhibition originates on the basis of conditioned excitation.

This is, of course, related to the fact that the question of the basic physiological mechanisms of the *origin* of conditioned inhibition was not the center of attention for investigators of the physiology of higher nervous activity. This serves as a basis for discussing several concepts as the premise for a deeper analysis of the whole problem of the origin of cortical inhibition.

As we have seen, the Sechenov-Vvedenskii-Ukhtomskii school solved the problem of the origin of inhibition in the central nervous system quite definitively, establishing the fundamental basis of the physiological concept, and thereby created an historic continuity in the development of this important question.

In this connection it is quite interesting to discuss the question of Pavlov's attitude toward the concept of Vvedenskii-Ukhtomskii and to what degree he utilized the ideas of his predecessors concerning the origin of inhibition as the result of an encounter of two impulses in his theory of conditioned reflexes.

It is appropriate to emphasize the physiological sense of three different concepts—"identity," "unity," "specificity"—which are invariably connected with the problem of the relationship between excitation and inhibition and yet are often not defined as to their meaning. It is at this point that various points of view concerning the relationship between excitation and inhibition meet.

Ever since the general scheme of chemical interactions occurring during a single impulse was established, it became clear that "excitation" is a complex metabolic process basically consisting of transformations of acetylcholine, with a rapid disintegration and just as rapid a regeneration of phosphate compounds. Leaving aside the differences in interpretation of the chemical essence of the various aspects, we must call to mind only one exceedingly important fact to which we have previously referred.

Independent of the constituents and directions of the metabolic processes, the actual propagation of impulses inevitably proceeds by means of the depolarization of neural membranes. We have seen that the most outstanding theories of inhibition differ precisely in the evaluation of this final stage.

Regardless of differences in points of view concerning the role of depolarizing factors, the actual postulate that polarizing relationships are present is accepted by all as being a result of continuous metabolic transformations in the protoplasm of the neural elements. Consequently, in the existence of polarizing relationships, the unity of the physical and biological factors of excitation is manifested. Thus, the presence of long-lasting processes of depolarization and hyperpolarization must inevitably accompany certain changes in the metabolism of the excitable system. These concepts alone suffice to demonstrate definitely that there cannot, in the literal sense, be an *identity* between excitation and inhibition. However, all the latest data on the chemical characteristics of excitation convince us that inhibition does not have its own special chemistry. It is a *modification* of that chemical constellation which ensures the propagation of impulses, a modification which prevents an explosive depolarizing process of the nerve fiber. And so we are confronted with the question of direct interest to us: can excitation and inhibition be identical?

In regard to this, Pavlov's attitude toward Vvedenskii's theory of inhibition is of great interest. Pavlov most completely expressed his point of view concerning Vvedenskii's theory of inhibition when he discussed the investigations of N. N. Nikitin. In these he found Vvedenskii's thesis that *inhibition is a stable, stagnant excitation*. Pavlov objected to such an *identification* of the nature of these processes. Many times, Pavlov had pointed to the fact that these processes are very closely *related* in the integrated activity of the brain, and yet he definitely differentiated them as *independent* processes having their own "apparatuses" in the nerve cell.

Pavlov wrote (1949c, p. 96): "It is much more convenient to understand all the data thus: we are dealing with an excitatory process which constantly watches over another process, the arresting process, which under certain conditions interrupts the first process. Consequently, there is no question of an identity in these cases." Concerning the identification of excitatory and inhibitory processes as expressed by Vvedenskii, Pavlov elsewhere said flatly: "We do not agree with his theory . . ." (Pavlov, 1926, see Pavlov, 1967, p. 349).

What is it in Vvedenskii's theory that can be considered as an index of *identification* between excitation and inhibition? Probably his popular expression that *inhibition is a stable, stagnant excitation*. Yet it is difficult to believe that Vvedenskii thought that excitation, having lost its most characteristic property, the capacity to spread, and having become "stagnant," *should remain the same in its intimate chemical nature*. That it cannot spread by means of an explosive depolarizing process indicates that the normal chemical constellation of excitation has undergone definite changes. Consequently, inhibition, in spite of its direct chemical relationship to excitation, is nevertheless *something different* in its nature. This difference may be chemically insignificant, and yet, by stopping the explosive process of excitation, it leads to a qualitatively opposite effect on the periphery.

Vvedenskii's theory establishes a *unity* between excitation and inhibition *based on the genesis of inhibition*, and this is one of the greatest achievements of the Vvedenskii-Ukhtomskii school. Nonetheless, this unity of origin, due to the inaccuracy of formulation and after a number of transformations, has changed into an *identity* between excitation and inhibition. The first formulation fully corresponds to the experimental findings and is a progressive one; the second, on the contrary, does not correspond to reality and leads to unnecessary disagreements. In this point lies the source of the contradiction between the views of Pavlov and Vvedenskii on the nature of the inhibitory process or, more specifically, on its relation to excitation.

Having established the unity of excitation and inhibition *on the basis of genesis*, Vvedenskii drew far-reaching conclusions concerning the *identity* of these processes. This was facilitated by the fact that all of Vvedenskii's investigations on the nature of inhibition were conducted on a model of an isolated excitable system, i.e., on properties of specialized protoplasm (nerve, muscle). The *features of the genetic resemblance* between excitation and inhibition were therefore correctly emphasized, but the final functional results in the activity of the integrated organism were not taken into account, although these results determine the *contradictory* character of these processes. On the other hand, from the very beginning of his research, Pavlov encountered these contradictory features of the external adaptive activity of the animal, i.e., essentially the functional consequences of inhibition. Therefore, he gave his chief attention to the contradictory character of the adaptive acts, or, as he vividly expressed it, to the various forms of "yes" and "no" interaction.

This decisive role of the external adaptive effect in Pavlov's evaluation of the processes of excitation and inhibition was clearly apparent when he discussed Vvedenskii's point of view. He said (1949c, p. 92): "I maintained that the excitatory and inhibitory processes are different; we cannot say they are completely opposite, but in *appearance and in results they are opposite*" [italics—P.A.]. It is therefore natural that he should have a negative attitude toward all attempts to *identify excitation with inhibition*. As a naturalist who based his creative activity on causality (determinism), he could not grant that two processes of the central nervous system leading to *opposite forms* of behavior could be identical.

It clearly follows that the contradictions in the views of Russian physiologists on the nature of inhibition must be regarded as the result of characteristics of the method of investigation and of the experimental data themselves. All the data on the nature of inhibition presented above convince us that always and under all conditions only excitation spreads over the central nervous system. Consequently, the difference is determined by the *structural and chemical composition of the final stage—the postsynaptic membrane*.

Thus, the two processes are "identical" since they originate as excitation, but they are substantially different in regard to the processes on the postsynaptic membrane.

Even more serious is the contradiction which results from the postulate about "the conflict between excitation and inhibition." However, this will be discussed in detail later.

Of special importance at present is the fact that, by demonstrating the contradictions

between these processes, Pavlov postulates that inhibition can originate in a quite definite sequence in the development of the processes; *first excitation, then inhibition*. Essentially, this is the *common basis* for the creative development of Pavlov's and Vvedenskii's views on inhibition.

Having established the conditions of transition from one process to another, we come closer to understanding the mechanisms of the relationship between excitation and inhibition, and the difference between these processes acquires a definite character.

In this connection, Pavlov more than once pointed to the dependence of the inhibitory process on the development of excitation, emphasizing the definite sequence of conditions in its origin. For example, Pavlov said: "Evidently there is some kind of [substantial] relation between the processes of excitation and of inhibition; if the former is diminished, then the latter becomes weaker or even fails altogether" (Pavlov, 1924, see Pavlov, 1967, p. 336).

In light of Pavlov's statements, Rusinov, who said that Pavlov did not in any way demonstrate the genetic unity between excitation and inhibition, must be considered incorrect. Attention is called to the fact that in the statement quoted, Pavlov also emphasized the dependence of the inhibitory process on the strength of the initial excitatory process.

However, did Pavlov raise the question concerning the origin of the inhibitory process in the cerebral cortex as the result of the encounter of two impulses? A careful study of Pavlov's statements in regard to conditions for the appearance of the inhibitory process convinces us that in explaining the *origin* of the inhibitory process, he frequently came close to understanding it as Vvedenskii and Ukhtomskii did. And yet he never gave a direct and concise formulation to this question.

If one evaluates all those examples which Pavlov examined in connection with the relationship between excitation and inhibition, then there remains no doubt that he often approached the problem of the *interaction of two mutually exclusive integrated activities of the organism*.

Thus, in examining the question about the difficulties involved in the elaboration of conditioned reflexes to cutaneous stimulation, he explains this difficulty by saying that the direct unconditioned reflex arising from cutaneous stimulation causes an *integrated defense activity* in the experimental animal. The defense activity becomes an *inhibitory excitation* with respect to the alimentary integrated activity, as a result of which the conditioned secretion is inhibited.

Many examples from Pavlov's works may be cited in which he comes quite close to the problem of the origin of cortical inhibition; moreover, the examples always illustrate the relationship of two nervous activities, two excitatory systems. It is very important to evaluate his statements more thoroughly.

The fundamental importance of the views of Pavlov on this subject is so great that I will take the liberty to quote him verbatim. This is necessary because, in my opinion, the established view on this subject unreasonably ignores the diversity of Pavlov's attempts to give a definitive solution to this "accursed problem."

In examining the difficult elaboration of the inhibitory process in animals and man, Pavlov wrote: "If, for example, I am occupied with something—*i.e.*, I am under the

influence of a definite process of excitation—and if someone suddenly proposes to me to do another thing, it is unpleasant for me. For it means that I must inhibit the strong excitatory process in which I was engaged, and only after this can I start a new one. . . . you experience a powerful stimulation, but are compelled by the circumstances of your life to suppress, to inhibit it" (Pavlov, 1924, see Pavlov, 1967, pp. 333–334).

Examining the problem of the absence of secretion in response to inhibitory stimuli, he asked: "What then! Have they become indifferent? By no means. Instead of showing a positive effect they have taken on an inhibitory one" (Pavlov, 1928, see Pavlov, 1967, p. 373).

Another example shows even more clearly the actual genesis of the concept of the "conflict of the excitatory and inhibitory processes." Pavlov cited the following example: "For instance, somebody has deeply insulted me and I for some reason or other have not been able to respond to it by corresponding words, or, moreover, by a certain action, with the result that I had to overcome the struggle or conflict between the excitatory and inhibitory processes within myself" (Pavlov, 1935c, see Pavlov, 1957, p. 468).

By citing all these descriptive examples from life which were numerous in all of Pavlov's lectures, we by no means want to say that the idea of the collision of two systems of excitations was already clearly expressed by him, nor that he used this idea in constructing his working hypotheses. Every one of Pavlov's students knows well that neither was the case. Pavlov never connected the genesis of internal inhibition with the encounter of two impulses.

We cannot, however, overlook the important fact that when Pavlov needed examples of inhibition from natural life situations *he always cited those relationships containing an obvious conflict between two complex and elaborated activities of the nervous system*. We could not help seeing here the significant fact that the *natural* activity of the brain as a whole compels us to extend the initial laboratory concept concerning the mechanisms of the origin of internal inhibition in the cerebral cortex.

Examination of the first example alone will convince us of the correctness of our conclusion. Indeed, how else can one understand Pavlov's expression that "you . . . are compelled by the circumstances of your life to suppress, to inhibit . . ." the already existing nervous activity which is a "strong excitatory process"?

There is no doubt that in this concrete case, the "excitation to be inhibited" is the "strong excitatory process," while the "inhibitory excitation" is formed in the cerebral cortex by "the circumstances." Physiologically understood, these "circumstances" are always a sum total of external factors, and for man they are almost always a sum total of social factors. As a whole they create in the central nervous system of man some stimulatory motive to a higher form of behavior; in the *physiological sense*, "circumstances" invariably are the source of a very complex system of excitations which becomes an "inhibitory excitation" in the end.

In a social sense, any inhibitory action by some circumstances presupposes, as a rule, a prolonged elaboration of extensive *complexes of excitation* perpetually acquiring stimuli throughout life. Often acquiring an unbelievable complexity and encompassing what is referred to as the "personality," these systems of excitation then allow some external

stimulus, as Pavlov expressed it, "to excite inhibitions in the central nervous system."

Pavlov's views on the origin of internal inhibition were very clearly expressed when he comparatively evaluated external and internal inhibition. Speaking of the origin of external inhibition, he wrote that it ". . . is an exact repetition of inhibition, well known for many years in the physiology of the lower parts of the nervous system when *stimuli*, acting on various nervous centres and provoking *various nervous activities, meet*; the second [i.e., internal inhibition] may relate only to the cerebral hemispheres. Probably, however, the difference between these two inhibitions has to do only with the conditions of their origin, but not necessarily with the process itself" [italics—P.A.] (Pavlov, 1926, see Pavlov, 1967, p. 339).

The above emphasizes once more the fact that the *question of the origin* of the inhibitory process in the cerebral cortex insistently demands an answer. One would wish that the comprehensive investigation of all the mechanisms of the origin of inhibition would more widely attract the attention of the physiologists and pathologists who are studying higher nervous activity, the behaviorists, and especially the adherents of the Vvedenskii-Ukhtomskii school, who are experts in the general physiology of the inhibitory process.

In order to check the validity of all considerations concerning the *origin* of inhibition in the cerebral cortex, we must apply them to the actual appearance of cortical inhibition under experimental conditions.

Let us use the most typical and frequently occurring form of cortical inhibition, extinctive inhibition, and with this example attempt to trace the *origin* of the inhibitory process.

Evidently, in the case of extinction, the *primary* excitation must be taken to be that excitation which the conditioned stimulus to be extinguished (e.g., the visual conditioned alimentary stimulus) evokes in the peripheral end of the analyzer on the corresponding receptor surface (i.e., the retina). This excitation subsequently propagates along the optic nerve, the geniculate body, and finally it arrives at the cortical end of the visual analyzer, i.e., the *area striata*. There can hardly be any doubt that the process of excitation, caused by the stimulus which was extinguished to zero, is a true excitation until its actual arrival in the cerebral cortex. Until this stage of propagation it undoubtedly resembles any other excitation originating in the receptors of the organism. All the data on the general physiology of nervous processes and of analyzers force us to accept this.

But here we have come to the critical point in the development of the inhibitory reaction: what physiological conditions transform the *excitation* which has arrived at the cortical cells from the visual stimulus into an *inhibition* which stops the alimentary excitation of the animal? This is just the question which Pavlov called the "accursed question."

Let us attempt to present the solution which is most probable from our point of view. From the investigations of Vvedenskii and of Ukhtomskii, it follows that any active inhibition in the central nervous system is predominantly a pessimal inhibition.

In what way can our stimulus to be extinguished acquire the capacity to evoke a pessimal inhibition? The simplest answer to this question could be the assumption that

as nonreinforcement continues, the stimulus to be extinguished acquires a greater force and evokes a higher frequency of nerve impulses in the receptors.

However, this assumption has no physiological basis whatever; the stimulus to be extinguished, such as light, does not change its physical qualities (energy) during the entire course of extinction. Consequently, the number of nerve impulses evoked in the retina and sent to the cerebral cortex cannot noticeably change.

What factors, then, are the cause of the origin of the inhibitory process?

On the basis of the commonly accepted experimental setup involving internal inhibition, we are certain that the primary excitation of the given analyzer is later transformed into inhibition only because the *conditioned stimulus is not accompanied by eating*.

However, the purely descriptive statement of this commonly known fact does not yet, of course, solve the problem concerning the nature of the physiological mechanisms of the origin of the inhibitory process. On the contrary, it presents us with still more questions which now insistently demand solution.

The greatest impetus towards the solution of these problems came from Pavlov. Establishing the fact that, upon nonreinforcement of the conditioned reaction, the primary conditioned stimulus "... becomes sooner or later a negative, an inhibitory stimulus," Pavlov added: "Relating to this indisputable fact there arose the question, Why is this so? *But until now there has been no answer*. Therefore we must begin with this fact without having analysed it. Such is the *first basic relation between excitation and inhibition*" [italics—P.A.] (Pavlov, 1926, see Pavlov, 1967, p. 340).

From the statements quoted it can be seen that more than 40 years ago Pavlov raised the question concerning the then obscure inhibitory action of *nonreinforcement with food*, but at that time he did not find a direct answer. In later years many different data were obtained in Pavlov's laboratories which, as we shall see below, undoubtedly provided a basis for indirect opinions concerning the mechanisms of this crucial phenomenon of higher nervous activity. However, the problem as a whole was not once systematically analyzed, and therefore up to the present it has not been given a satisfactory solution.

The solution of this initial problem did not become the necessary link in the development of our general concepts regarding cortical mechanisms of higher nervous activity, which has become a marked obstacle to the elucidation of the physiological mechanisms of cortical inhibition. Our experience convinces us that any systematic work on elucidating the mechanisms of internal inhibition is *unavoidable* and *first of all* requires the solution of this "*first and basic relationship between excitation and inhibition*" formulated by Pavlov.

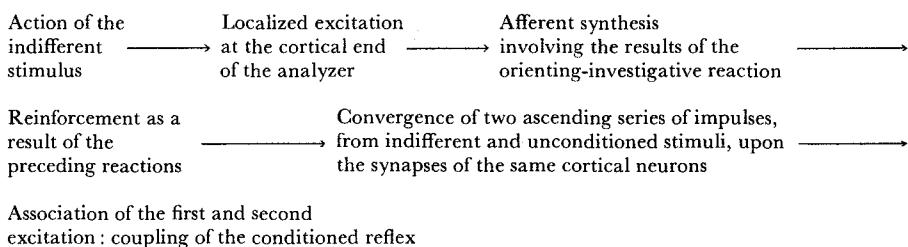
Strictly following the law of causality, we must pose the question: on the basis of what known physiological principles can nonreinforcement with food, i.e., *the absence of the unconditioned stimulus*, convert the existing process of excitation into the opposite process of inhibition?

At this point in our concepts concerning cortical inhibition, there is an obvious gap in the physiological causal relationships. It is clear that as long as "*nonreinforcement with food*" serves us as a technical concept indicating the loss by the conditioned stimulus of a positive signal meaning, it will fully satisfy us. However, with such a meaning it cannot become a regular link in the chain of uninterrupted processes of the

brain which ultimately lead to the development of the inhibitory process. In order that "nonreinforcement" may become a link in the cause-effect relationships, we must definitely answer two questions: how can "nonreinforcement with food," i.e., *the absence of a real stimulus*, become a stimulus for something? Precisely what does "nonreinforcement" evoke in the central nervous system?

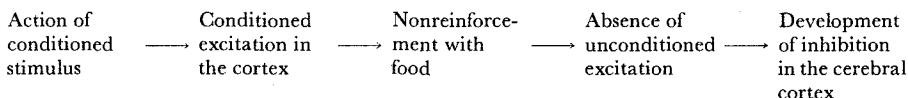
Since these questions will form the basis for our further analysis, I shall attempt to clarify them by using a simple outline.

When elaborating a conditioned reflex, the chain of nervous phenomena leading to the formation of a temporary connection appears before us as physiologically completely defined. Briefly, and taking into consideration the material discussed in the preceding chapters, this chain of phenomena can be expressed in the following way:



Although not everything in this series has as yet been physiologically clarified, all links of this series have a *physiologically understandable causative relationship*. For example, as we have seen above, at the present level of our knowledge of the general physiology of the nervous system, we cannot doubt that the action of the indifferent stimulus and the action of the unconditioned stimulus on the corresponding receptors lead to the appearance of intense volleys of impulses, propagating over the lemniscal and over the reticular and hypothalamic systems. Nor can there be any doubt that, originating in the cortex in a definite time sequence, the excitations must enter into some kind of interaction. Everything here is physiologically correct; everything is in agreement with the general physiology of nervous processes. Consequently, the whole chain of phenomena becomes physiologically convincing.

Something quite different is apparent in regard to the origin of internal inhibition. Here, as is known, the following chain of phenomena occurs:



Comparing these two outlines reveals their fundamental difference. It is quite obvious that in the second series of phenomena immediately after the development of conditioned excitation in the cerebral cortex, the *causative sequence of the physiological phenomena breaks*, and in place of the missing physiological link is the methodological expression "nonreinforcement with food." This break in the physiological causality makes the appearance of the inhibitory process in the cerebral cortex quite incomprehensible. In calling the problem of the relationship between excitation and inhi-

bition an "accursed problem," Pavlov undoubtedly had this question in mind: what causally determines the appearance of inhibition on the basis of a preexisting process of conditioned excitation?

As far as we know, up to the present time only one attempt has been made to explain the mechanism of the origin of conditioned inhibition. I refer to the ideas of P. S. Kupalov and of S. V. Kleshchev, according to which conditioned inhibition appears by way of the development of "supramarginal inhibition." In view of the fact that this concept pertains directly to the question being discussed, we must consider it in greater detail.

The essence of Kupalov's point of view is that in the higher nervous system there are essentially no impassable boundaries between unconditioned and conditioned inhibition. As an example, he cites the reaction of an animal to a supramaximal auditory stimulus. At first this reaction has an unconditioned character, but then, as the "training" proceeds, the reaction of the animal to this supramaximal stimulus stabilizes at some intermediate values, i.e., a compromise transition from unconditioned to conditioned inhibition develops. Kupalov believes that during the development of extictive inhibition, unconditioned inhibition appears first and is later replaced by conditioned inhibition.

In Kupalov's concept the idea of an "inhibited state" plays an important role. This state is capable of becoming the basis for elaborating inhibitory or negative conditioned reflexes.

As I have shown in the preceding discussion, one of the essential conditions for solving the "accursed problem" of cortical inhibition is the establishment of a *precise determinism* in the sequential development of phenomena. Not a single concept of inhibition can be convincing without this.

Kupalov's concept that "unconditioned inhibition" appears first and is then replaced by conditioned inhibition does not eliminate the questions: *what is the origin* of the unconditioned inhibition, and *why* did it later become conditioned inhibition?

From Kupalov's concept it follows that internal inhibition, as a temporary process which adapts the organism to a given situation, must inevitably pass the stage of supramarginal inhibition.

But are there appropriate conditions for the development of supramarginal inhibition during the elaboration of conditioned inhibition? According to Pavlov's concept of supramarginal inhibition, we can say that it appears when demands are made on the cortical cell which exceed the limit of its efficiency. Such conditions are created in the cerebral cortex when an actual "supramaximal" stimulus acts on its cells or when a stimulus of optimal strength acts exhaustively over an especially long period. Evidently Kupalov was speaking of this "excessive intensity."

However, there are no such conditions in the case of the usual extictive inhibition of the "acute intermittent" type nor in the case of differentiating inhibition. The stimulus to be extinguished, as we know, can sometimes even after the third or fifth nonreinforcement with food become an inhibitory stimulus, whereas reinforcement with food, even dozens of times in succession, may fail to decisively influence the magnitude of the conditioned secretory effect.

It must also be added that the first nonreinforcement during the first extinction usually evokes an orienting-investigative reaction because of the sudden change in the stereotype of the experiments. Therefore, one cannot speak of a *prolonged* action of the conditioned excitation.

All the more is there no reason to assume the development of supramarginal inhibition during elaboration of a differentiating inhibition, inasmuch as the differentiating stimulus is generally applied no more than once or twice during a session.

The postulation of a stage of supramarginal action of the inhibitory stimulus also fails to fit the concept of the actual *sum* of peripheral nerve impulses arriving in the central nervous system during reinforcement as well as during nonreinforcement with food. During reinforcement with food, i.e., during massive stimulation of the taste and other analyzers, the cerebral cortex is bombarded with volleys of nerve impulses from the periphery. On the other hand, during nonreinforcement with food all these impulses are absent and, consequently, the cortex seems to change to a regimen of activity demanding less energy.

These findings convince us that in the development of the common adaptive forms of internal inhibition, none of the necessary conditions are present for the development of a supramarginal inhibition precisely in the cells responding to a given conditioned stimulus. This, in turn, means that we cannot connect the origin of the inhibitory process in the cerebral cortex with the *supramarginal action* of the inhibitory stimulus, which develops only in relation to the number of times it was applied. It is well known, for example, that differentiation is elaborated in an animal with greater difficulty the closer the differentiating stimulus is to the positive alimentary stimulus. Consequently, it is the *proximity of the given stimulus* to the alimentary excitation, i.e., the marked state of "conflict," which creates difficulties in developing differentiation and not only the number of times the conditioned stimulus was applied. It is also very important to emphasize that attention is focused only on the characteristics of the stimulus, while processes of a biological nature, i.e., *depriving the animal of an important factor of life (food)*, are ignored.

In his last article Kupalov attempted to present the mechanism of the *origin* of conditioned inhibition, but this attempt does not lead us out of the difficulties which we encounter when comparing all the data of the Pavlov school. Nevertheless, particular concepts of this article come quite close to our theory of the mechanisms of the origin of cortical inhibition. Therefore, I consider it necessary to make a physiological analysis of what we consider acceptable and unacceptable in these statements.

As I have said, Kupalov adheres to the idea that unconditioned and conditioned inhibition are related, and that each form of conditioned inhibition begins to develop through the obligatory stage of unconditioned inhibition. It is clear that such a concept can acquire some kind of cognitive significance if an exact physiological characterization is given to both forms of inhibition as well as to those *physiological causes* which transform unconditioned into conditioned inhibition. In its very essence unconditioned inhibition is *inborn*, i.e., it is brought about by *genetically determined* synaptic apparatuses. Consequently, it must be convincingly demonstrated how this inhibition can become conditioned, i.e., variable in accordance with changing external conditions.

Characterizing the distinctive properties of unconditioned inhibition, Kupalov wrote (1955b, pp. 159-160) :

The second type of unconditioned cortical inhibition is an inhibition of negative induction common to the entire central nervous system. This inhibition makes possible the coordinated action of the nerve centers, ensuring the accomplishment of one leading reflex with simultaneous suppression of other competing reflexes. When the centers of the strongest reflex are excited, the centers of the other reflexes are inhibited.

Several important questions should now be asked : is "coordinated action of the nerve centers" needed only for the interaction of unconditioned reflexes? Does not coordination in the sphere of conditioned reflex activities proceed according to the very same mechanism? Is it possible that in the course of some *conditioned reflex* activity all other activities are also present? Are they not eliminated just as decisively as every other competing activity in the sphere of unconditioned reflex relationships?

By limiting the mechanism of mutual elimination to the sphere of unconditioned reflexes, Kupalov considerably decreases the significance of the universal law of the action of the brain which could be called the *law of exclusiveness*.

We can formulate its basic physiological content in the following manner: *any integrated activity of the organism and the central nervous system has a tendency to be exclusive and the only one, the process of inhibition being the sole method of eliminating other activities.* Probably this universal principle led to the origin of inhibition in the historic development of organisms. It is the common basis for the occurrence of all forms of coordinated inhibitions studied in lower as well as higher nervous activity. Regardless of the form of coordinated inhibition we analyze, we invariably come across this principle. Its significance is so universal that in *all cases of inhibition* of any integrated activity of the organism, we must always seek the other integrated activity which inhibited it.

However, we *never sought* this other inhibitory activity, but rather limited ourselves to the inhibition of the activity under observation.

Thus it follows that the *mutual exclusion* of two nervous activities is not peculiar to unconditioned inhibition. Since it is a general characteristic of all forms of coordinated inhibition, it should not be used as a reference to determine the differences between unconditioned and conditioned inhibition. This problem will, however, be discussed in more detail below.

It is of interest that the experimental data cited by Kupalov completely agree with the above-described principle if one thoroughly analyzes them.

In dealing with the question of "explosiveness," Kupalov (1955b, p. 170) cites the following example: "The same phenomena can be observed in human life. Often, after repeated and prolonged restraint, a person suddenly has a burst of excessively strong excitation which he cannot restrain." What physiological phenomena does this concern? What is a "prolonged restraint" in the life and behavior of man? It is clear that for "restraint" to occur there must be an excitatory action by some external or internal agents which prompt the activity that must be restrained. This is one activity, one contending side. But what is "restraint"?

Without any basis, "restraint" is usually identified with "inhibition." Is this, however, actually so? In man any restraint can occur only as the result of some higher motives, or as the result of the action of social factors controlling our social behavior. Is it not clear that in both cases the motives and the factors are vast systems of excitation, activities of the brain?

Thus, in this example the same principle applies: the origin of inhibition is a result of the encounter of two systems of excitation.

Those data cited in Kupalov's article demonstrate the universal significance of the encounter of two nervous activities. By slightly changing the approach to evaluating the observed phenomena, we can clarify this question.

For example, in arguing for the postulate that the very same stimulus may have both an excitatory and an inhibitory effect, Kupalov wrote (1955b, p. 159): "Consequently, a tone may have both an excitatory and an inhibitory effect. With a sudden decrease in the intensity of the tone its *inhibitory value appears*" [italics—P.A.]. It is quite evident that Kupalov was here dealing with the inhibition of an orienting-investigative reaction which must inevitably occur if even an insignificant change in the stereotype conditions of the experiment is made. If, in addition to the secretory component, he had also considered the respiratory or cardiovascular component, he would have seen that the stimulus "had not acquired an inhibitory value," but that the new stimulus (weak tone) had evoked an orienting-investigative reaction capable of evoking a secondary inhibitory effect on the alimentary conditioned reaction.

The simultaneous recording of many components of the conditioned reaction makes it possible to discern the changes in the nervous activity of the animal. In fact, it leads us to a more profound understanding of the integrated activity of the brain, bringing us close to the physiological evaluation of the *natural* shift in various activities of the organism.

As was shown in a number of experiments, the orienting-investigative reaction, being a clearly defined *integrated* state, is very *exclusive*, consisting of very strong excitations and, consequently, having a strong inhibitory effect on all other activities of the organism.

Of interest in this respect is that particular form of inhibition Kupalov (1955b, p. 166) called the "reorganizing" inhibition which in his opinion "matches the magnitude of the conditioned reaction with the magnitude of the unconditioned reaction." Such a "matching" must occur when the "stable relationship between conditioned and unconditioned excitation" is disturbed.

Since this point of view of Kupalov approximates the idea already developed by us on the role of "reverse afferentations" in the integrative processes and the appearance of a "reorganizing" inhibition cannot be fully explained without the principle of exclusiveness, we will further analyze it.

If unconditioned reinforcement does not correspond to a conditioned excitation, then there occurs a "collision" of the established conditioned excitation with the "new" unconditioned excitation. As the result of this "collision," inhibition appears which has been called "reorganizing" inhibition. Unfortunately, the data already existing on this question have not been utilized in the explanation.

In 1933 we (Anokhin and Strezh, 1934) developed the method for "substituting the unconditioned stimulus," which has been discussed above. We intended to verify the physiological results of the sudden substitution of unconditioned stimulation, i.e., when the matching between conditioned and unconditioned stimuli is disrupted, as mentioned by Kupalov. In our experiments a piece of meat was placed in one of the two feeders instead of the usual bread crumbs to follow the usual conditioned stimulus. On the basis of these experiments we concluded that between the established conditioned excitation determining the conditioned reflex and the reverse afferentation from the unconditioned stimulus a *matching or adequacy* is established as a result of training. Even the slightest disturbance of this adequacy creates a *noncorrespondence* (discordance) between the prepared action acceptor and the reverse afferentation from the unconditioned stimulus. It is precisely this noncorrespondence which, as a rule, evokes the orienting-investigative reaction. The strength of this orienting reaction is sometimes so great that it can inhibit the conditioned secretion usual for the given conditioned stimulus as well as the alimentary reaction.

Such an inhibitory effect of the orienting-investigative reaction can be so strong that an animal having usually received bread crumbs as reinforcement will not start eating for some time when the bread crumbs are replaced by meat. This circumstance demands special attention: it demonstrates the strength of those "inhibitory" impulses which arise from the orienting-investigative reaction when the matching between conditioned excitation and reverse afferentation from the effect of the conditioned stimulus is disturbed (Zachinieva, 1949).

Our idea of the "action acceptor" as the constantly acting afferent apparatus of any reflex activity of an animal was described above in detail. At the moment it is only important to show that in the case described by Kupalov there is no "collision" of two impulses in the usual physiological sense. Indeed, the normal reinforcement with 20 g of bread crumbs evokes stimulation of a number of receptors which has a very specific intensity. This stimulation is then directed, in the form of afferent impulses, towards the newly developed conditioned excitation ("reverse afferentation"). Let us designate the sum of these afferent impulses as *A*.

In another case, in the example given by Kupalov, when the experimenter decreased the amount of reinforcement to 3 g of bread crumbs, there also occurred a reverse afferentation which in amount and strength of the component impulses was much less. We will designate this as *B*.

On what physiological basis does the stronger afferentation *A* not "collide" with the established, i.e., conditioned, excitation, while the weaker afferentation *B* does "collide" with this excitation? No possible bases in contemporary neurophysiology exist for the "collision" and, consequently, there are no bases for the development of inhibition according to this mechanism.

This becomes even more evident in the case of complete nonreinforcement, i.e., when there is no unconditioned excitation at all, meaning that the reverse afferent impulses in their usual sense are absent. It is known that in such a case inhibition develops after the first nonreinforcement of the conditioned stimulus with food (extinction). The question is, *what* collides with *what*? And how can this collision

develop, if one of its elements, the afferent impulses *B*, is completely absent? Clearly, Kupalov's explanation cannot satisfy us if we attempt a more thorough understanding of the mechanisms of the origin of the inhibitory process.

In conclusion we may say that the most important deficiency in Kupalov's concept seems to be that it solves all the complex functions of higher nervous activity by ascribing a commanding and, chiefly, an initiating role to inhibition. Thus, inhibition "reorganizes," inhibition "regulates," inhibition "matches," etc. This incomprehensible independence and "primordial" character of the inhibitory process shows clearly in such expressions as: "two basic processes: excitation and inhibition," "simultaneous occurrence and coexistence," etc. One can hardly speak, in a profoundly physiological sense, of some kind of "coexistence" of excitation and inhibition in the cortical processes. We can no more speak of this than of the "coexistence" of electricity and the bell.

From Kupalov's presentation, the origin of such a universal power of inhibition is not clear.

This emphasis on the universal importance of inhibition without a convincing analysis of the mechanisms of its origin inevitably led to the deficiencies in Kupalov's concept as mentioned above. Nevertheless, we consider it our duty to point out that Kupalov's statements represent a serious attempt to explain one of the most perplexing questions of higher nervous activity and should rightfully become an impetus for further thorough creative discussion in the elucidation of this problem.

Another idea has recently been discussed which must also examine very carefully. I have in mind Asratian's (1955) assumption that the cessation of conditioned secretion in all cases of nonreinforcement may be the result of a *simple decrease in the excitability* of the cortical cells not receiving tonic impulses from the unconditioned center.

Similarly, Maiorov (1954) explained the origin of cortical inhibition as a "decreased efficiency" of the cortical cells. Upon analyzing this idea carefully, it becomes quite apparent that such an explanation cannot be considered satisfactory at all.

Throughout the entire history of the development of the concepts of cortical inhibition, it was always presented as an *active process* which *forcibly* removes some positive activity, and on this was based its adaptive significance. This idea of the character of inhibition coincides with the concept held by the Vvedenskii-Ukhtomskii school where it was referred to as "active tranquilization." On the other hand, admission of a passive *decrease in excitability* inevitably leads to a complete denial of any cortical inhibition. Indeed, what happens then to the *conflict* between excitation and inhibition? And how can a simple *decrease in excitability* "be in conflict" and with what can it actually "be in conflict"? This contradiction alone to the quite obvious phenomenon of the *active nature* of cortical inhibition would be sufficient for the rejection of the propositions of Maiorov and Asratian. However, a number of questions of a physiological and biological nature arise in connection with this. How is one to explain the appearance of a "stressful state," the "yelping," and other signs of reaction which develop in an animal in response to nonreinforcement with food?

The position of the physiologist becomes especially difficult if he wants to under-

stand, on the basis of Maiorov and Asratian's hypothesis, the *biological consequences* of such a mechanism of the origin of cortical inhibition.

Imagine an animal in its natural environment which for some reason did not obtain alimentary satisfaction in response to a definite conditioned signal at the usual place. According to our interpretation of cortical inhibition, it is from this moment that there begins a "decrease in the excitability" of the cortical elements which earlier determined the adaptive activity of the animal under the given conditions. If we assume that with this "decrease in excitability" the matter ends, which is what the ideas of Maiorov and Asratian imply, we will immediately realize that this species of animal would long since have become extinct, being completely unadapted to the conditions of its existence.

Ideas concerning the origin of inhibition through the mechanism of decrease in excitability are usually related to the statement by Pavlov on the "Wednesday" of December 19, 1934. Some authors see justification for their ideas in this very statement. However, Pavlov's view expressed in 1934 has a somewhat different meaning: it is based on the assumption that the anabolic effect of negative induction depends on the unconditioned stimulus, and in this sense it needs strong experimental proof.

Pavlov presented this concept as a working hypothesis, saying that "if this should prove to be true" it will be possible to start solving the problem of the relationship between excitation and inhibition.

Proceeding from the concept of a "decrease in excitability" of the cortical cell as a result of nonreinforcement with food, the above authors could not eliminate important contradictions in their theories and could not give a convincing argument for this concept.

Actually, the phenomena appearing in the central nervous system *in response to nonreinforcement of conditioned excitation with food* are much more profound and varied. These phenomena adapt the animal far better to its environment than the proposed concept of "decreasing excitability" assumes. All these phenomena will be discussed in more detail below.

Because the above-described ideas on the causes of the origin of conditioned inhibition are not convincing enough, we necessarily return to Pavlov's initial and basic implication that in the origin of cortical inhibition *nonreinforcement of the given stimulus with the food and the resulting active character of inhibition are of decisive importance*.

Thus, once more and with greater insistence we ask: *what is the mechanism by which nonreinforcement of the conditioned stimulus with food had led to the development of inhibition in the cerebral cortex?*

In the course of the last 40 years of study of conditioned reflexes, there have appeared data and statements which gave an adequate basis for attempting to answer this question. However, this material has never been synthesized, and therefore the actual question concerning the *mechanisms of the origin* of conditioned inhibition has not been subjected to a systematic analysis.

In discussing the significance for conditioned inhibition of nonreinforcement of passive flexion of the hind leg of an animal, Pavlov wrote: "... this movement is a signal of the animal's difficult state caused by inducing but not satisfying the alimentary excitation. Naturally, there must be a struggle against it: it must be eliminated—and

this is attained by extension" [italics—P.A.] (Pavlov, 1935b, see Pavlov, 1957, pp. 309–310).

These remarks reflect Pavlov's highly significant idea that if the alimentary excitation caused by the conditioned signal is not reinforced with food it will create a "stressful state" in the animal, i.e., it will lead to a biologically negative reaction.

Such a combination exists in the elaboration of any kind of internal inhibition, since in all forms of internal inhibition the alimentary excitation evoked at the beginning invariably remains "unsatisfied."

The behavior of the experimental animal is a direct indication of the development of such a biologically negative reaction when a well-established conditioned reflex is not reinforced with food. The animal usually yelps, barks, whines, turns away, etc. In other words, a number of clearly biologically negative phenomena appear.

In regard to this Pavlov wrote: "If I have produced a process of excitation and now limit it with one of inhibition, this is trying on the animal; it begins to whine and bark and attempts to free itself from the stand" (Pavlov, 1924, see Pavlov, 1967, p. 333).

What, however, is the physiological meaning of "limiting the existing excitation by an inhibitory process"? Where can this inhibitory process originate which prevents the emergence and release of a specific system of impulses to the periphery?

The data from the Pavlovian laboratories provide many examples of such a transition from a biologically positive to a biologically negative reaction in the case of nonreinforcement with food of a conditioned reflex which has been stabilized.

For example, in one of our investigations in Pavlov's laboratory carried out under his direction, the extinction of an old, well-established conditioned alimentary reflex was suddenly undertaken. After the very first nonreinforcement with food, the dog started towards the feeder with growling, rushed at the screen which covered the feeder, tore off the screen, and took possession of the dish. This reaction as a whole must be considered to be an active food-procuring reaction. However, during subsequent applications of an extictive stimulus when measures were taken to prevent the obtaining of food, the animal exhibited all those signs of a negative reaction which were described in the words of Pavlov quoted above.

Thus, on the basis of the great mass of data from the Pavlovian laboratories, one can draw the following conclusion: *nonreinforcement with food of alimentary excitation caused by a conditioned stimulus leads to the development of a new integrated reaction in the animal (orienting, food-procuring, biologically negative), and the formerly positive conditioned stimulus, after nonreinforcement with food becomes the signal for the "stressful state" and therefore begins to evoke a biologically negative conditioned reaction in the animal.*

During systematic nonreinforcement of a given stimulus with food it gradually becomes an *inhibitory stimulus*, the negative reaction becomes stabilized, and the alimentary excitation is completely inhibited. *The latter corresponds to the absence of the secretory effect.*

Thus, the same conditioned stimulus which evoked an alimentary excitation evokes an *inhibitory conditioned reflex* after the beginning of extinction. The biologically negative reaction of the animal acquires the character of an *inhibitory conditioned reflex*, which is accompanied by the formation of a new action acceptor.

In discussing the well-known experiments of Fol'bort (1912) described in his doctoral dissertation, Pavlov wrote (Pavlov, 1923b, see Pavlov, 1967, p. 320) :

We have employed for some time the terms positive and negative reflexes (from the experiments of G. V. Volborth). The advantage of this conception of our facts is that it enables us to understand all different states of the nervous elements in any circumstances and under the influence of any stimulating agents, as a *continuous uninterrupted succession of processes*; and this corresponds to the facts [italics—P.A.].

As a result of the analysis of all processes which develop in response to nonreinforcement of the conditioned excitation with food, we can make one principal conclusion which opens possibilities for further physiological analysis of the conditions under which the inhibitory process originates in the cortex: in response to the stimulus being extinguished, a specific physiological situation arises in the cerebral cortex just after the first nonreinforcement. This situation can be characterized as follows:

1. Nonreinforcement as a procedure has a number of physiological consequences related to the fact that the action acceptor does not receive the usual afferentation from all the parameters of the act of eating.
2. If this phenomenon is considered from the point of view of the functional system, i.e., the behavior of self-regulating systems, this is essentially a case of discordance.
3. Discordance between the goal and the actual results leads as a rule to a pronounced orienting-investigative reaction, i.e., to the active gathering of additional information or afferent signalization (scanning).
4. From the biological point of view, any discordance evoked by the deprivation of vitally important factors immediately leads to the appearance of negative emotions, which ensure a more successful scanning and the elimination of the discrepancy between the goal and the results achieved.

In connection with this I will discuss in greater detail the physiological structure of integrated acts of a different biological nature.

CHAPTER 13

The Physiological Characteristics of Biologically Positive and Biologically Negative Reactions of Animals

WHEN discussing the role of the afferent complex of conditioned excitation intended for the prediction of future results, for purposes of illustration I have analyzed almost exclusively examples of the *substitution* of one unconditioned stimulus by another. However, for solving the problem of the *origin of conditioned inhibition*, the most interesting case is, of course, the complete absence of unconditioned reinforcement, i.e., the *total absence* of reverse afferentations evoked by unconditioned stimulation.

Since historically our concepts of conditioned inhibition in the cerebral cortex *have developed entirely during the study of conditioned alimentary reflexes*, I shall for the time being discuss *nonreinforcement with food*.

Let us consider the physiological interrelations that will occur in the cerebral cortex when a previously developed conditioned alimentary excitation is not reinforced with food. This excitation has already emerged onto the effector pathways: the animal is moving towards the food, it is salivating, its respiration and blood pressure have changed, etc. At this very moment, as we know, certain afferent cells of the cortex, and probably also of the subcortex, are in an active state. Together they constitute the action acceptor. After several seconds the excitation of this action acceptor inevitably encounters the appropriate afferent impulses coming in from the periphery from the results of an action. In the case of nonreinforcement with food, however, the excited action acceptor is unstimulated, and its own impulses fail to be appropriately discharged at the peripheral working organs and in the corresponding emotional state. In other words, the cyclic system of impulses in the elaborated and well-stabilized adaptive act remains open, the biologically positive alimentary emotion remains unreinforced, and the established conditioned excitation, in Pavlov's words, "fails to receive satisfaction."

The observations of our laboratory show that a "dissatisfied" condition of an initially excited complex of afferent cells of the cerebral cortex *immediately stimulates* in the central nervous system one of three possible integrated activities of the animal: (a) an orienting-investigative reaction; (b) an active food-procuring reaction, if the experimental setting permits such a reaction; and (c) a biologically negative reaction, a reaction of dissatisfaction, characterized by Pavlov as a "stressful state."

These three possibilities are characterized by the following features: the first and last are always observed whenever the unconditioned reflex is not reinforced with food,

whereas the second one, i.e., the food-procuring reaction, may or may not occur, depending on experimental conditions. In the above-described case of the extinction of the conditioned alimentary reflex in the dog Vizgun, it was manifested in a distinct active reaction which terminated in the forceful removal of the dish from behind the screen. In other cases of extinction it may be absent, evidently inhibited by experimental conditions (an arrangement of the feeder precluding the taking of the food, the previous experience of the animal, etc.). This facilitates the appearance of the stressful negative state and, consequently, the inhibitory process in the system of the alimentary reaction. It is likely that in all those motor methods (locomotor) used in the study of higher nervous activity in which an active food-procuring complex is a necessary component in the conditioned reaction of the animal (Rokotova, 1953; and others) the extinction of these reactions may lead to especially evident food-procuring movements, which nevertheless must be preceded by an orienting-investigative reaction in response to the absence of appropriate reverse afferentation.

The overall significance of that diversity of reactions which inevitably occurs after a sudden nonreinforcement with food of an already developed alimentary excitation consists of the animal striving in all possible ways to *retain* this excitation, to transform it into a more powerful unconditioned alimentary excitation, i.e., to *consummate the positive emotional state*, to close the cycle of appropriate peripheral excitations in response to the action acceptor that has already been called forth.

Another matter needing discussion is the *biological aspect* of all of our investigations of higher nervous activity. Without understanding this we may be unable to comprehend the diversity of the *external manifestations* of the behavior of the animal.

On the basis of the nonreinforced conditioned alimentary reaction we discovered the mechanisms of the established action acceptor in the capacity of an afferent mechanism of the cerebral cortex, which on the basis of reverse afferentations compares and regulates the effectiveness of the adaptive act.

The absence of appropriate recurrent impulses going to the action acceptor leads to diverse new reactions of the animal, among which the general negative reaction constitutes that inhibitory excitation which finally inhibits the conditioned alimentary reaction.

Will all the above-described phenomena develop according to the same mechanism if a conditioned *defense* stimulus is not reinforced and if the actual nonreinforcement consists of the animal failing to receive a nociceptive electrical stimulus? It would seem that common sense would tell us that the animal is far from indifferent to whether it is deprived of food or "deprived" of an electric shock to the leg.

However, the terminology and concepts of inhibition which had developed *on the basis of experiments in which the dog was deprived of alimentary reinforcement* were automatically transferred to the cases involving conditioned defense reflexes as well, i.e., to cases in which the dog is "deprived" of a nociceptive stimulus. Thus, the methodological aspect of the subject was emphasized, while the biological significance of the different relations of the animal to the two different "nonreinforcements" was overlooked. Meanwhile, it is quite evident that the nature of the behavior of an animal will depend not only on whether a given conditioned stimulus is "reinforced" or "not reinforced," but also on

what it is reinforced with and *what* it is not reinforced with, i.e., of what biological significance this reinforcement is.

In this respect, Pavlov's views concerning the biological differentiation between these two situations are particularly important. We consider it necessary to speak of these views in more detail at this point.

In analyzing the two opposite forms of animal behavior, Pavlov characterized them very distinctly. He stated (Pavlov, 1935b, see Pavlov, 1957, pp. 308-309) :

The general physiological law of the work of the skeletal musculature, on the one hand, consists in constant movement towards everything, in grasping everything that preserves and ensures the integrity of the animal organism, that equilibrates it with the surrounding medium; this is a *positive reaction, positive movement*. On the other hand, it is constant movement from everything, throwing aside and ejecting everything that hinders and threatens the vital process, that violates the equilibration of the organism with the environment; this is a *negative reaction, negative movement* [italics—P.A.].

Unfortunately, this "general physiological law" did not exert the necessary amount of organizing influence on the classification of the conditioned reactions we are studying. Let us try to apply it to the comparative evaluation of the alimentary and defense reactions of animals.

How does the biological meaning of the reactions of an animal change in accordance with this general physiological law upon nonreinforcement with food? The *biologically positive* reaction of the animal changes upon nonreinforcement with food into a *biologically negative* one, and the nonreinforced conditioned stimulus itself becomes a signal for the *negative state* of the animal, or its "stressful state."

And how does the biological meaning of the reactions change upon nonreinforcement with electric current? Here the change occurs in reverse order: the *biologically negative* reaction of the animal changes upon nonreinforcement with electric current into a *biologically positive* reaction, and the conditioned stimulus itself becomes a signal for the *positive state* of the animal.

Can the physiological mechanisms of these two *diametrically opposed* transitions be identical?

It is easy to see that this analysis of the *natural* physiological interrelations does not coincide at all with our usually accepted terminology which is based not on an evaluation of the true biological meaning of the physiological processes studied, but on a methodological scheme. We are calling the conditioned *defense* stimulus "positive," and the absence of an alimentary reaction upon nonreinforcement with food "negative." Actually, adhering to Pavlov's classification, we must point out that in the case of nonreinforcement with food the change in the integrated reactions of animals proceeds *from a positive reaction to a negative one*, while in the case of nonreinforcement with electric current the change in the reactions proceeds *from a negative reaction to a positive one*. Is it possible to reveal this distinction by any objective methods? Certainly. If one systematically studies the respiratory component of the conditioned reaction, which,

as was shown by our investigations, clearly reveals the distinctions in reactions of a different emotional nature, one can see that the respiratory component behaves in the two cases very typically and quite differently. My collaborator Balakin (1935) performed an experiment in 1931 to compare the conditioned alimentary and the conditioned defense stimuli (Fig. 13.1).

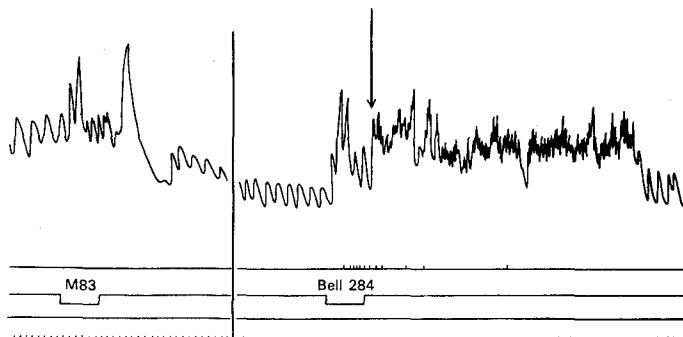


FIG. 13.1. Comparison of two pneumograms resulting from the nonreinforcement of an alimentary and a defense conditioned reflex. Left pneumogram, defense conditioned stimulus not reinforced; right pneumogram, alimentary conditioned stimulus not reinforced at time indicated by arrow. The qualitatively different reaction to nonreinforcement can be seen.

As is shown by this figure, nonreinforcement with food (arrow on right pneumogram) is immediately manifested by an increase in the frequency of the respiratory movements and by a raising of the entire respiratory curve to the level of inspiration. We know from our experience that this directly indicates the appearance of an orienting-investigative reaction and a stressful state, i.e., a biologically negative reaction. This reaction, undoubtedly, proceeds with a greater exertion of all the strength and energy resources of the animal. The intensity of the respiration is only one of the many symptoms of this integrated state. An entirely different relation is seen on the curve of the left pneumogram, where the conditioned defense stimulus is not reinforced. As is evident, here the conditioned stimulus itself evokes a strong negative reaction: the movements intensify, and the respiration becomes inspiratory. This is understandable, since in this case the conditioned stimulus is the signal for a destructive action of agents of the external world on the organism and therefore, being biologically negative, it mobilizes every possible resource of the organism for the struggle against this destructive agent. If, however, this destructive action did not follow and the signal was not reinforced with an unconditioned defense stimulus, an immediate demobilization of all the heretofore excited mechanisms sets in, and the central nervous system of the animal *immediately* changes to the optimum level of activity of the working systems of the animal. As a rule, a very deep additional inspiration is observed at this moment, followed by a complete relaxation of respiration, *serving as a direct indication of the absence of a negative reaction of the animal*.

An additional circumstance characterizing the change of the central nervous system to its optimum level of activity, i.e., to a *resting* state, is a change in the so-called

intermediate defense reaction which occurs to some degree in almost all animals receiving electrocutaneous reinforcement. As is known, in the intervals between conditioned defense stimuli the experimental animals sometimes continuously jerk the extremity to which the electrodes are attached, and some of the animals are in a state of continued restlessness throughout the greater part of the interval between conditioned stimuli. However, one only needs to apply a *differentiating*, i.e., unreinforced, stimulus, and immediately all "spontaneous" motor activity ceases, respiration shifts to the optimum level of rest, and the animal relaxes completely *during the presentation of the differentiating stimulus*. These relations can be easily understood if one visualizes the physiological architecture of those reactions and states which exist at the given moment in the central nervous system.

The continuous jerking of the extremity during the interval between conditioned stimuli proves that the central nervous system of the animal is in a state of a *defense dominant*, which raises the level of excitability of all those neural structures and working systems which maintain the animal in a state of anxious readiness for the nociceptive action. But as soon as the differentiating signal is presented, *signaling the absence of the destructive or nociceptive action of the unconditioned stimulus*, the animal immediately shifts to the state of a biologically positive reaction. It is interesting that an equally rapid transition to a biologically positive reaction occurs immediately after unconditioned stimulation terminates. This is understandable if we consider that the animal adapts not only to the moment of action of the signal, but also to the time sequence of all phenomena in the experiment. In fact, in accordance with the experimental conditions, the unconditioned stimulus, the electric current, is presented only after the conditioned stimulus, which is presented in definite intervals. As a result of these relations, *any unconditioned nociceptive stimulation subsequently becomes a distinct signal for an ensuing period of rest during which the unconditioned electric stimulus is never presented*. These interrelations of the defense dominant and the optimum resting state of the central nervous system may be represented by a composite curve typical for most experiments involving conditioned defense reflexes (Fig. 13.2).

It is easy to see that this interrelation of conditions gives one no reason to identify the sum total of the nervous processes developing in the case of "nonreinforcement with food" with that in the cases of "nonreinforcement with electric current." What the results of these two nonreinforcements hold in common is that *in both cases two competing integrated activities appear*, and yet the order of their appearance is diametrically opposed in the biological sense.

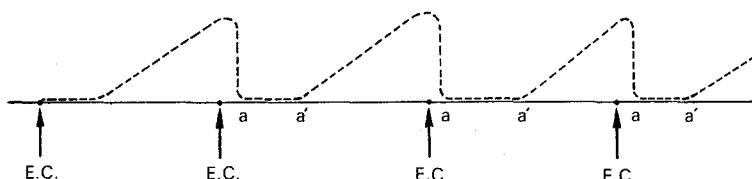


FIG. 13.2. Schematic representation of the variability of the defense dominant between recurrent reinforcements of the conditioned stimuli with electric current (E.C.). In the interval $a-a'$ can be seen the maximum calming of the animal following the cessation of the electrical stimulus.

I see no reason to doubt that the newly arising negative reaction of the animal in nonreinforcement with food conflicts with the positive alimentary reaction, and that the latter is eliminated by means of inhibition. Here the state of conflict is determined by the fundamental biological law according to which the animal *strives by all physiological means to maintain a positive state, i.e., to maintain all the functions of the organism at the optimum level*. Consequently, internal inhibition arising on the basis of nonreinforcement with food inevitably starts with the *forcible suppression* of the positive reaction and the positive state of the animal. This *forcible suppression* is the characteristic feature of any central inhibition, especially coordinative inhibition.

By what mechanisms does the transition from a negative defense reaction to a positive reaction proceed when the conditioned stimulus signaling the absence of nociceptive reinforcement becomes the signal for a biologically positive reaction and a positive state of the animal? Does the positive reaction also arise through the forcible elimination of the negative reaction existing at the given moment?

Since this question is of great biological and physiological significance, neglecting it will considerably impede the resolution of the manifest contradictions resulting from equating the two reactions of opposite biological meaning.

If a positive state of the organism with all its functions at the optimum level is recognized as the normal state, then any elimination of a given system of excitations can be accomplished only by means of active inhibition. Is the same physiological need for the forcible elimination of a biologically negative reaction by means of an active inhibitory process apparent if we know that this reaction had previously been *forced upon the nervous system of the animal through the action of destructive agents*? By comparing all these interrelations with Pavlov's propositions concerning the characteristics of the positive and negative reactions of animals, we arrived at the following conclusions:

1. Internal inhibition is a necessary consequence of the conflict between two excitations, two integrated activities of the organism.
2. The encounter of nervous activities involves conflict only when a *positive reaction* of the animal is actively eliminated, i.e., mainly when discordance occurs at an action acceptor having a pronounced positive emotional nature. In other words, the encounter of two nervous activities of the organism involves the greatest conflict when the optimum level of physiological constants and functions is disturbed.
3. The elimination of an elaborated negative reaction of the animal or of its "stressful state" through the excitation of positive reactions *does not involve conflict*, and it is therefore highly improbable that it is effected by the same nervous mechanisms, i.e., by active internal inhibition.

The appearance of a biologically negative reaction of an animal, i.e., the deviation from the optimum level of its vital activity toward a negative emotional state, may be compared to the forcible *deflection* of a pendulum from its resting position. On the other hand, the transition of the nervous system from a biologically negative reaction upon nonreinforcement to a biologically positive reaction having a positive emotional overtone is equivalent to a *return* of the pendulum to this position.

On the basis of general principles of physiology, it is obvious that both the positive

and negative emotional states of an animal result from a synthesis of processes of excitation and inhibition. At the same time, physiological theory would fail to advance if we are satisfied with this generalization and do not attempt to determine *what specifically is the physiological distinction between the excitations of these two biologically opposite states*. Without considering this problem, there would be no way to understand the *clinical consequences* of those human emotional states of conflict which are states of conflict only because they constitute a collision between *positive and negative emotional excitations* (Lang, 1950; Miasnikov, 1954; and others).

Our concept inevitably leads to an entirely new and fundamental question: what physiological properties and parameters distinguish the two antipodal biological states of positive and negative emotion? Not by accident did this question arise during the investigation of inhibition, for inhibition is by its very essence a means of suppression, a means for the highest equilibration of animals and especially man with the environment. This equilibration necessarily proceeds through more or less pronounced collisions between antagonistic emotional reactions.

Thus, including a *biological criterion* in the evaluation of the role of excitation and inhibition in the behavior of an animal must certainly advance the development of new concepts about the actual mechanism of the *change* of integrated activities of the animal.

As we shall see below, there is no basis for assuming that the reappearing biologically positive reaction of an animal (or rather, the returning optimum state) eliminates the previously existing negative reaction similarly by force, i.e., by means of active inhibition.

It is known that Pavlov resorted to the electrocutaneous stimulus only rarely and for a special purpose. Only in recent years did the defense procedure become widespread due to the "procedural simplicity" of this method of elaborating conditioned reflexes. This, however, led to a completely unfounded application of all the data obtained previously by using the alimentary procedure to these fundamentally different experimental conditions.

In summarizing all the data and considerations analyzed above, we may conclude that the transition from a biologically negative reaction to a biologically positive one occurs without active inhibition as we know it from the example of internal inhibition. Consequently, the concrete physiological mechanism of this transition must become the urgent task of physiological investigations.

In relation to this it is appropriate to ask whether every disappearance of an activity of the organism happens through its forcible elimination, i.e., through its elimination by means of active inhibition. Evidently, this kind of elimination of activities of the organism occurs only when the organism is being actively withdrawn from the state of the biological optimum when the elaborated cyclic interrelations of the positive emotional excitations of the organism and their appropriate reinforcements, i.e., the reverse afferentations that correspond to the action acceptor, are being broken.

Here it is necessary to point out one special combination of conditions under which a positive reaction is at first sight *actively* eliminating a negative one. What I have in mind are experiments involving the deliberate collision of defense and alimentary

conditioned reflexes. If in the evaluation of these experiments one takes into consideration either the secretory or the motor indicator, it outwardly appears that one of the two reactions dominates. It seems that each one of them eliminates the other by means of active inhibition.

An example of such interrelations is found in the classical experiments of Erofeeva (1912a, 1912b). In these experiments the electrocutaneous, i.e., a biologically negative, stimulus was assigned the role of a signal for alimentary reinforcement, i.e., the role of a biologically positive stimulus. Two fundamentally different forms of reactions were specifically compared. How do they interact?

First it must be noted that in the creation of deliberate conditions of conflict there is always an *alternation* of reactions, i.e., at times one of them seems to overtake the other and vice versa. However, just as in Erofeeva's experiments, there arises the same question concerning the *direction* of the change of reactions, the significance of which was analyzed above.

In principle, in such situations three possible forms of reactions may occur: a purely negative form, a purely positive form, and mixed forms. They have already been clearly noted in the experiments of Konradi (1932). We must first be concerned with the "pure" reactions since one of them must inevitably be eliminated.

The generally accepted point of view is that when there is a complete and well-defined negative reaction in an animal during such experiments, one may speak of an *inhibition of a positive reaction*. If a reaction which is just as positive occurs, we likewise speak of the *inhibition of the negative reaction*. Thus, between these biologically opposite reactions of the integrated organism, *reciprocal* interrelations are established which *liken them to the equivalent interrelation of the motoneurons of the flexors and the extensors in the spinal cord*.

Was there, however, a basis for such an identification? May one so easily make this "transfer" from the principles of lower nervous activity to those of higher nervous activity? I would consider such a transfer erroneous. In any case it is not always applicable to the integrated acts of an animal which have biologically positive and negative signs.

The situation is entirely different in this case. Here the central and initial condition of the animal is the optimum condition of vital activity with a positive emotional tone. It may be forcibly eliminated by means of active inhibition. It returns, however, by an entirely different mechanism as soon as the causes that had evoked the negative condition are removed. Here there are not two *equivalent* processes of excitation that are activated at a certain phase in the general integration of movement, as is the case in the interrelations of the spinal cord.

The biological characteristic of a positive activity and its corresponding positive "emotional resources" (Pavlov) is that the organism actively retains it and strives to prolong and maintain it.

A biologically negative activity and its corresponding negative emotional state, on the other hand, is a kind of antphysiological phenomenon which is forced upon the organism against its natural tendency toward optimum and normal activity. Negative emotions always indicate unfavorable conditions of the vital activity of an

organism. Consequently, only an actively retained form of behavior and state of animals and man can be actively inhibited.

By means of what specific physiological mechanisms can a negative activity and the "stressful state" corresponding to it be eliminated?

Such questions have never been asked in the physiology of higher nervous activity; therefore, we naturally do not yet have sufficient experience or data to answer this question. Nevertheless, two possibilities are conceivable by which a biologically negative condition or "stressful state" of animals and man can be eliminated. For convenience of discussion I shall dwell upon examples from the experimental practice of the physiological school of Pavlov.

As we have seen, the development of a sufficiently strong negative reaction invariably leads to the development of a "stressful state" in the animal and to the suppression of the positive alimentary reaction. While this interrelation of biologically opposite reactions may occur when the negative reaction appears as a result of the absence of alimentary reinforcement, therefore inhibiting the alimentary reaction, it may also occur under other conditions.

Where does such an inhibition occur, with one integrated reaction inhibiting another integrated reaction of a different biological modality?

Since in such cases the activity being inhibited is eliminated completely in the entire cortex, it must be assumed that this inhibition occurs at the level of subcortical integrations. This assumption is supported by the experiments of Sudakov (1963), who demonstrated in our laboratory that if the hypothalamic hunger center is inhibited, every alimentary activation of the cortical cells is immediately eliminated. Moreover, the inhibition of an integrated activity is facilitated by the structural interrelations of different complexes at the subcortical level. These complexes differ in biological modality and could be compared with the mechanism of "direct inhibition" which is accomplished by means of stable hyperpolarizing synaptic relations.

Since the optimum level of the basic vital functions of the organism must be recognized as its normal physiological state, any change or shift in these optimum vital constants *inevitably evokes a reaction of resistance*. In the case of sufficiently great stress and excessive expenditures of energy this reaction will be manifested in a negative emotional state. The biologically negative reaction becomes dominant and therefore inhibits all other kinds of adaptive activity.

Consequently, the appearance of a negative reaction always indicates a deviation from the optimum conditions of vital activity and is always a consequence of the *elimination of something* which maintains these conditions of vital activity that correspond to the physiological norm.

It is therefore natural that the temporarily suppressed or eliminated optimum activity of the organism will be immediately restored as soon as the factors that had evoked and maintained the negative reaction and the "stressful state" are eliminated. This, then, is the first possibility of eliminating a biologically negative reaction having a negative emotional nature. Since the normal positive activity returns *immediately* upon elimination of the factors that had effected the negative reaction and stressful state of the animal, it may *outwardly* appear that the positive reaction has "inhibited" the negative reaction.

An example of interrelations of this kind is the *sudden nonreinforcement* of a well-stabilized conditioned defense reflex based on electrocutaneous reinforcement (see Fig. 13.1). The condition and reaction of the animal can be well seen and evaluated only from the vegetative components of the reaction: respiration, blood pressure, and heart rate. As is evident from the curve indicating the isolated action of the conditioned defense stimulus, which signals nociceptive stimulation, the respiratory activity sharply changes toward an increase in the frequency and an elevation of the inspiratory tone.

An evaluation of these components in relation to the jerking of the extremity and the overall symptoms of a biologically negative reaction persuades us that the intensity of the excitations comprising this reaction is extraordinarily great. By not applying the unconditioned nociceptive reinforcement, an even respiration is immediately restored following a deep inspiration, so that the optimum normal condition of the animal returns.

Thus, there is here no "inhibition" of a biologically negative reaction by a biologically positive one. The latter is automatically restored from its inhibited condition as the permanent normal background of the vital activity of the organism as soon as those factors are eliminated which had evoked the *strong inhibitory excitations* of the negative reaction.

Another possibility for the elimination of a biologically negative reaction is presented in the classical experiments of Erofeeva involving the elaboration of a conditioned alimentary reaction to a nociceptive stimulus serving as a conditioned signal. The interrelation of the two antipodal biological reactions is more complex and more difficult to explain since for such an explanation considerably more data are needed than are presently available.

Up to now I have spoken of such an optimum positive state of the animal which is inhibited by negative reactions and restored after the elimination of the latter. In this case the positive alimentary reaction, if we judge its strength by the intensity of the vegetative components, is considerably inferior in its strength of excitations as compared to the negative nociceptive reaction.

However, under special conditions a situation is conceivable in which a nociceptive stimulation, establishing *at the optimum level of the positive state a nociceptive negative dominant*, may itself be subordinated to a stronger system of excitation—a completely dominant alimentary excitation. Such conditions exist in Erofeeva's experiments.

What form do the interrelations of the negative and the positive reaction assume in this specific case? Does the strong positive alimentary excitability exert an *active inhibitory* effect on the nociceptive reaction here, or are the excitations of the latter attracted by the stronger dominant of the alimentary excitation? The second possibility is more probable since between the nociceptive stimulus and the alimentary center *signaling* interrelations have been specially established.

This question must become the subject of a more detailed physiological analysis, particularly involving a consideration of the vegetative symptoms specific for the two opposite reactions. Only after this analysis will it be possible to reach any definite conclusion. At present, the phenomenon observed in Erofeeva's experiments is being investigated in our laboratory, and we are hoping that on this remarkable experimental

model it will be possible to characterize in more detail this unusual case in which a biologically positive reaction and the corresponding emotional state of the animal dominate the system of biologically negative excitations evoked by a nociceptive stimulus.

The material analyzed above shows that the specific physiological mechanisms of the transition from a positive reaction to a negative one, and vice versa, cannot be physiologically identical.

Returning to the case of the deliberate opposing of the biologically negative reaction to a nociceptive stimulus and of the biologically positive one to an alimentary stimulus (Erofeeva's experiments), we can say that in this case too the phenomena develop according to the same principle. From a broad biological point of view, the nociceptive stimulus and state are themselves but a signal for the *destruction of the organism*. It is thus only in this respect that they motivate the organism to search for ways of preserving life and to avoid very probable destruction.

It is a different matter when, as a result of *experience*, nociceptive stimulation leads to a positive alimentary state. In this case the nociceptive stimulation immediately patterns an action acceptor having all the parameters of strong alimentary excitation.

As a result of the dog's experience, the nociceptive signal thus evolves toward a *positive* one in two ways: its life-destroying significance is extinguished, and it becomes a signal that patterns an action acceptor with pronounced positive emotional characteristics. Both of these ways lead to overcoming the threat to life which is posed by the nociceptive stimulus.

As can be seen, essentially the same conditioned reflex principles operate in Erofeeva's experiment. Only the time and place of the conflict are different. In the ordinary extinction of a conditioned alimentary reflex the conflict appears at the end of the functional system, i.e., *at the final moment of evaluation of the results of the action in the action acceptor, and this is where discordance occurs*. In Erofeeva's experiments, on the other hand, the conflict shifts to the beginning of the formation of the functional system, i.e., to the stage of afferent synthesis: the unconditioned nociceptive action and state enter into conflict with the positive signal value of the food during the stage of decision making and patterning of the action acceptor.

CHAPTER 14

The Vegetative Components of the Conditioned Reflex as Indices of Interaction of Integrated Activities of the Organism

In the preceding discussion I proceeded from the highly probable premise that any form of coordinative central inhibition can appear only as the result of a collision of two systems of excitation, with one having a tendency to predominate. As we have seen, this concept fully corresponds with the basic ideas of Russian classical physiologists and can also be applied to the origin of *internal inhibition*. It has been noted that in the latter case there is an encounter of "inhibitory" excitations and those "to be inhibited."

Thus, any attempt to discern the ultimate nature of internal inhibition invariably requires the complete understanding of the physiological peculiarities of "inhibitory" excitations as well as those "to be inhibited."

Returning to extinctive inhibition, we must ask: what are the "inhibitory" excitations and those "to be inhibited"?

In all our experiments it is the secretion of saliva which is ultimately inhibited. Since this is one of the specific components of total *alimentary excitation*, we can maintain with certainty that of the two competing nervous activities which take place during extinction of the conditioned alimentary reflex, the alimentary excitation or, more accurately, *excitation of the cortical representation of the alimentary center*, is "to be inhibited." Consequently, the *excitations of those reactions of the animal which appear according to the above-described mechanism in response to nonreinforcement of the conditioned stimulus with food* can become "inhibitory." This conclusion fully agrees with the observed conditions frequently described in the works of Pavlov and his students. From laboratory observations it is known that, with continued nonreinforcement of the conditioned stimulus to be extinguished, its signal value for the development of a stressful state and of a negative reaction of the animal gradually increases up to a certain moment, which is undoubtedly the result of an intensification of the impulses constituting a biologically negative reaction.

Consequently, in the final analysis inhibition in the cerebral cortex occurs during nonreinforcement of the conditioned stimulus with food always as a result of the action of a stronger *inhibitory* excitation of a biologically negative reaction on a weaker excitation of the alimentary reaction. Although the actual conflict of two integrated activities is evident, serious difficulties are encountered in attempting to explain the

more detailed and intimate mechanisms of the inhibition which occurs in one of the activities. First of all, each of these activities has an integrated character. They are formed by their system of central excitations and appear as a complex of characteristic effects.

As an example we may mention the alimentary reaction, which has a completely distinct composition of effectors, and the defense reaction, which has an entirely different complex of effectors. To this may be added the orienting-investigative reaction, which has completely different peripheral components than the other reactions.

This important observation puts before us three specific questions which, when answered, will bring us close to understanding the physiological essence of internal inhibition. These questions are :

1. What integrated reactions of the organism are most likely to give "inhibitory" excitations if one considers that they appear from the moment of discordance?
2. What physiological properties and parameters determine the inhibitory effect of these reactions?
3. What is the nature of this inhibitory effect at the *points of encounter* of two systems of excitation of different intensity?

As noted above, the most probable mechanism for inhibiting one of the nervous activities is some kind of combination of impulse and electrotonic action. This means that if inhibition of a certain kind of activity of the organism is present, then one of the competing activities, the remaining one, *must inevitably be supported by a more intense and higher-frequency system of impulses*.

These physiological concepts do not presently seem to have any essential contradictions which could be objectionable. However, there is a serious point which could cause difficulty in the further physiological development of them. The point is : as long as the excitation is of the alimentary center, we can evaluate it *quantitatively*, calling it "weak" or "strong." As a criterion of such an evaluation the secretory index may be used, thus permitting a quantitative evaluation of the intensity of alimentary excitation.

But if we maintain that the biologically negative excitation caused by nonreinforcement with food is *more intense* than the excitation of the representation of the alimentary center in the cortex, then we are thereby making a probable assumption inasmuch as we do not have *direct* means of measuring the intensity of the negative reaction. In experiments on higher nervous activity, the intensity of excitation of the biologically negative reaction of the animal is usually measured indirectly : *by its capacity to inhibit, to a certain degree, the existing alimentary excitation, which we measure by the decrease in the conditioned secretory effect*.

This can sometimes, of course, be useful. However, these difficulties show that such a theory on the mechanism of inhibition cannot be considered comprehensive and final. The failure to evaluate per se the characteristics of the negative reaction of the animal, which may replace the alimentary reaction, has had the consequence that the negative reaction as the *complete and independent reflex reaction of the organism with all its specific effectors has, to a considerable degree, remained uninvestigated*.

As is known, if the conditioned reaction of the animal is not reinforced with food, we mostly limit ourselves to pointing out that the animal "growls," "yelps," "whines,"

"behaves violently," etc. But never has a constant, measureable indicator been introduced for this biologically negative reaction, as was done in choosing salivary secretion for the evaluation of the biologically positive alimentary reaction.

Thus, a somewhat strange concept of the "inhibitory reflex" has resulted. Its triggering stimulus, for example, the differentiating stimulus, has its own receptor elements in the cortical end of the analyzer, such as a cell. Not being reinforced with food, this stimulus causes a complete negative reaction with all its specific effectors. However, for the evaluation of the negative reaction, its own peripheral effects are not used, but rather the *decrease in the secretory effect*, that is, the side effect on a completely different and positive activity. Due to such an evaluation, the "inhibitory reflex" has become a peculiar physiological hybrid, the initial part of which is classified as the stimulus of a biologically negative reaction and the end of which is a positive alimentary reaction.

Therefore, in the process of extinction of the conditioned *alimentary* reflexes, it was quite valid to attempt to compare the changes in conditioned secretion with some kind of characteristics inherent *only* in a negative reaction arising from nonreinforcement.

Which of the components of the negative reaction of the animal can be used as its constant indicator?

In the choice of this component we were guided by several considerations. Since we wanted to give a comparative evaluation of the quality and intensity of the excitations comprising the positive alimentary and the biologically negative reactions of the animal, we had to select a component which would be common to both these reactions. This would make it possible to evaluate comparatively the two selected reactions. Moreover, the selected component had to have sufficient mobility and reactivity to make it possible to observe all the stages of the transition from one integrated reaction to another. Finally, since the negative as well as the positive reactions of the animal are accompanied by a definite emotional state under these conditions, it is necessary that the selected indicators also be capable of reflecting the intensity of these emotions. As is known, Pavlov attributed great significance to the "emotional resources" in the development of the conditioned reflex and in some cases directly pointed out that in excluding emotions "*the cortex is deprived of its chief source of strength.*"

Comparing all the above-named requirements, we concluded that the vegetative components of conditioned reactions, such as respiration and blood pressure, most completely satisfied these requirements. For this reason we chose the first of these some 35 years ago as the indicator for solving the problem of cortical inhibition.

In order to describe the role of the respiratory component in the conditioned reaction we must briefly pause to consider the physiological architecture of the conditioned reflex as an *integrated reaction of the animal*. I have previously described all the components of the conditioned reaction in detail (Anokhin, 1949c). Therefore, I will now clarify only the significance of the respiratory component in the system of a conditioned reaction.

Biologically, the participation of the respiratory component in the reactions of the animal is related to ensuring those oxidative processes needed in various stressful life situations. In higher animals and especially in man, the respiratory component often appears as a peculiar vestige of a very important adaptive reaction in the distant past.

Among reactions of this kind are abrupt changes in respiration upon sudden stimulation and at the appearance of fright or some other emotional reaction. In all these cases the respiratory rhythm changes sharply and usually shifts to the inspiratory level.

However, in spite of the convincing nature of the changes in the respiratory component of the conditioned reaction in certain cases, we must necessarily ascertain the specificity of these changes with respect to certain reactions of animals, particularly the three most often appearing in experiments: the alimentary, defense, and orienting-investigative. Many years of work on the comparative evaluation of the respiratory component of these three integrated reactions have convinced us that it is specific for each of these reactions, and can therefore be used for evaluating the character of reactions appearing during experiments and during transitions between them. Even in those types of nervous activity where the respiratory component is not an indication of the condition of the animal but is evidence of unavoidable changes in the respiratory system involved in some adaptive act, it nevertheless has a specific character (eating, barking, etc.) (Fig. 14.1).

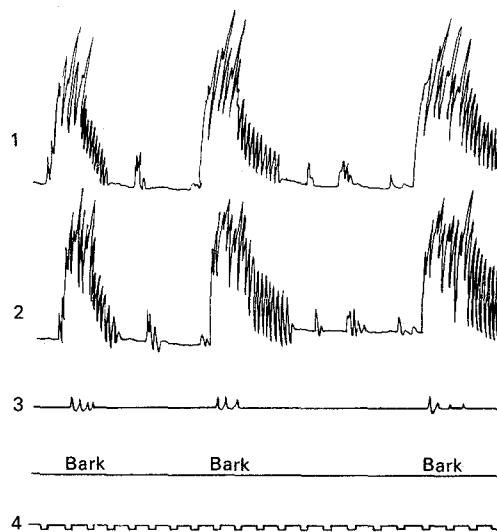


FIG. 14.1. Typical changes in respiratory movements during barking. Lines 1 and 2, left and right sides of thorax; line 3, lifting of paw; line 4, time in seconds.

Before characterizing the specific features of these three reactions according to their respiratory components, it is necessary to establish to what degree the respiratory component is able to reflect the *intensity* of a given reaction. Are there some physiological bases for justifying this ability?

In order to answer this question affirmatively, it is only necessary to recall the decisive role in the formation of the respiratory act played by the frequency of nerve impulses which are sent by the respiratory center to the periphery. As is known, inspiration begins with the respiratory center sending a comparatively high-frequency

discharge of nerve impulses (up to 100/sec) along the phrenic and intercostal nerves. These impulses, causing a gradual contraction of the respiratory muscles, thereby dilate the thorax, expand the lungs and, as a result, gradually increase the frequency of the afferent impulses from the receptors of the alveoli. At a definite frequency of these recurrent afferent impulses the excitation of the inspiratory center is inhibited and the thorax returns to its original position.

From these experimental data it follows that the transition from inspiration to expiration is the result of delicate correlations between the level of excitability of the inspiratory center and the frequency of afferent impulses returning from the lung to the inspiratory part of the respiratory center.

Let us imagine a situation in which the inspiratory center, depending on influences from the higher centers, is in a state of increased excitability. Inspiration will then be more intense and deeper and the afferent impulses from the lungs more frequent.

Since the *initiative* in these correlations always remains with inspiration, and the afferent impulses from the lung are only its result, any increase in excitability of the respiratory center will invariably be expressed in a *more intense and deeper inspiration* (Fig. 14.2a).

It follows that if, in response to some external stimulus, the amplitude of the respiratory movements increases as compared to those during a state of rest, we can justifiably presume that *the higher centers which control respiration are in a state of increased excitability, and the total intensity of excitation of a given reaction expressed as the frequency of nerve impulses of the phrenic and intercostal nerves will be higher than when at rest*. This is especially evident when the whole respiratory curve is at a high inspiratory tonus or even stops at the height of inspiration (Fig. 14.2b).

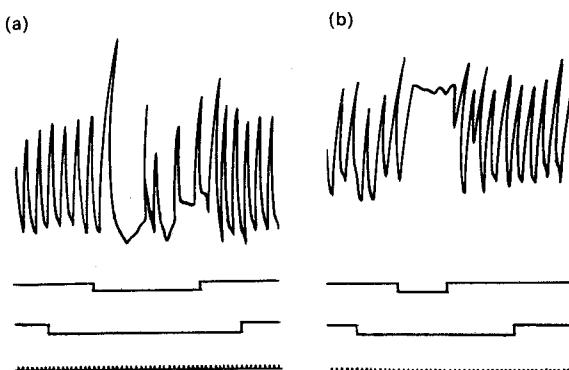


FIG. 14.2. Illustration of a case of high excitability of the respiratory center. For explanation see text.

From the physiological point of view the interpretation of such a pneumogram presents no particular difficulties. *A continuous, and not rhythmic, series of nerve impulses from the respiratory center is necessary to maintain the diaphragm and intercostal muscles in a constant state of tonic contraction*. This also means that the intensity of the excitations comprising the integrated reaction to which the given respiratory component belongs

must be especially high. Experiments have shown that whenever the general excitability of the nervous system of the animal increases, as indicated by external behavior, the activity of the respiratory musculature also increases. The mobility of the respiratory center and the sensitivity of the respiratory function as a whole are so great for all types of the organism's activity that, by using a pneumogram, the experimenter can correctly discern the state of excitability at a given moment. This, then, can be a direct indication of the intensity of the excitations which constitute the given reaction as a whole.

Presented below are Figs. 14.3 and 14.4. The latter clearly illustrates the above-

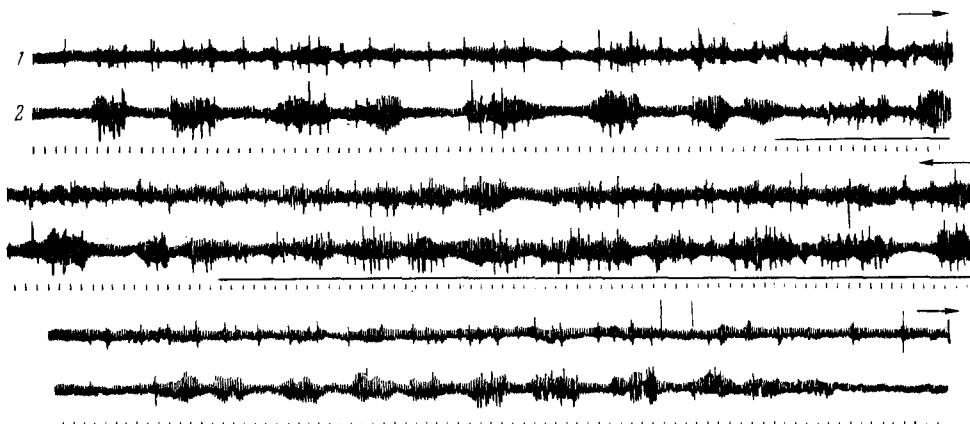


FIG. 14.3. Oscillographic recording of electric potentials from intercostal muscles of the right (1) and left (2) half of the thorax. One can see the increase of electric potentials at the moment of application of a conditioned stimulus (solid black line).

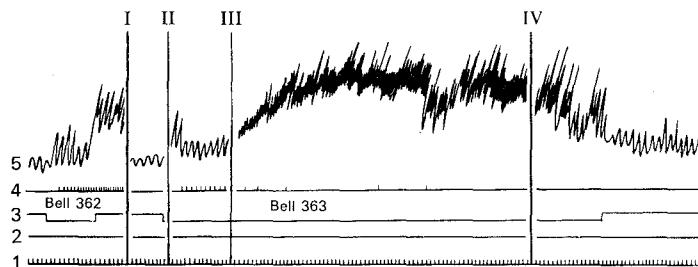


FIG. 14.4. Change in the respiratory component as an index of the transformation of one reaction of an animal into another. A continuous extinction of the alimentary conditioned reflex is conducted for 10 min. An abrupt change in the respiratory component can be seen beginning at the moment when the animal usually received alimentary reinforcement. 1, time in seconds; 2, record of unconditioned reinforcement; 3, record of conditioned stimulus; 4, salivary secretion; 5, respiration. Lines I, II, III, and IV indicate that part of the record was cut off. Interval I-II indicates baseline respiration between stimuli. Interval II-III indicates respiratory and salivary responses at the beginning of the application of the second nonreinforced conditioned stimulus.

described properties of the respiratory component of the reaction. The electrical component of the defense reaction is shown in an oscillogram recorded from the intercostal muscles by means of two needle electrodes.

Immediately upon application of the conditioned stimulus, the frequency of electrical oscillations increases considerably. Such an oscillogram with the electrodes always in the same position may serve as a direct indication of an increase in the arrival of nerve impulses from the respiratory center to the intercostal muscles.

Because of this mobility of the respiratory apparatus, it has long been used for the evaluation of the general condition of man, especially of his emotional reactions (Gaskell, 1933). Being necessary components of any general emotional excitation, the respiratory and heart rates can serve as very important additional means for a deeper analysis of the physiological architecture of the conditioned reflex. On one of Pavlov's "Wednesdays" in 1932, I reported on the significance of the vegetative indices (respiration and circulation) in the investigation of the general principles of higher nervous activity (see Pavlov, 1949b, p. 185).

It should be noted that one of Pavlov's students, W. H. Gantt, widely applied this form of investigation when working on the problem of higher nervous activity. Since 1940 he has systematically studied the vegetative components of the conditioned reflex, respiration and heart rate. As a result of a number of his studies he formulated the theory of "schizokinesis" and "autokinesis," both being especially important in the pathology of higher nervous activity. Although Gantt's concept will be given serious consideration in Chapter 16, we must here acknowledge that he presented some questions of the pathology of higher nervous activity from a new and interesting aspect.

In recent years the question concerning the significance of the vegetative components of conditioned reactions acquired such great importance in the Pavlovian laboratory directed by Gantt that for a discussion of it a conference was convened in Baltimore in 1955.

Summarizing what has been said of the intensity characteristics of reactions as indicated by the respiratory curve, we may conclude that the respiratory component of any integrated reaction enables us to judge the intensity of the excitations which comprise this reaction. Just as each separate component of any reaction cannot have its own isolated expression independent of the level of excitability of the reaction as a whole, so to the same extent can the respiratory component be a *direct* indication of the intensity of the excitations of a given reaction.

Another peculiarity of the respiratory component of the conditioned reaction which should be mentioned is its extreme sensitivity to an external stimulus. Due to these characteristics, in response to any conditioned stimulus, the respiratory component changes *first*, and then, within a few seconds or even a fraction of a second, the other components of the conditioned reaction appear: the motor, secretory, and others. According to the data of Robinson and Gantt (1947), the cardiac component is still faster. For example, in studying the orienting-investigative reaction, Gantt showed that its most mobile component is the cardiac.

Our laboratory encountered this phenomenon in its very first investigations of the respiratory component of the conditioned reflex (Balakin, 1935). Later, in the studies

of our collaborator Kas'ianov (1950a, 1950b), it became the object of a special investigation with a precise oscillographic analysis of the electric potentials of the intercostal muscles.

Synchronized recordings were made of the respiratory movements of the thorax, defense movements of the limbs, and electric changes in the intercostal muscles. A comparison of these components of the reaction showed that strong excitation of the intercostal muscles occurs, as a rule, somewhat earlier than the motor defense reaction itself. "Anticipation," as we called this phenomenon, usually fluctuates depending on a number of conditions, especially on the quality of the conditioned stimulus. In general, however, anticipation has a relatively constant value for each stimulus.

For example, the interval between the appearance of change in respiration and the appearance of the defense reaction itself to an auditory stimulus (tone) equals 0.55 sec, while for light it equals 1.40 sec. It is of interest that the *latent period* for the appearance of primary changes in respiratory functions remains relatively the same for light as for sound (0.5–0.6 sec).

For more detailed information on the peculiarities of this phenomenon I refer the reader to the work of Kas'ianov, but now I wish to call attention to one more point. The change in the central excitation in the respiratory system is more pronounced the closer to the expiratory level is the thorax at the time the conditioned stimulus is applied. And conversely, if the action of the conditioned stimulus coincides with the height of inspiration, the change in the respiratory curve will be delayed, that is, "anticipation" is decreased.

This problem was investigated most fully in our laboratory by Shidlovskii (1963, 1964). He studied the most important vegetative components (heart rate, arterial blood pressure, respiratory rate, as well as muscular tonus) of the conditioned reflex during the artificial and deliberate aggravation of the last moment of eating by removing the food from the animal. He found that from the very beginning of the action of the conditioned stimulus, all vegetative components of the conditioned reflex are manifested in that combination and with that intensity which will be needed only when the food will be removed. *The future effort is anticipated by the entire complex of vegetative components of the conditioned reaction.*

A convincing illustration of this concept is found in the interesting work of Marshak (1948). He showed that any training of man to a definite rhythmically repeated cycle of physical exercises leads finally to the result that in response to a signal stimulus there first appears a change in the respiratory function which corresponds quite accurately to the *impending* physical exercises.

These data undoubtedly show one of the interesting peculiarities in the organization of the integrated activity of the organism. As soon as this activity is integrated (in this case as a result of the experiment), its external manifestation immediately becomes subject to general biological principles: *each component of this activity occupies in time and space precisely that place which imparts to that reaction the maximally useful adaptive significance.*

The same principle was clearly shown in the investigations of the laboratory directed by K. M. Bykov. For example, it was demonstrated that in conductors who are on trains going from south to north and north to south, the metabolism assumes *beforehand*

the character suited to the climatic conditions where the conductor will be several days later. Undoubtedly, all these phenomena have the same biological meaning. Any reaction must necessarily be provided with the appropriate metabolic and respiratory processes. As a result of this, in the course of evolution a principle has developed: *in the elaboration of conditioned reflexes their metabolic components appear first.*

It would be erroneous, however, to think that this "anticipation" by the cardiac and respiratory components of all the other components of the conditioned reaction is the result of a *greater physiological mobility* of the nervous processes which ensure the respiratory function. The early appearance of the respiratory component is the result of *coordination* in time of the individual fragments of the integrated act and not the result of a *greater physiological mobility* of some impulses as compared to others.

Similarly, when the trumpeters ride in front of the rest of the cavalry regiment, this is due to the general organization and by no means because the horses of the trumpeters have outstanding racing qualities.

What determines this temporal distribution of the components? If one examines this process with reference to the functional system, the answer becomes clear. This temporal distribution of the components is already established in the action acceptor just as all the words of a phrase are represented in the action acceptor even before the first word is uttered.

During the patterning of the action acceptor, not only the afferent parameters of the end result are encoded in it, but also the afferent parameters of all the intermediate stages of approaching the result. More specifically, the *effort* expended on the achievement of the result also has its afferent component. This promotes its appearance before the necessity for the effort itself arises.

Very likely it cannot always be stated that the respiratory component belongs to the conditioned reaction only. For example, the change in the respiratory component may belong to a significant degree to the already eliminated *orienting-investigative reaction* which is somewhat apparent even for a well-established conditioned stimulus.

Taking the respiratory component into account, one must always remember that its very first changes may have a different physiological meaning. This becomes particularly significant if one leaves the purely phenomenological characterization of the respiratory component of the conditioned reaction and asks: what concrete mechanisms involve the respiratory component in the conditioned reaction as an organic component in exact correspondence with the biological sense and significance of the given conditioned reaction?

Unfortunately, this question was never seriously analyzed in laboratories studying higher nervous activity. We are therefore compelled to explain its significance chiefly by utilizing some indirect data from contemporary literature. First we must establish what data we have at our disposal concerning the connection between the cerebral cortex and the respiratory system.

It has long been known that in stimulating certain zones of the cerebral cortex one can obtain a well-defined effect on the respiratory movements (V. Ia. Danilevskii, V. M. Bekhterev, and others). At the same time, Christiani (1885) had shown that significant changes in the respiratory movements of rabbits occur also when the

diencephalon is stimulated. These observations later made it possible to assert that the "respiratory center" is localized in gray matter of the third ventricle and even in the thalamus.

Interest in the question concerning the relation of the cortex to the respiratory function has increased in recent years because of the fact that the relation of the changes in respiratory movements to the orbital convolutions of the cortex has been precisely localized to zone 13 on the cytoarchitectonic map constructed by Walker (1940).

Somewhat unexpectedly the experimental results of the study of the orbital cortex have led to broad generalizations of its role in forming various emotional states. It has been demonstrated that stimulation of the central stump of the vagus nerve also leads to noticeable changes in the electroencephalogram of the orbital cortex. Neuronographic investigation (by the method of electroencephalographic recordings of strychnine discharges at a distance from the site of stimulation) reveals an intimate connection of this area of the cortex with the limbic area and gyrus cinguli. These areas are, in turn, very closely connected by the system of Ammon's horn with the area of the hypothalamus in the form of a continuous circular flow of nerve impulses. Such an intimate relationship between cortical and subcortical formations in the development of the vegetative components of emotional states and discharges could, of course, not remain unnoticed. Therefore, the orbital cortex and its connections were, by various authors, given designations of similar meaning. Herrick (1933a, 1933b) called it "activator of brain functions," Papez (1937) attributes to it the function of "extension of emotional states," and MacLean (1949), as the result of comprehensive investigations of the functions of the orbital cortex, referred to it as the "visceral brain."

Investigations of the role of the orbital cortex in the respiratory function were focused mainly on two questions:

1. Along which pathway does the influence of the orbital cortex spread to the system of the strictly "respiratory centers," which have been well studied in the bulbar and stem areas of the central nervous system?
2. What is the physiological significance of the connections of the orbital cortex with the respiratory and cardiovascular functions?

In regard to the first question, during the past 20 to 25 years many experimental data have been obtained which have been closely related to the results of the study of the role of the reticular formation of the brain stem and the hypothalamus in the formation of the general reactions and states of the organism.

Since the discussion of all these data would lead us far from our interest in *the place of the respiratory component in the conditioned reaction of the organism*, we will limit ourselves to some comments concerning the participation of the reticular formation of the brain stem in the transmission of cortical influences to the respiratory function.

As was shown by morphological and neuronographic investigations, the reticular formation encompasses the system of connections between the thalamus, the hypothalamus, the brain stem, and the medulla oblongata.

Every afferent stimulation will invariably excite the reticular formation along the

collateral connections in the brain stem and in the region of the thalamus (lemniscus medialis and lateralis). The reticular formation, as an *activating system*, maintains the corresponding tonic state of the cortical cells and ensures a definite level of cortical activity. It is interesting to note that direct experimental investigations demonstrated a dual excitation of the cerebral cortex from each single stimulus applied, for example, to the sciatic nerve.

First there appears the fastest change in the potential of the cortex, precisely localized along the projection of the corresponding thalamo-cortical pathway. This excitation is limited to a definite point of the cortex and has no tendency to irradiate. After 8-10 msec this potential is followed by a change in the electrical activity (second Forbes discharge), which is *simultaneous and generalized over the entire cortex* (Forbes and Morison, 1939). This generalized phase of excitation is achieved through the reticular formation of the brain stem and the thalamus.

If one takes into consideration that the reticular formation of the brain stem is very closely related to the inhibitory and excitatory reticular formation of the medulla oblongata, then the influence on the respiratory center of any afferent impulses causing a rapid change in the respiratory cycle will be clearly understandable.

Let us recall that electrical stimulation of the orbital cortex results primarily in cessation of breathing in the *inspiratory phase*, while the blood pressure rises. It is easy to see that it is just this synergism between the respiratory and cardiovascular functions which, as a rule, takes place in all general reactions of the organism demanding rapid energy expenditures and is usually connected with biologically negative states in man and animals. This also permits us to answer, to a certain degree, the second question posed above.

Many investigations by Soviet scientists (the laboratories of Bykov and others) have shown that the cerebral cortex can enter into a functional connection, according to the principle of conditioned reflex coupling, with any vegetative function of the organism.

The involvement of the vegetative functions of the organism in conditioned reflex activity follows from the integrated character of the conditioned reflex itself, which includes essentially all the vegetative processes of the organism. However, in the experiments of Bykov's laboratory they were concerned with the specific conditioned reflex process which adapts a *particular vegetative function* to the demands of a specially created situation. For example, by means of a conditioned reflex, one can produce either a greater or lesser intensity of diuresis depending on both the changes in water metabolism signaled by the given stimulus and the cortical mechanisms determining this kind of adaptation of the vegetative functions.

In view of the experimental material discussed above, one can explain the physiological significance of the relation of the orbital zone and other cortical zones to the respiratory and cardiovascular functions.

The continuous regulation of these functions at a characteristic constant level is satisfactorily achieved even at the level of "lower self-regulations." However, as soon as the need arises in the organism to adapt to environmental conditions, these "lower self-regulations" which efficiently maintained a constant level of definite functions,

we must ask : by what mechanisms does the cortically organized behavioral act utilize the lower self-regulations *in exact accordance with its own general physiological architecture and biological meaning?*

At present the only conceivable answer to this question is the following : *the share of participation of some vegetative component in reactions of the integrated organism must be determined where the given acquired act is integrated, that is, in the cerebral cortex.* Consequently, some structures of the cerebral cortex must be more intimately connected with the lower self-regulations of the functions than others. Evidently, this function of adapting and *stabilizing* the vegetative components to the problem of a conditioned reflex is fulfilled by the orbital cortex, the limbic system, the amygdaloid nucleus, the cingulate gyrus, etc. Herein lies the meaning of the participation of the given neural structures in the organization of emotional discharges and general biological conditions. They act as the intermediary between the individually acquired behavioral act and its *vegetative supporting reaction*, which in the final analysis is always fulfilled by the subcortical integrative mechanism.

Let us imagine that the incorporation of the vegetative components into the conditioned reflex act occurs differently. Let us assume that the conditioned reflex motor act is formed in the cerebral cortex, and the vegetative components are incorporated later into the series of impulses from the conditioned stimulus when they pass through the subcortical mechanism. Under these conditions, could there be established a precise coordination between the characteristics of the behavioral act itself and its vegetative supporting reactions? From a physiological point of view such a coordination is difficult to accept.

In light of the above considerations, the inaccuracy of the expression "the cortex regulates the vegetative functions" should especially be stressed. The cortex adapts the already well-regulated functions to the demands of the whole organism in its adaptive behavior in response to external stimuli. Figuratively speaking, it can only present its "claims" to the precisely functioning mechanisms of the lower self-regulation and vary them depending on both the sum total of external stimuli and the character of the integrated reaction being formed at a given moment.

Returning to the characteristics of the respiratory component of the conditioned reaction, we should point out that the extent of its participation and its character are already determined in the cerebral cortex on the basis of the interaction of the orbital and limbic cortex with the other areas of the cerebral cortex. Organized as a result of this interaction is a system of cortical and subcortical excitations which fully determines the harmonious participation of the individual components (somatic and vegetative) in the integrated reaction of man and animals.

A final conclusion is self-evident : *the respiratory component of a conditioned reaction with such mechanisms of organization must be specific for each particular condition of the animal.*

After this general description of the respiratory component with respect to its intensity, dynamics, and the mechanisms of its participation in the general reactions of the organism, we can now describe its specific features under various new experimental conditions :

1. Upon sudden shortening and lengthening of the usual time of the isolated action

- of the conditioned stimulus and during the gradual adaptation of the animal to this new condition.
2. Upon the sudden summation of conditioned stimuli which were previously applied separately.
 3. Upon a single nonreinforcement of a well-stabilized conditioned reflex.
 4. Upon extinction of the conditioned alimentary reflex.

Comparing these experimental conditions, one can see that they all lead primarily to the disturbance of the usual conditions of the experiment, i.e., in the final analysis to the formation of a reaction to "novelty." This reaction is the result of discordance in the action acceptor which includes all the parameters of the conditioned stimulation as they were used in previous experiments (strength, duration, time of appearance, etc.).

From these experiments we have concluded that the respiratory component is distinguished by its exceptional dynamism and reveals the change in its character sooner than any other signs of changes appear in the other components of the reaction (movement, secretion, etc.).

As a rule, during disturbance of the usual conditions of the experiment, changes quickly arise in the stereotypic, quiet respiratory rhythm which consist of a general rise in the respiratory curve and an acceleration of the respiratory rhythm. As was already noted, the rise of the inspiratory tonus and acceleration of respiration indicate a considerable rise in the intensity of impulses in the system of the integrated reaction of the organism which develops at a given moment.

Figure 14.4 shows one of the experiments involving the continuous extinction of the conditioned reflex to a bell. The conditioned reflex was previously well stabilized and followed a standard course: its respiratory component was always constant and of a definite type, and the conditioned secretion was quantitatively always the same during a definite period of an isolated application of the conditioned stimulus.

On the graph (see Fig. 14.4, interval III-IV) it is clearly shown that in the process of continuous extinction, parallel with the change in the pneumogram, the conditioned secretion also gradually decreases.

How must one understand the change in the pneumogram? The usual background is seen between the vertical lines I and II, the reaction to the conditioned alimentary stimulus is seen between II and III. The respiratory component of the conditioned reaction always includes two phases. The first consists of two deep inspirations with a noticeable increase in the inspiratory tonus. However, the respiratory rhythm here differs very slightly from the rhythm of the respiratory movements which were present before the application of the conditioned stimulus. This phase of change in the respiratory component reflects the orienting reaction which as a rule appears at the beginning of the application of the conditioned stimulus, regardless of the number of applications. In view of its great constancy, even in a well-stabilized conditioned reflex, one can believe that it is the result of the *direct* action of afferent impulses on the reticular formation of the brain stem. In any case, such a possibility was shown in a number of investigations (Moruzzi and Magoun, 1949; Magoun, 1950).

In the second phase of the conditioned reaction the pneumogram returns almost to normal, which characterizes the *course of the alimentary excitation and alimentary reaction in pure form without complications from extraneous influences*.

Since maximum salivation corresponds to this phase of the conditioned reaction, we may assert that this is the type of respiration which is characteristic of a normal, uncomplicated, positive conditioned alimentary excitation. However, as soon as there is a sudden disturbance of the usual stereotype, i.e., an absence of reinforcement, sharp changes immediately occur in the pneumogram, reflecting first of all discordance in the action acceptor and the appearance of an orienting-investigative reaction. From this moment the respiratory component is a part of the orienting-investigative reaction and not of the alimentary one.

The entire subsequent section of the pneumogram represents a *type of respiration characteristic of the gradual development of the "stressful state" of the animal due to the aroused but unsatisfied alimentary excitation*. A constant characteristic feature of such respiration is the exceedingly high frequency of respiratory movements with a marked inspiratory tonus. As I said before, such a pneumogram is, from a physiological point of view, a true indication of the high level of excitability of the whole central nervous system. And this in turn indicates that the excitation of the negative reaction which caused these changes in the pneumogram must possess a high *inhibitory capability* with respect to other activities of the cerebral cortex, i.e., in this case with respect to alimentary activity.

Thus, it is proven that the internal or conditioned inhibition is the result of the interaction of "two nervous activities," since the chief demand upon the "inhibitory" excitation (greater intensity and consequently higher frequency of impulses) has been satisfied.

Still more clearly seen is the relationship between the pneumogram and secretion during intermittent extinction. At the stage of extinction when the conditioned secretory reaction is completely inhibited ("zero secretory effect"), the pneumogram, during the action of the conditioned stimulus, can show extreme changes with regard to both frequency and intensity of inspiratory tonus (Fig. 14.5).

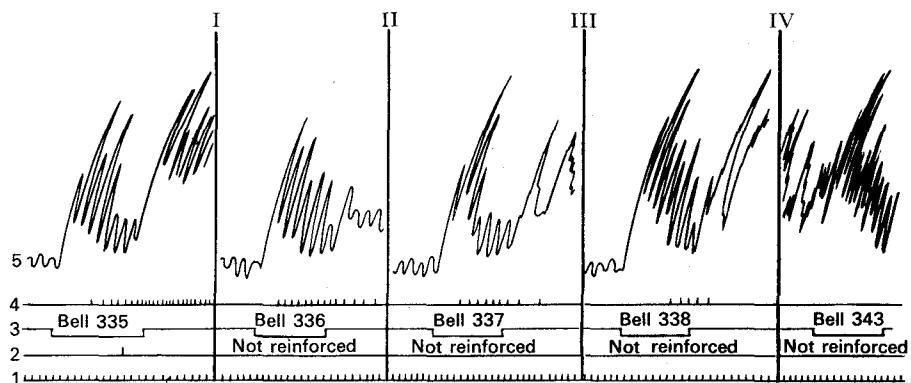


FIG. 14.5. Changes in a pneumogram in the course of several nonreinforcements of the conditioned alimentary stimulus. The first pneumogram (left) is typical for the given experimental animal. After the first nonreinforcement the respiratory component clearly changes and, moreover, this change is characteristic of the orienting-investigative reaction. The last of the indicated conditioned stimuli produced complete inhibition of conditioned secretion, but at the same time the pneumogram indicates that the reaction has acquired a biologically negative character ("stressful state"). Designations the same as in Fig. 14.4.

This case is additional proof that such a reaction, arising under *conditions of non-reinforcement with food*, may serve as an objective indicator of the "stressful state" of the animal, i.e., a reaction of a negative character. Actually, a complete inhibition of conditioned secretion in the second example (see Fig. 14.5) was achieved at the eighth application of the stimulus to be extinguished when the orienting reaction to the "novelty" of the whole procedure of nonreinforcement with food was already extinguished.

This is also corroborated by the pneumogram in Fig. 14.4, which shows a continuous 10-min extinction of the auditory reflex without subsequent reinforcement. The normal pneumogram appears as soon as the effect of the conditioned stimulus stops. This is direct evidence that the negative character of the whole reaction of the animal is connected with the effect of the conditioned stimulus to be extinguished, which in the fifth minute has already become a signal for a negative reflex. By this time the conditioned salivary effect also is completely inhibited.

A closer examination of the changes in the pneumogram during qualitatively different reactions of the animal convinces us that, aside from the above-described quantitative changes in respiration, it possesses a very definite specificity, making it possible to unerringly determine the character of the reaction. This is especially valuable for the experimenter, since under certain conditions qualitatively different integrated reactions of the animal can rapidly replace one another.

In this sense the respiratory component, always recorded in a given animal, can be a very valuable addition to the secretory and motor components since *neither one can give us an idea, for instance, about the evolution of the orienting-investigative reaction throughout the period of elaborating and stabilizing a conditioned reflex*.

As already noted, the orienting-investigative reaction, arising in response to some new stimulus, has an especially pronounced inhibitory capability. Pavlov gave special attention to this fact and described it in detail in his *Lectures on the Function of the Cerebral Hemispheres* (Pavlov, 1927, see Pavlov, 1960, pp. 110–130).

Later, in the investigations of collaborators in the Pavlov laboratory, the very fact of presenting new stimuli to the animal or a sudden change in the established stereotype of the experiments, was called a "novelty," which was recognized as a "special stimulus" (Anokhin, 1926a).

In experiments of my collaborator Balakin (1935), novelty as a special stimulus was for the first time described as a change in one of the vegetative components of the conditioned reaction—respiration. Subsequently the orienting-investigative reaction (the reflex "what is it," according to Pavlov) was subjected to a thorough investigation by a number of authors.

For example, Gantt studied the changes in the cardiac, respiratory, secretory, and motor components of the conditioned reaction under the influence of an orienting-investigative reaction. As a result of his investigations Gantt (Robinson and Gantt, 1947) concluded that taking into account many components, especially the vegetative, makes it possible to more fully characterize an integrated reaction of the animal than is possible from any other one component.

From these experiments it follows that the most labile and significant component of the orienting-investigative reaction is the cardiac component.

Especially to be mentioned are the systematic investigations of Sokolov (1957) in which he increased the number of components of the orienting-investigative reaction used earlier by other authors. Besides the usual vegetative indicators such as respiration and cardiac activity, he used the galvanic skin reflex, electroencephalogram, etc. Like the earlier investigators, Sokolov noted the gradual extinction of the orienting-investigative reaction to a new stimulus and, moreover, that this extinction spreads to all components of the reaction.

The essence of this extinction is a subject for special investigation and does not concern our present task : the characterization of the specific features of the respiratory component of the orienting-investigative reaction.

The respiratory component as a rule is markedly apparent when a new stimulus is applied. The individual respiratory cycles become deeper, more frequent, and usually there is a shift to a higher inspiratory level (Fig. 14.6).

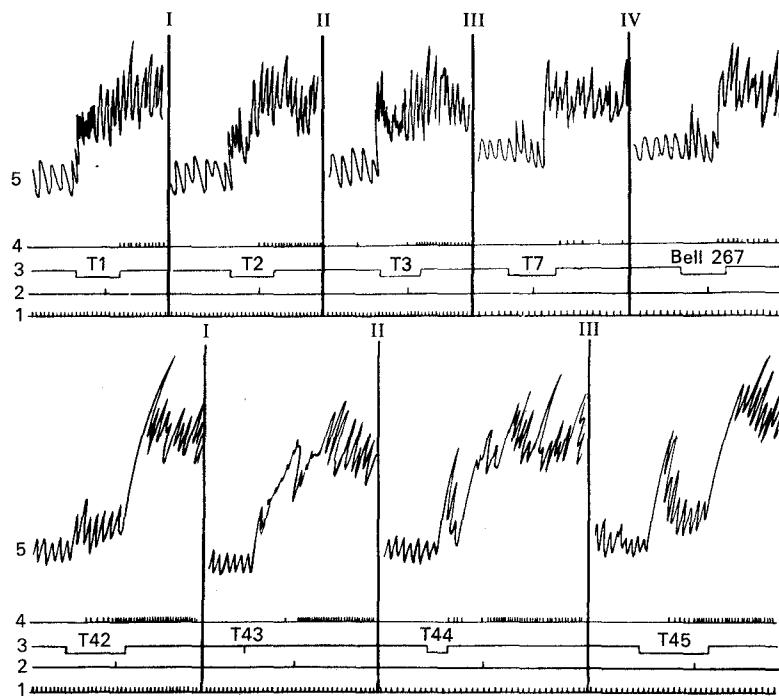


FIG. 14.6. The upper row of graphs shows the gradual transition from the orienting-investigative reflex to a reaction of a typically alimentary character, after several initial reinforcements of the indifferent stimulus (tone). For comparison, the upper right graph illustrates the reaction of the animal to a bell reinforced with food the 267th time. The lower row of graphs shows the effect of an extreme shortening of the duration of the conditioned stimulus (T 43) on the transition from the alimentary to an orienting reaction. Designations the same as in Fig. 14.4.

One can then see a gradual calming of the respiratory component, usually passing into barely noticeable changes during the first fractions of a second of the application

of the stimulus (Fig. 14.7). These small changes are hardly ever extinguished. It is interesting to note that the respiratory component of the orienting-investigative reaction to a bell always appears more quickly and is more pronounced than an orienting-investigative reaction in response to the action of a visual stimulus. This phenomenon fully corresponds with the "law of strength" of the conditioned stimulus. Experimental investigations in recent years have exhaustively explained this phenomenon. As was shown by Gellhorn *et al.* (1954), the afferent paths of the auditory stimulus have considerably larger collateral branches in the brain stem to the reticular formation than do the optical afferent pathways. It is because of this that quite extensive neural elements of the cortical and subcortical structures can be involved in the orienting-investigative reaction to a bell. The reticular formation contributes, as we have seen, to the rapid change in the respiratory component in response to the conditioned stimulus.

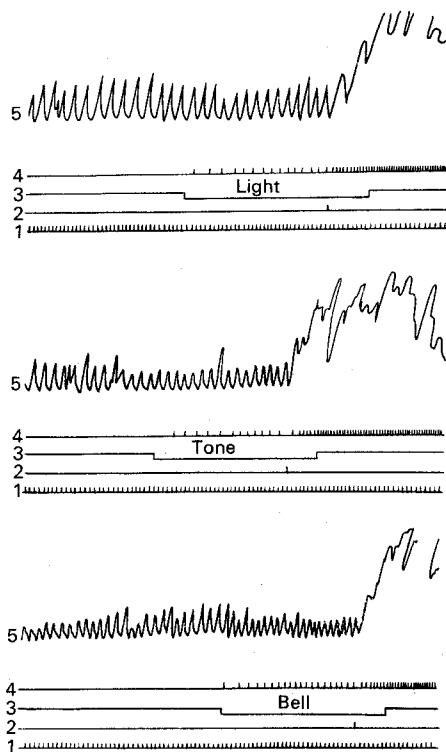


FIG. 14.7. Examples of reduced respiratory components of a conditioned reaction: to light, to a tone, and to a bell. Barely noticeable changes are found only at the very beginning of the application of the conditioned stimulus. Designations the same as in Fig. 14.4.

Returning to the extinction of the respiratory component of the orienting-investigative reaction, we must note that it appears again as soon as the "indifferent" stimulus is reinforced with food. The orienting-investigative reaction is accentuated after the

reintroduction of reinforcements, and in this period it clearly increases its intensity due to an increase in the alimentary dominant.

However, after many presentations of the given conditioned stimulus, the respiratory component of the orienting-investigative reaction is once more decreased and remains permanently in the form of a brief change at the moment of application of the conditioned stimulus (Fig. 14.8). It is only necessary to introduce into the stereotypic experimental conditions some kind of "novelty," and the respiratory component will immediately give evidence of a considerable intensification of the orienting-investigative reaction.

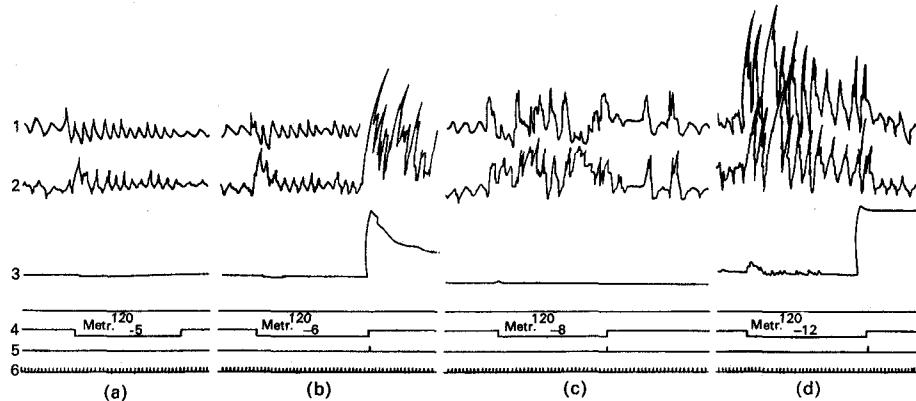


FIG. 14.8. Four fragments of an experiment with preliminary extinction of the orienting-investigative reaction. After the fifth nonreinforcement of the indifferent stimulus (a), a metronome at 120 beats/min = M_{120} , the orienting reaction survived only at the beginning of the action of the stimulus. The investigative stage is completely extinguished. Application of electrocutaneous reinforcement (b) sharply changes the respiratory component in response to the presentation of the same stimulus (M_{120}) later (c,d). (a) Presentation of M_{120} for the fifth time without reinforcement; (b) presentation of M_{120} with first reinforcement of the paw with electric current; (c) presentation of M_{120} after two pairings with electrocutaneous reinforcement; (d) presentation of M_{120} after 6 electrocutaneous reinforcements causes a change in respiration characteristic of a defense reaction. 1, respiratory movements of the left half of thorax; 2, respiratory movements of the right half of thorax; 3, lifting of paw; 4, recording of the indifferent and subsequently conditioned stimulus; 5, recording of the unconditioned stimulation; 6, time in seconds.

Throughout these experiments the respiratory component of the orienting-investigative reaction shows absolutely specific features so that, from its character and degree of manifestation, one can determine with sufficient accuracy from which phase of the experiments the corresponding indicators originated. Thus we can actually say that the respiratory component has specific features.

The respiratory component of the conditioned defense reaction is always more pronounced with wide fluctuations of amplitude, disrhythmia, and usually an increase in inspiratory tonus (Shumilina, 1959). These peculiarities of the respiratory component of the conditioned defense reaction of the animal once more emphasize the above-mentioned contradiction in our evaluation of the biological meaning of the

reaction of the animal. They indicate the energetic character of all excitations constituting this reaction, which imparts to them a strong inhibitory side effect on all the other integrated activities of the animal, particularly on the alimentary reaction.

As previously noted, the respiratory component of a stabilized conditioned alimentary reaction has a very low magnitude and often differs little from normal and calm respiration (see Fig. 14.7).

The great intensity of the excitations of the conditioned defense reaction becomes especially apparent in cases in which, after extinction of the orienting-investigative reaction, to a metronome for example, the conditioned stimulus is reinforced with an electrical nociceptive stimulus (see Fig. 14.8). At the first application of the metronome there was an orienting-investigative reaction to the "novelty," with a characteristic change in the respiratory component. However, neither the first nor the following four applications were reinforced by an unconditioned stimulus. As a result, the sixth application of the same metronome already produced an insignificant change in the respiratory component.

The sixth trial was already reinforced by an electric current, which of course evoked a defense reaction in the animal, a leg lift. This single reinforcement was sufficient to sharply intensify the respiratory component of the conditioned reaction and to give it the disrhythmia characteristic of the defense reaction. The respiratory component then became increasingly intense and finally acquired the characteristics of typical panting.

Concluding this brief description of the peculiarities of the respiratory component of the various integrated reactions of the animal, we may state that it can fully serve as the characterization of the transition from one integrated activity of the animal to another, especially if this component is always compared with the other components of the corresponding reaction (secretion, cardiac activity, motor activity, and others).

How should such a change in the respiratory component be physiologically characterized? All our experiments reveal that the presence of conditioned defense reflexes in an animal can considerably change the magnitude of the respiratory component as well as that of the other components, although in this case the actual defense reaction may not be apparent at all. It acquires special significance when it is impossible to assess the general state of the animal from other indicators.

In the experiments of Shumilina, the following interesting incident occurred. For some time the experimental animal in all experiments had received only alimentary reinforcement and was consequently in a biologically positive dominant state. The conditioned salivation was well established, and the respiratory component was very weak as is characteristic of the conditioned alimentary reflex. But one had only to apply several conditioned stimuli with nociceptive reinforcement, *while still using the former alimentary stimuli*, and the respiratory component changed sharply. The experiment was conducted in the following stereotyped order: the first three stimuli were always conditioned alimentary stimuli and the following three were defense stimuli with reinforcement by electric current. In Fig. 14.9 one can clearly see that after introduction of defense stimuli, in the alimentary reaction, together with the well-stabilized conditioned secretory component, the respiratory component acquires a different expression: the frequency becomes higher and the amplitude of each respiratory cycle increases.

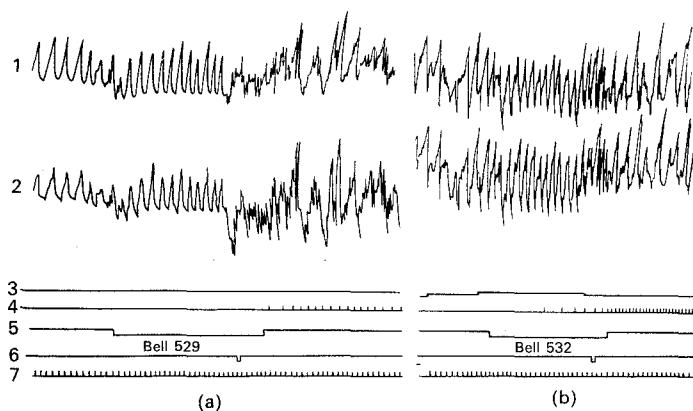


FIG. 14.9. Two examples of the presentation of a positive alimentary stimulus (bell) at various periods of the stereotype. (a) Presentation during first half of experiment when only alimentary reinforcement was used; (b) example from second half of experiment when all defense unconditioned stimuli had already been applied. In the first case secretion is inhibited; in the second, one sees a positive alimentary reaction, although the respiratory component is somewhat greater. Designations are the same as in the preceding figure with the addition of the line of secretory reaction (fourth from the top).

Similar changes in the respiratory component of the conditioned alimentary reflex are also observed after a single reinforcement of the conditioned stimulus with current (Fig. 14.10).

What should be the physiological characterization of this relationship of processes in the system of an integrated reaction of an animal? Undoubtedly, the presence of a defense reflex has considerably intensified all of the animal's activity; however, this biologically negative dominant has not developed to a degree at which it could exert an inhibitory side effect on the alimentary reaction.

This intensifying effect of the defense excitation has a generalized character, and it is quite probable that its substrate consists of diffuse structures of subcortical and cortical apparatuses.

As can be seen, an evaluation of the respiratory component of conditioned reactions helps us to reveal very interesting principles in the mechanisms of the relationship of two biologically opposite integrated activities of an animal. Having examined all the above characteristics of the respiratory component of the conditioned reaction, we have begun in recent years to study the relationships of the biologically positive (alimentary) and biologically negative reactions.

For this purpose we recorded the blood pressure along with the usual respiratory component of the conditioned reaction (Shidlovskii, 1963, 1964). Besides the biologically negative reaction arising from nonreinforcement with food and the orienting-investigative reaction to a new stimulus, we studied in detail the orienting-investigative reaction during switching (Polezhaev, 1953, 1958) and during differentiation between two positive conditioned stimuli (Zachiniaeva, 1949), using in both cases our own

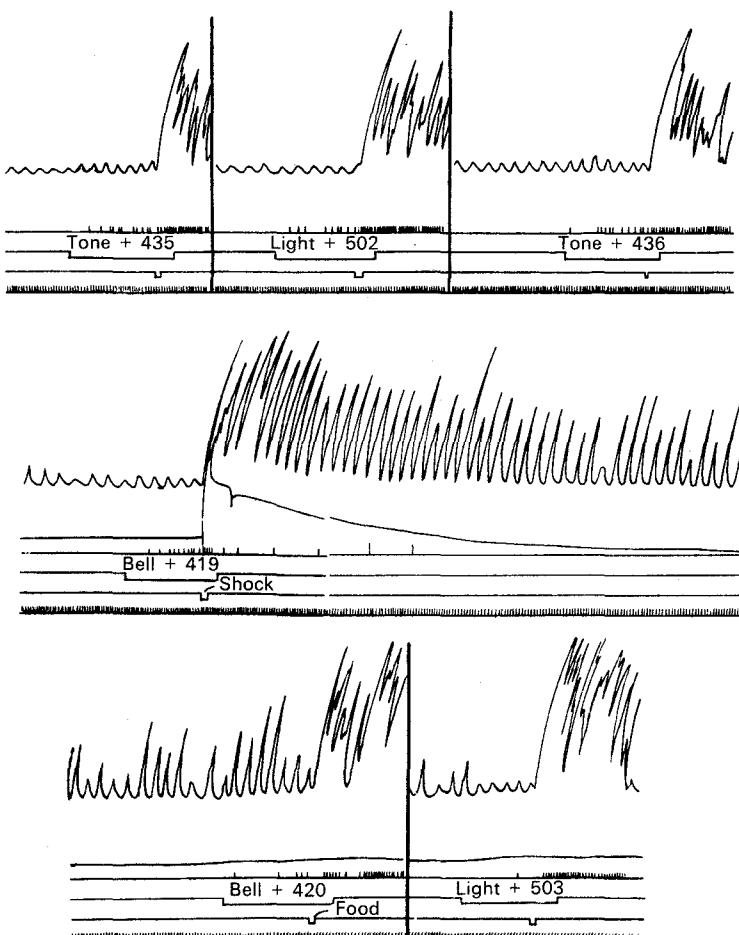


FIG. 14.10. Change in the respiratory component of the conditioned alimentary reaction after a single extra electrocutaneous stimulation of the animal. At the beginning of the experiment all three well-established conditioned stimuli produce very small changes in the respiratory component of the conditioned reaction. However, after a single sudden application of an electrocutaneous stimulus ("shock"), the respiratory component acquires an active character (see Bell 420). Designations the same as in Fig. 14.4.

secretory-motor method (Anokhin, 1932b). The major results of these investigations are described below.

First of all, external inhibition was characterized since it had been given the most definite formulation by Pavlov as the *direct result of the inhibitory effect of the orienting-investigative reaction on the alimentary reaction*. Experiments have shown that in all cases in which the orienting-investigative reaction was accompanied by strongly expressed changes in blood pressure and respiration, it also exerted an inhibitory effect on the

conditioned secretory reflex. And, conversely, if the vegetative components of the reaction under the influence of the special stimulus were significantly changed or the action of the external inhibitor itself was extinguished, the conditioned secretory effect was always present to some degree.

Thus, in many experimental variations it was demonstrated that the inhibitory effect of the orienting-investigative reaction on the conditioned alimentary reflex of the animal depends directly on the intensity of its constituent excitations. This intensity is manifested as great changes in all components of the investigative reaction: the respiratory component, the cardiovascular component, motor activity in the form of "looking," "smelling," etc.

We gave special attention to the orienting-investigative reaction which arises in the case of a directionally indefinite reaction of an animal during differentiation between two sides of the platform (Polezhaev, 1953, 1958). This case shows very clearly the significance of the respiratory component in the evaluation of the relationship of the various integrated activities of the organism.

As is known, after prolonged training of the conditioned secretory-motor reflexes, a fairly standard respiratory component is finally established (Fig. 14.11a). When the conditioned stimulus is initially presented, as usual there appears a change characteristic of the orienting-investigative reaction. Then the pneumogram reflects the movement towards the appropriate feeder and, finally, when the animal stands at the feeder and waits for the food to be given, the pneumogram assumes a calm, rhythmic character specific for a simple alimentary reaction.

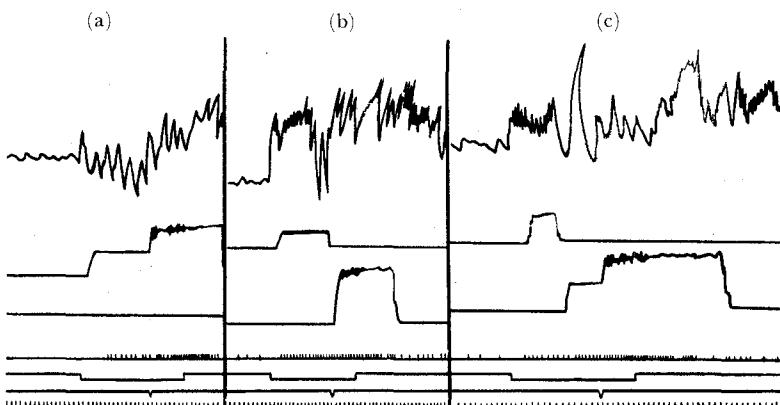


FIG. 14.11. Examples of the introduction of the orienting-investigative reaction upon incorrect motor conditioned reactions of an animal and the resultant change in the respiratory component of the conditioned reaction. (a) Correct reaction with normal respiratory component; (b and c) incorrect reactions with abrupt change in the respiratory component. Designations the same as in Fig. 14.4.

However, if the motor reaction is incorrect, i.e., the animal moves to the opposite side, the respiratory component shows quite clearly a change which corresponds to a pronounced orienting-investigative reaction (Fig. 14.11b, c).

Similar experiments show that the process of conditioned excitation caused by the given conditioned stimulus does not proceed directly and without hindrance onto the corresponding effectors which in turn cause an orienting-investigative reaction which, in these cases, helps to select the correct feeder. Taking advantage of the possibility to observe the vegetative components of the conditioned reaction, we made a special

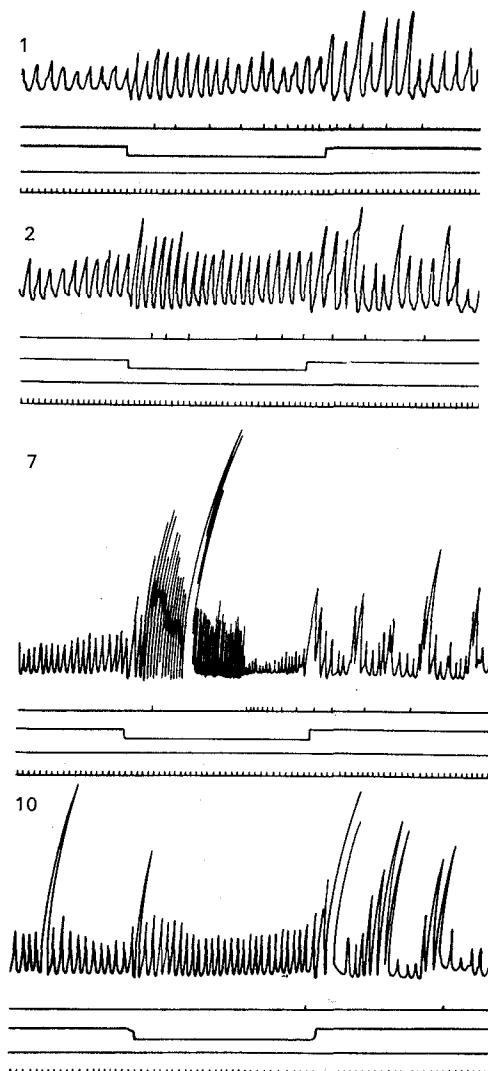


FIG. 14.12. Individual presentations of a conditioned stimulus to be extinguished (1, 2, 7, 10), showing the evolution of the respiratory component in comparison with the gradual decrease of the secretory component. Note the sharp transition between two opposite activities with components specific for them (7) during the action of the conditioned stimulus. Designations the same as in Fig. 14.4.

detailed investigation of the transition from conditioned excitation to conditioned inhibition. Those forms of conditioned, or internal, inhibition were investigated which had been well studied in Pavlov's laboratory: extinction and differentiation. The main attention in these studies was directed towards finding the initial physiological phenomenon initiating the action of the inhibitory process.

Figure 14.12 presents stages of an experiment involving the extinction of a well-established conditioned reflex. The four graphs correspond to four applications of a conditioned stimulus to be extinguished: the first, second, seventh, and tenth applications. As the graphs show, the respiratory component has a quite interesting evolution.

During the first nonreinforcement the respiratory component is typical for standard conditions. As soon as the conditioned stimulus was applied, the usual slight change in the pneumogram occurred, corresponding, as previously mentioned, to a residual orienting reaction. Then the respiratory movements increased in frequency and amplitude, which is also typical for the *auditory* conditioned stimulus, probably because of its potentiating action through the reticular formation of the brain stem. The conditioned secretory response occurred, as usual, with a characteristic latent period of 3–4 sec.

As might be expected, the main feature of this pneumogram of the first nonreinforcement is the sharp change in the respiratory component at the moment when, according to the usual schedule, reinforcement with food should occur. Since this was the first disturbance of the usual conditions of the experiment, the animal showed a sharp orienting reaction which changed into another state characterized by regular, deep respirations and a disturbance of the normal rhythm during the entire interval until the second application of the stimulus to be extinguished. For the time being we shall disregard what state of the animal appears after the orienting-investigative reaction. It is now important to demonstrate that *it occurs in close relation to the fact that the established conditioned alimentary excitation (the action acceptor) did not receive a reverse and adequate reinforcement and thus there occurred a dissociation in the relationship of these two processes.*

But the most interesting aspect in this first nonreinforcement is that the bell, as a conditioned alimentary stimulus, proved to be "reinforced" by withholding the food and consequently must acquire a somewhat negative signal meaning. The second application of the bell fully substantiates this conclusion. Immediately after the bell is introduced, the frequency and amplitude of the respiratory movements increased considerably. Accordingly, the usual conditioned secretion decreased by half (see Fig. 14.12, 2).

Let us attempt to more fully analyze the above-described phenomena, limiting ourselves here to the first two nonreinforcements, since it is at this stage of extinction that the process begins which somewhat later acquires the features of conditioned inhibition.

One essential point must first be mentioned: *the change of the sign of the conditioned reaction in response to the second application of the bell* demonstrates that only one nonreinforcement of the conditioned stimulus with food is sufficient to change its character. In other words, the very first nonreinforcement with food and the resulting negative state of the animal gave the conditioned alimentary stimulus a negative signal meaning.

Consequently, there has occurred a coupling of the temporary connection between the conditioned stimulus and the negative reaction of the animal to nonreinforcement with food. The very strong shift in the vegetative components of the reaction just at the moment when reinforcement with food was usually given demonstrates that it is exactly the moment of nonreinforcement which is most stressful for the animal, and that it is on the basis of precisely this "stressful state" that the conditioned stimulus acquires a negative signal meaning.

This can be seen in all examples of the extinction of conditioned stimuli. Usually after the moment of nonreinforcement the animal begins to show restlessness, to whine, etc. This state of the animal is completely reflected in the respiratory component.

Indicating the behavior of the animal in the interval between the conditioned stimuli to be extinguished are the sections of the pneumogram between the 8th and 9th nonreinforcements (Fig. 14.13). As can be seen from this pneumogram, the respiratory component in the interval before the conditioned stimulus and in the period of isolated action of the conditioned stimulus does not show any noticeable changes, disregarding the increased frequency of the respiratory movements. The conditioned secretion is almost completely inhibited. However, beginning exactly at

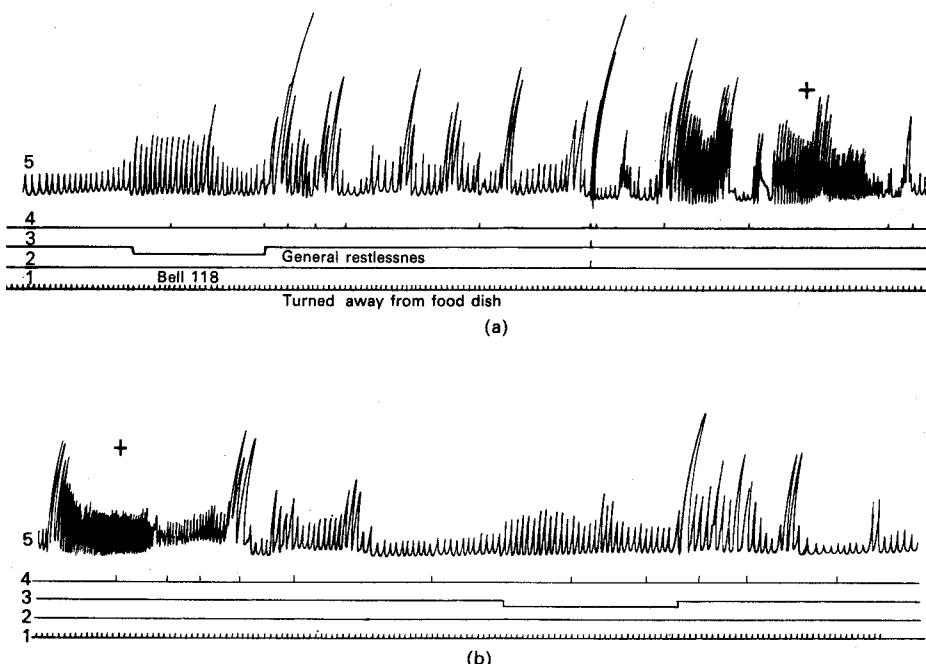


FIG. 14.13. Behavior of the respiratory component between the 8th and 9th nonreinforcement during extinction of a conditioned alimentary reflex. One can see the already fading change in the respiratory component at the moment of action of the conditioned stimulus itself and the considerable intensification in these changes in the interval between the presentations of conditioned stimuli (the "panting" type of respiration). Designations the same as in Fig. 14.4.

the moment when food was given in the usual experiments, the respiratory component changes sharply: it becomes arrhythmic with separate deep inspirations interrupting respiration which is basically irregular. This condition of the respiratory component persists for the entire interval, and one also sometimes observes periods of polypnea. All this indicates that the impetus in the origin of *new integrated reactions* of the animal is the absence of a reverse afferentation, i.e., unconditioned reinforcement "satisfying" the action acceptor (an established conditioned excitation).

One constant fact is obvious. In the process of extinction of the conditioned stimulus, from time to time reactions appear in which the biological sign clearly changes from negative to positive or the reverse. This change is especially interesting in those cases where it occurs in the course of action of the conditioned stimulus to be extinguished.

As can be seen from the pneumogram (see Fig. 14.13), during the 16th application of the conditioned stimulus to be extinguished the change in the respiratory component splits into two phases of essentially different significance. The first phase proceeds with a clear biologically negative sign, with a considerable increase in both the amplitude and frequency of the respiratory component. This serves, as we have already seen, as a *direct indication of the great intensity and high frequency of impulses of the negative reaction*. In exact correspondence we also see on the same pneumogram a complete inhibition of secretion—a clear proof of the inhibitory effect of the impulses of a biologically negative reaction. Already, however, during the action of the conditioned stimulus to be extinguished, the character of the respiratory component *suddenly* changes. There appears a calm type of respiration characteristic of the interval between the stimuli and of a simple alimentary reaction. Simultaneously with the sudden change in the respiratory component, there appears conditioned secretion in a fairly considerable amount. This leaves no doubt as to the character of the entire integrated reaction which has replaced the biologically negative reaction: *it is clearly an alimentary reaction according to all its characteristic components*.

The rapid interchange of two different integrated activities directly demonstrates that in the process of extinction of the conditioned stimulus there is a continuous alternation of two competing integrated activities. In view of the above considerations, this conclusion is not unexpected.

As can be seen, even after the first nonreinforcement of the conditioned stimulus, it acquires a different signal value, the signal of the biologically negative state of the animal. Thus, in all subsequent tests of the conditioned stimulus to be extinguished the evoked excitation has two possibilities for propagation: (1) towards the cortical representation of the alimentary reaction, and (2) towards the cortical representation of a biologically negative reaction with all effective components characteristic of both these reactions. Which of these will appear depends on the integrated result of many conditions, demanding in each individual case a special characterization.

Such a relationship between the alimentary and negative reactions is a definite phase in the development of conditioned inhibition. It is a direct corroboration of our earlier position that any conditioned inhibition is the result of the inhibitory action of a stronger system of impulses of a biologically negative reaction on an equally integrated activity, the alimentary reaction. This concept was particularly supported by the

experiments of Shidlovskii (1963, 1964). Under similar conditions of extinction, he investigated not only the respiratory component but also blood pressure. For this purpose he developed a method permitting the evaluation of the cardiovascular component of the conditioned reaction (Fig. 14.14).

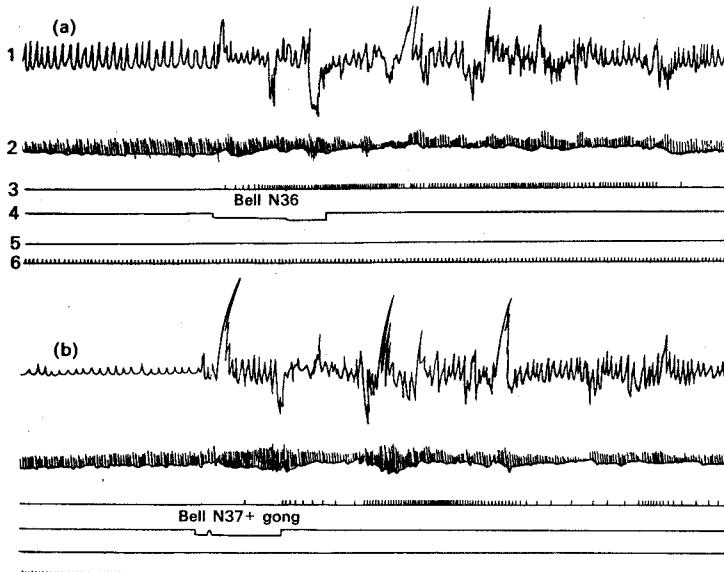


FIG. 14.14. Effect of an extra external stimulus (gong) on the various components of a conditioned alimentary reaction (secretion, respiration, blood pressure). (a) Usual presentation of bell; (b) gong is sounded before bell. 1, respiration; 2, blood pressure; 3, secretion; 4, stimuli; 5, feeding dish; 6, time in seconds.

An analysis of the further development of extinction by comparing the secretory and respiratory components of the conditioned reaction with the general behavior of the animal gave somewhat unexpected results which later became an impetus for new investigations.

According to the generally accepted idea, during extinction of any conditioned stimulus the developing process of internal inhibition from its first signs to full inhibition of the conditioned secretion *will not change in quality, but will show only wavelike quantitative changes*. From this concept it follows that during the increasing inhibition of conditioned secretion, fundamental changes do not occur: zero secretion as an index of the intensity of the inhibitory process at the end of extinction indicates only that the inhibition which began after the very first nonreinforcement of the conditioned stimulus to be extinguished became more intense. The origin of such a point of view is understandable. Since the sole indicator of the developing extinction is the intensity of the secretory effect, which is gradually eliminated, one could not evaluate any qualitative changes during the process of extinction.

Different results were obtained when the dynamics of vegetative components of the

conditioned reaction, such as respiration and cardiovascular activity, were compared with the process of extinction of conditioned secretion.

As we have seen, throughout the entire first period of extinction of the conditioned alimentary reflex, one can observe by means of the respiratory index a competition between two completely specific integrated activities of the animal, the alimentary reaction and the biologically negative reaction ("stressful state"). It might seem that this competition should increase especially when nearing the moment of appearance of the first zero conditioned secretion, i. e., parallel with the increase in the inhibitory action of the negative reaction.

However, the final result of extinction, the zero conditioned secretion, is not an index of maximal conflict between two integrated activities, as might be expected in accordance with the usual concepts concerning the growth of inhibition. Rather, as we will see below, it is a result of this state of conflict but has a different mechanism and a different physiological content. In any case, this zero inhibition lacks the features of conflict discussed above.

As Fig. 14.14 shows, at a definite stage of extinction the vegetative reactions of the animal, previously showing a pronounced excitation of a negative nature, change abruptly to a regular rhythm characteristic of a calm state and of the reaction of the animal to a well-established conditioned alimentary stimulus. Almost simultaneously the secretory component, which up to now had a wavelike fluctuation, quickly subsides and reaches zero.

More than once I have pointed out that the secretory component is the most specific indicator of the *integrated alimentary* reaction as long as there is alimentary excitation.

From a physiological point of view it is impossible to believe that a general alimentary excitation can occur without salivary secretion. Consequently, in the described phase of extinction two completely distinct processes occurred simultaneously: while the alimentary reaction was more or less completely inhibited, the pronounced vegetative components of the biologically negative reaction disappeared. These components usually indicate the dominance of a negative state and an active suppression of the alimentary reaction.

Therefore, it is quite clear that the process of extinction of the conditioned alimentary reflex proceeds from the normal amount of conditioned secretion to zero in two phases, differing from each other in the *quality of the relationship* between two integrated activities of the organism. The first of these phases is quite clear and can be fully analyzed and formulated in common physiological concepts. The second stage, undoubtedly occurring as the *result of a primary conflict between the negative and positive reactions of the organism*, can be interpreted as being the result of the formation of a new action acceptor and the elimination of discordance.

One can positively assert that the sudden appearance of the respiratory component characteristic of the biologically negative reaction is, *even at the end of extinction*, always accompanied by a varying amount of residual conditioned secretion. This phenomenon has been observed many times in our laboratory. It seems that the state of conflict in the central nervous system, due to nonreinforcement with food and to the appearance

of a biologically negative reaction, may occur only when the *stimulus to be extinguished newly establishes an action acceptor of an alimentary nature and discordance is restored.*

Sooner or later in the elaboration of a conditioned inhibition a form of inhibition of the alimentary reaction, and consequently a decrease in secretion, sets in which *develops without intensifying the vegetative components of the reaction, i.e., without initial signs of a "stressful state" in the animal.*

It is of interest that this stage of reduction of the biologically negative reaction coincides with the period which was termed the concentration phase of inhibition in Pavlov's laboratory. As is known, the concentration of inhibition has characteristics such that *application of an inhibitory stimulus, in spite of zero secretory reaction, does not inhibit subsequent conditioned positive reflexes.*

We shall try to understand this phase from the general physiological point of view, but right now it is important to note that the concentration of inhibition is undoubtedly a more perfect form of inhibitory reaction, proceeding without visible signs (of course within the limits of the chosen indices) of conflict and without extensive involvement of the vegetative processes of the organism in the reaction. It would appear that the concentration of inhibition, i.e., zero conditioned secretion without subsequent inhibition, can be evoked by very few components of the former negative reaction with minimal involvement of neural elements.

Thus, we reach a conclusion, at first sight paradoxical, that an absolute concentration of inhibition demands less energy than a partial inhibition occurring in the first phase with clear signs of conflict.

These properties of this stage of conditioned inhibition constituted the reason for calling it *economical inhibition*. This distinguishes it from inhibitory reactions accompanied by a generalized excitation of the entire vegetative system of the animal and by a conflict between two integrated activities of the organism.

Therefore, in the development of extinction there are at least two fundamentally distinct phases. This obviously contradicts our usual concepts of a *simple quantitative growth* of the same process throughout the entire period of elaboration of an internal inhibition.

It is true that long ago, both in the laboratories of Pavlov and in the laboratories of his students, it was observed that two stages can be distinguished in the extinction of the conditioned reflex. In the first stage the conditioned secretory effect decreases very rapidly and stops at a relatively low level which is approximately a third of the initial value of the reflex to be extinguished. Subsequently, the extinction of the conditioned secretory effect proceeds very slowly, and this constitutes the second, or slow, stage of extinction.

Sokolova (1954) undertook special investigations in order to determine the influence of alcohol on the development of extinction. Her experiments showed that alcohol evidently influences the second, slow stage to a greater degree than the first, rapid stage.

Pleshkov (1948), investigating the effect of anesthetics on extinction, found that only the second stage is subject to the effect of narcotics, while the first remains unchanged.

It is important to note that both stages are to various degrees subject to the influence

of alcohol. Consequently, the different nature of the primary and secondary stages of the elaboration of extinction has been shown by various types of experiments. But the investigators did not attempt to elucidate the physiological nature of this difference between the two phases in the development of extinction. They only made a number of comments on this subject.

Observing that anesthetics only slightly affect the first stage, Pleshkov expressed the opinion that the first phase is the result of unconditioned inhibition, and the second phase that of conditioned inhibition. Sokolova reaches an opposite conclusion, stating that "both phases of extinction reflect a single conditioned reflex process."

Pleshkov fails to indicate where and how the unconditioned inhibition in the initial part of extinction of the conditioned reflex originates and what mechanisms then change it into conditioned inhibition. In view of this his explanation remains unconvincing. However, it should be emphasized that the difference in the course of extinction between the initial and final phases of extinction of the conditioned alimentary reflex has been correctly stated. It fully corresponds with our observations of the change in the vegetative component of the conditioned reaction throughout the entire period of extinction.

As we already noted, the second stage proceeds "without conflict," and according to its vegetative indices is a more economical reaction.

An analogy can well be stated in regard to our own behavior. How difficult is the childhood acquisition of some inhibitory conditioned reflexes and habits demanding the participation of the inhibitory process, and how difficult it is for adults to inculcate them! With the passing of time, the same conditioned inhibitory stimuli evoke in us "zero" reactions without any negative emotional tone.

Herein lies the contradiction of some of the concepts concerning the nature of internal inhibition. For example, we justifiably accept that internal inhibition is an active process, costly in energy and "stressful" for the animal. And yet all life's experience, consisting of an accumulation of positive and inhibitory connections, constitutes a "cortical mosaic."

Why, then, is this "mosaic" in its final form not as acutely painful and stressful as it should be on the basis of our concepts on the active nature of internal inhibition? Imagine the continually painful state in which we would be if the "stress" of the inhibitory reflexes elaborated in the course of our entire life were to remain in the form in which it was at the beginning of its elaboration!

What form does active internal inhibition assume when it becomes an established life experience of animals or man? The most intimate physiological mechanisms of this transformation of inhibitory reactions are as yet not exactly known and must therefore be given special attention in physiological laboratories. Nevertheless, individual observations conducted in our laboratories as well as in others give some indications as to the nature of this transformation. Thus, the above-analyzed mechanisms of transition of extinction at some stage into the second phase has something in common with those mechanisms observed during action of the orienting-investigative reaction on the alimentary reflex.

I am referring to the "switching" of conditioned secretory-motor reflexes. As is

known, "switching" under the conditions of our method means that the established conditioned stimulus, usually reinforced with food at one side of the stand, begins at a certain moment to be reinforced with food at the opposite side of the stand. The quality and quantity of the meat-bread crumb mixture remain the same. Only the side of the reinforcement is changed. The secretory, motor, and respiratory components of the conditioned reaction were recorded.

It has been noticed that under these conditions, even without nonreinforcement, the switching also proceeds by definite stages with the participation of the acute orienting-investigative reaction.

At first, as the respiratory component shows, in response to the application of the conditioned stimulus being switched, there occurs an evident rearrangement of the central interactions towards a mobilization of the excitations of the orienting-investigative reaction. At the same time the respiratory movements acquire a special activity with a predominance of the inspiratory tonus (Polezhaev, 1953, 1958).

The whole picture convinces us that switching, i.e., the change of place of the reinforcement of the conditioned stimulus, having the factor of discordance in pure form, stimulates in the animal an energetic orienting-investigative reaction. A highly interesting observation demands attention: as the animal solves the task of "switching," i.e., as adequate relations are established between the conditioned stimulus, running, and feeding, the respiratory component of the conditioned reaction is normalized, indicating a decrease in the strength of the excitations of the orienting-investigative reaction.

Summarizing the description of observations, we can make one supposition which must determine our further search for the physiological mechanisms of all these transitory stages. Seemingly, both the orienting-investigative reaction, as it switches the positive conditioned motor reflex as to place of reinforcement, and the biologically negative reaction, during the elaboration of inhibition according to the classical type, *fundamentally are a consequence of discordance* which determines the initial state of conflict of two integrated activities. Both of them bring the nervous system to a radical change in the behavior of the animal.

Applying the theory of the functional system to the explanation of the elaboration of conditioned inhibition, we can thus identify four stages:

1. The first trials of nonreinforcement of the conditioned stimulus lead to discordance in the action acceptor, which immediately evokes the orienting-investigative reaction.
2. After the first case of discordance there is a gradually increasing state of conflict caused by the still appearing alimentary action acceptor and the existence of a negative reaction resulting from the nonreinforcement.
3. The progressive elimination of the alimentary reaction accompanied by decreasing conflict signifies the formation of a new action acceptor having the parameters of nonreinforcement. This means that discordance, which is the source of conflict, is eliminated. With it, the conflict and the disturbances of the vegetative components disappear as well.

4. In all cases in which a stimulus being extinguished again evokes a positive reaction, discordance, a state of conflict, and a change in the vegetative components inevitably return.

In our opinion, all types of reactions appearing in animals during the elaboration of conditioned inhibition are satisfactorily explained on the basis of the theory of the functional system.

CHAPTER 15

The Problem of the Localization of Internal Inhibition in the Cerebral Cortex

As a materialistic investigator, Pavlov constantly endeavored to maximally define every stage of a physiological process being studied. He strove to determine the tangibility of the processes being studied, their causal relations, and the connection with the material structure of the organism. This is particularly apparent in Pavlov's following words, taken from his speech delivered in 1912 in memory of Sechenov:

. . . the study of the reflex mechanism, which forms the basis of the activity of the central nervous system, is here reduced in its essence to a study of space relations, of the definition of the paths along which the excitation at first spreads, and then concentrates. If this is so, then it is comprehensible that *a sure probability of mastering the subject in all its extent is given only by conceptions which are characterised by notions of space.* . . . You must be able, so to say, to point with the finger where the excitation process was at a given moment, and where it has gone. If you conceive of these relations as they are in reality, then you will understand the truth and power of that science which we are vindicating and developing—the science of the conditioned reflexes [italics—P.A.] (Pavlov, 1912a, see Pavlov, 1967, p. 192).

It would be difficult to express more convincingly and eloquently the *absolute necessity* of relating all our concepts of the dynamics of the cortical nervous processes to the characteristics of cortical structures and to the *spatial* interactions of the individual processes. Herein is the strength of Pavlov's materialistic physiology. The quoted statement of Pavlov is an imperative demand for every physiological investigation. In our concepts we must always maintain a close relation with the neural substrate and avoid purely verbal compositions, which will never be able to ensure us of the "sure probability of mastering the subject in all its extent."

In order to grasp the methodological significance of Pavlov's statement, I will indicate as an example the pathway onto which the study of the second signaling system has now entered. In this field of study the use of mere verbiage has become so great that in essence the entire investigation is no longer of a physiological nature. However, the original purpose of the physiologist in this delicate field of specifically human forms of higher nervous activity was to impart a physiological specificity without removing it from the spatial interrelations of the material substrate.

For example, "verbal reinforcement" or "instruction" form the *basis* in many investigations of the second signaling system. And yet not a single attempt has been made to understand the true *physiological meaning* of instruction and its role in the experimental setup. In the analysis of the *spatial* localization of the inhibitory process in the cerebral cortex, we shall follow Pavlov's demand.

We must "point to" where the initial excitation of the analyzer evoked by the inhibitory stimulus *goes*, and where and why inhibition appears on the basis of this excitation. Proceeding from what has been said in the previous chapters on the mechanisms of the origin of the inhibitory process, we can state our question more specifically: one must "point to" where the "inhibitory" excitation of the negative reaction of the animal *encounters* the excitation "to be inhibited," i.e., the conditioned alimentary excitation.

Naturally the analysis of this entire problem should begin with a presentation of Pavlov's point of view concerning the localization of internal inhibition in the cerebral cortex. His views concerning this problem evolved gradually, but he had never formulated them with his usual clarity.

Analyzing the experiments of Beliakov (1911) on differentiating inhibition, Pavlov wrote: "There arises an interesting question: Where does this inhibition which lies at the basis of the differentiation take place? Naturally one thinks that it develops in the corresponding analyser, i.e., in that place where the stimulations are analysed. But this must be proved" (Pavlov, 1912b, see Pavlov, 1967, p. 175).

After a number of experiments involving the effect of successive inhibition on the conditioned stimuli acting on various analyzers, Pavlov concluded that the inhibitory process is localized in the same analyzer at which the differentiation is aimed.

This was Pavlov's earliest assumption concerning the location of the transformation of the original excitation into inhibition. It is interesting that subsequently he never formulated his point of view concerning this question in such a definite way, admitting, as we shall see below, various possibilities in this regard. At the same time, there were no experiments directed specifically at a study of the localization of conditioned inhibition. Beginning a systematic presentation of the entire material on the physiology of higher nervous activity in his "Lectures on the Activity of the Cerebral Cortex," Pavlov again cites Beliakov's experiments, but this time only in connection with an analysis of successive inhibition, *and he does not deal at all with his initial assumption concerning the localization of conditioned inhibition in the cortical structures.*

Without, however, presenting the question of the localization of conditioned inhibition as a special research problem in his laboratory, Pavlov resorted to an explanation of inhibitory reactions based on a localization of conditioned inhibition *in the analyzers*. This can be readily seen from his explanation of the processes of irradiation and concentration of the inhibitory process in the cortex, from the reciprocal induction of the excitatory and the inhibitory process, etc. Thus, the concept of the localization of conditioned inhibition in the analyzers gradually became the generally accepted point of view, even though no *direct* physiological evidence for such a concept has been presented either then or in recent years.

In order to proceed successfully with the analysis of the localization of internal

inhibition in the cerebral cortex, it is essential to compare the two possibilities of the origin of internal inhibition: on the one hand, the classical hypothesis of its origin within the conditioned reflex arc; on the other hand, its origin as a result of discordance between the established action acceptor and the inadequate reverse afferentation resulting from the nonreinforcement. This is not an easy task, since we have seen that in the systemic approach to the origin of internal inhibition one cannot avoid the question of *what specific integrated activity appears, instead of the conditioned alimentary activity, as a result of discordance*. Only then can one ask *how and where* this new activity inhibited the original conditioned reflex.

Consequently, Pavlov's basic postulate on the localization of internal inhibition in the cerebral cortex is the most probable premise for an analysis of the entire question.

In his last years when dealing with the question of the origin of inhibition in the cerebral cortex, Pavlov attributed the origin to the "cortical cell of the conditioned stimulus," without further specifying it as a cell of the cortical end of the analyzer.

Thus, in evaluating the role of nonreinforcement in the appearance of cortical inhibition, Pavlov wrote: "If a conditioned positive stimulus, *i.e.*, producing a corresponding conditioned reaction, is continued alone for a certain length of time (minutes), without being accompanied any longer by its unconditioned stimulus, then the cortical cell corresponding to this stimulus necessarily passes into a state of inhibition" [italics—P.A.] (Pavlov, 1930a, see Pavlov, 1963, p. 48).

This conjecture subsequently assumed the nature of an axiom. However, no special experiments were conducted in order to provide evidence that the "cell of the conditioned stimulus" refers to the nerve cells of the cortical end of the corresponding analyzer and that the critical transformation of the original excitation into internal inhibition takes place precisely in these cells. On the contrary, data accumulated that did not support this assumption.

On account of this, in the theory of higher nervous activity two contradictory propositions have become firmly established. On the one hand, Pavlov's question remained unanswered: *why does nonreinforcement with food lead to the development of inhibition?* On the other hand, it was assumed and accepted that internal inhibition arises in the cortical cells of the analyzer, even though the "nonreinforcement" comes only when the process of conditioned excitation has gone far beyond the limits of the analyzer.

It is quite evident that an organic relation exists between these two aspects of the problem of internal inhibition. As was evident from the preceding chapters, it is entirely impossible to indicate the exact localization of cortical inhibition without having convincingly answered the question of why it arises on the basis of a preceding excitation. In short, the solution to the problem of the localization of conditioned inhibition was not sufficiently well grounded and, consequently, it was hypothetical.

At the present time, when neurophysiological investigations have made great strides and it has become clear that inhibition is an exclusively local process and does not spread anywhere, all questions concerning the localization of internal inhibition have become especially critical, needing immediate solution.

Recent data have made it clear that internal inhibition cannot be localized in the

focus of the analyzer. The general hypothesis concerning the development of inhibition in connection with the interaction of two activities makes this assumption very unlikely.

However, in the development of the theory of higher nervous activity, the concept that internal inhibition is localized in the cortical projection of the corresponding analyzer was at one time necessary and useful to organize the vast amount of experimental data and it helped to develop the general principles of the interrelation of excitation and inhibition.

If Pavlov's train of thought in connection with certain data obtained in his laboratory is carefully analyzed, the problem of the localization of inhibition may be solved differently.

As is known, Pavlov attributed great importance to the discrepancy between the secretory and motor components of the conditioned reaction and subjected this discrepancy to a detailed analysis in one of his special investigations.

In analyzing the case of the inhibition of the alimentary reaction in the dog, Pavlov wrote in 1932: "What is its mechanism? *From the points of the artificial conditioned stimulations one may think there proceeds a strong inhibition* to the entire subcortical food centre including its two chief components, the secretory and the motor, the inhibition also spreading to the corresponding cortical motor analyser" [italics—P.A.] (Pavlov and Petrova, 1932, see Pavlov, 1963, p. 80).

Thus, according to Pavlov, inhibition begins to develop "from the points of the conditioned stimulations." With this conclusion Pavlov established a quite definite causality in the propagation of the processes from one point to another. This clearly assumes that the inhibitory process spreads over the nerve fibers just as freely as does the excitatory process.

Pavlov did not propose an "inhibitory excitation" as an inevitable prerequisite for the origin of the inhibitory process. Therefore, he had to recognize the ability of the inhibitory process to propagate independently, since it was too difficult to conceive of another possibility. At the same time, Pavlov displayed extreme caution in the question of the "localization" of internal inhibition in regard to both specific structures of the cerebral cortex and individual components of the conditioned reflex pathway.

Pavlov's caution in questions of the exact localization of internal inhibition is understandable. To relate the origin of internal inhibition to a specific neural substrate was difficult if for no other reason than the fact that the very mechanism of the origin of internal inhibition in the cerebral cortex remained unclear. These two problems, the origin of internal inhibition and its localization, can be satisfactorily solved only in a definite sequence: *first the origin, then the localization*.

The assumption that inhibition arises in the cortical end of the analyzer contradicts the data obtained in Pavlov's laboratory and in those of his students. This contradiction becomes especially acute if one applies to the analysis of the localization of internal inhibition the principle of the functional system, by which all the integrated activities of the organism having an adaptive end effect are implemented. Therefore, the further development of the problem of the localization of conditioned inhibition can only proceed by eliminating these contradictions after a detailed analysis of their physiological essence.

In regard to this there arises first of all the difficult question: by what mechanisms can the cortical representation of the center of salivary secretion be inhibited, if it is assumed that the internal inhibition in response to the inhibitory stimulus appeared at the cortical end of the analyzer?

On the basis of data obtained by Pavlov's school it is known that the cortical representation of salivary secretion is located somewhere beyond the analyzer of the conditioned stimulus. Consequently, if a localization of the inhibition in the analyzer is assumed, then *the inhibitory process must inevitably be transmitted over the nervous pathway between the inhibited analyzer and the cortical representation of salivary secretion.* We know, however, of no physiological mechanism by which inhibition as a specific process could propagate from the analyzer to the cortical representation of the unconditioned reflex.

In view of the preceding material we must assume that inhibition always arises as a dynamic result of the propagation of a strong excitation and is a *purely local process* lacking any propagating mechanisms of its own. In all cases of nervous coordination, only the process of excitation propagates, while inhibition, in blocking and suppressing the existing activity of neural elements, always remains at the place of its origin. The basic physiological characteristic of the inhibitory process in the central nervous system is that it exists only as long as the strong excitation that gave rise to it exists.

Thus, there is no plausible physiological explanation of how an inhibition *that arose at the cerebral end of the analyzer* could inhibit the cortical representation of the center of salivary secretion.

We meet equal difficulties if we compare the assumption of a localization of inhibition in the analyzer with Pavlov's concept of "inhibitory reflexes." If we assume that the inhibition in the inhibitory reflex arises in the *afferent part* of the inhibitory reflex, what processes occur in the central and efferent parts of this reflex? If we base our views on the Vvedenskii-Ukhtomskii theory on the properties of excitation and inhibition, we do not see any possibility of answering this question convincingly at this time.

Let us assume that inhibition arises in the analyzer part of the reflex arc. Then it inevitably would *block* the propagation of any excitation, and no inhibitory reflex, being a reflecting activity, could appear. It is known that the inhibitory process suppresses one specific activity while allowing other activities to occur.

Obvious contradictions arise also when the supramarginal inhibition of conditioned reflexes, which appears upon the summation of two different conditioned stimuli, is to be explained on the basis of a localization of the inhibition in the analyzer. It is unlikely that anybody would doubt that the impulses from two summated conditioned stimuli enter *different* cortical cells of sometimes two *different* analyzers. It is therefore natural that inhibition cannot be localized in either one of the two analyzers involved, but must arise somewhere outside of them. Most probably it arises as a result of the interaction of the impulses from the two summated conditioned stimuli at that point where the conditioned reactions to each one of these conditioned stimuli are patterned.

We must emphasize once more that all these contradictions are already impeding our progress in the further development of Pavlov's ideas. The contradictions, however, arise only if one adheres to the assumption that inhibition sets in *immediately after the*

arrival of impulses from a conditioned stimulus in the cerebral cortex, i.e., within the cortical end of the analyzer of the given conditioned stimulus.

All this, quite naturally, impelled us to search for a more satisfactory solution to the problem of the localization of conditioned inhibition in the cerebral cortex. Without solving this problem it was difficult to move ahead. In essence, any attempt to incorporate newly obtained data with the established concepts concerning the localization of conditioned inhibition always led us to unresolvable contradictions.

In 1930 we performed a series of experimental investigations in the hope of answering this important question.

Our investigations were considerably enhanced by the secretory-motor method with bilateral unconditioned reinforcement. This method made it possible to relate some conditioned stimuli to one side of the platform and others to the other side of the platform (Fig. 15.1).

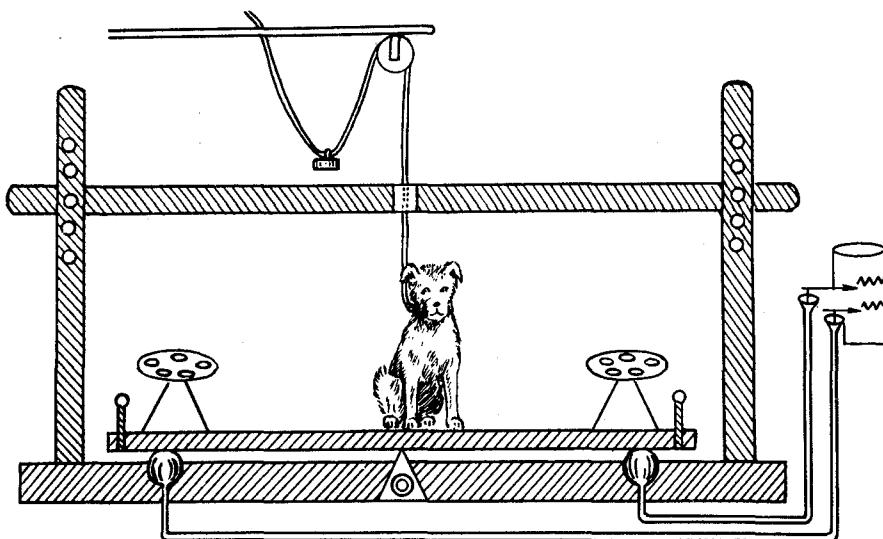


FIG. 15.1. Stand with two feeders for the simultaneous recording of the motor and secretory components of a conditioned reaction.

All conditioned stimuli were reinforced with food, but on different sides of the platform. This means that with respect to the unconditioned alimentary stimulus and the secretory component they were all *positive* conditioned stimuli, while the motor component of the conditioned reaction had to be differentiated depending on the side where the given conditioned stimulus was reinforced.

As a result of several dozen reinforcements with food of different conditioned stimuli on different sides of the platform we usually obtained a clear differentiation of the motor reactions to the right and the left feeder (Anokhin, 1939, 1949c, pp. 87-89).

It is quite evident that with this method, the secretory and motor components of the conditioned reaction were under unequal conditions. The secretory component to any conditioned stimulus had to reflect uniformly only the strength of the uncondi-

tioned stimulus and, consequently, the same degree of alimentary excitation. The motor component, on the other hand, had to reflect all the variable states of the cerebral cortex connected with the elaboration of differentiating the appropriate side of the platform. Thus, we were enabled to reveal certain aspects in the localization of the process of conditioned inhibition.

As early as 1930 we raised the question of more precisely defining the generally accepted concepts concerning the localization of conditioned inhibition. Since these experiments were historically the first, they were, on Pavlov's suggestion, discussed in detail on one of Pavlov's "Wednesdays" in 1932. I feel it is therefore necessary to discuss at this point the basic facts of the matter.

A conditioned reflex was elaborated in the experimental animal to the tone "la," which caused it to quickly jump up and go from the center of the platform to the right feeder. Here the animal would stand with its head bent down toward the feeder throughout the entire period of isolated action of the conditioned stimulus. Along with the motor component of the conditioned reaction, the secretory component was also pronounced, usually constituting 25-40 scale divisions.

After this conditioned reflex had become stabilized, we began to elaborate another conditioned reflex to the tone "fa," reinforced with the same portion of bread crumbs, but now in the *left* feeder. With the introduction of this new tone, the animal was placed in a situation of rather difficult differentiation which did not pertain to the actual reinforcement, since both tones were reinforced by the same amount of bread crumbs. The differentiation involved the separation of processes in the motor analyzer in relation to definite auditory stimuli.

For the convenience of analysis, the entire course of the elaboration of the conditioned secretory-motor reaction to the new tone should be divided into four clearly defined stages as we described them in 1932:

First stage. Presentation of the newly introduced tone "fa" does not give the usual conditioned motor reaction toward the feeder, evoking only a distinct orienting-investigative reaction (first presentations).

Second stage. A motor reaction to the new tone appears, but it is primarily directed toward the side of the old tone "la" (right side). This reaction is a consequence of the marked dominance of the excitatory processes connected with the numerous previous reinforcements from the right.

Third stage. Any motor reaction to the new tone "fa" disappears, even though the conditioned motor reaction to the old tone "la" is normal, i.e., correct, constant, and stable.

Fourth stage. Both tones evoke the conditioned motor reactions appropriate for them: the tone "la" to the right side and the tone "fa" to the left side of the platform, i.e., a stable differentiation of the two separately reinforced complexes of excitation has become established.

Since an analysis of the physiological essence of each one of these stages would divert us from the main problem, I refer the reader to my publication in which this analysis is carried out in more detail (Anokhin, 1932b).

At present we shall give special attention to the third stage, in which the old tone

"la" produces quite ordinary secretory-motor reactions, while upon presentation of the tone "fa" the animal remains sitting. In spite of the inhibition of the motor component of the conditioned reaction, however, its secretory component is fully manifested after the usual latent period of 2-3 sec. A quite distinct dissociation between the motor and secretory components of the conditioned reaction is thus manifested during this stage.

The actual selective suppression of the motor component appears to be a normal activity of the central nervous system of the animal and cannot, of course, be identified with the well-known hypnotic dissociation of the secretory and motor components of a conditioned reaction.

In view of our concepts concerning the action acceptor, this stage may be characterized as the manifestation of an incompletely established adequacy between "established conditioned excitation" and those reverse afferentations which are connected with the reinforcement with food specifically on the left side.

During the elaboration of conditioned reaction by our secretory-motor method, this dissociation appeared in all animals. We naturally, therefore, could not fail to notice it and subject it to a special analysis. We were faced with the question of whether we can understand the phenomenon of dissociation based on the localization of inhibition in the analyzer.

If we assume that inhibition arises at the initial point of propagation of conditioned excitation over the cerebral cortex, i.e., at the cortical end of the analyzer, then there is no physiological explanation for the appearance of *different* effects in the secretory and the motor components of the conditioned reaction in response to one conditioned stimulus (Fig. 15.2). In fact, if inhibition had arisen at the cortical end of the analyzer, then two individual points of the cortex—the representation of the alimentary center and the motor area of the cortex—should, in view of their opposite peripheral effects, have been affected by two opposite processes arising from this initial inhibition: the former by excitation, and the latter by inhibition.

In spite of our careful experimental analysis of the phenomenon of the dissociation of the secretory and the motor components of the conditioned reaction, we were unable

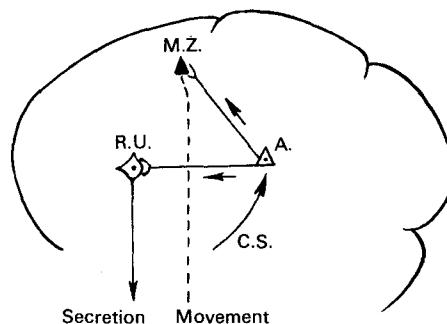


FIG. 15.2. Diagram illustrating the impossibility of assuming a localization of internal inhibition in an analyzer. A., analyzer; C.S., conditioned stimulus; M.Z., motor zone of the cortex; R.U., cortical representation of unconditioned alimentary reflex.

to adequately explain it in regard to the generally accepted assumption of a localization of the inhibitory process in the cortical end of the analyzer.

As it turned out, on the basis of this assumption one cannot understand the appearance of the rather complex architecture of an integrated conditioned reaction consisting of a considerable number of qualitatively different components (positive and negative ones), since this difference can only be established at the moment of the patterning of the reaction.

According to the very essence of reflex reactions, the "encounter" of impulses must occur precisely in the zone of patterning of the response reactions, for this is the only possibility of preventing the development of an activity unnecessary for the given moment, i.e., of blocking the emergence to the periphery of its constituent impulses by some form of inhibition. The unnecessary activity itself, however, must inevitably begin to be patterned. In any case, its individual constituents must already be present. These considerations fully agree with Ukhtomskii's point of view concerning the origin of inhibition at the lower levels of the central nervous system.

Characterizing the interrelation of excitations occurring during the origin of inhibition, Ukhtomskii (1936, see Bykov, 1952b, p. 528) wrote:

Inhibition is not a lack of potentials, not a decrease in efficiency, not an elimination of the possibility of excitation, but a specially organized urgent nervous act aimed at the likewise urgent elimination of a certain feature in a current reaction, a feature which *per se* remains, not only a possible and likely, but an *already initiated excitation* [italics--P.A.].

From the point of view of a localization in the analyzer, the inhibitory process arises immediately at the cortical end of the analyzer, propagates toward the cortical representation of salivary secretion, and here exerts an *inhibitory influence* on it. As a result, the experimenter observes the absence of a secretory effect at the periphery. As we have already seen, such an explanation is unsatisfactory and meets with a number of obstacles of a physiological nature that are difficult to overcome.

The hypothesis of the localization of inhibition in the analyzer contradicts certain well-known data from Pavlov's laboratory as well. In fact, if this hypothesis is accepted, the inhibitory stimulus, as we have seen, is without its specific reflex effect. Its action is perceived at the periphery by the absence of the secretory effect, which was considered to be a specific indication of the biologically positive alimentary reflex. Meanwhile all investigators of conditioned reflexes are well aware that the *first* nonreinforcements of the conditioned stimulus with food lead to a number of effects characteristic of the presence of a "stressful state" in the animal: yelping, whining, growling, turning away, etc. In other words, these would be all the symptoms of a biologically negative reaction which require a complex system of excitations for their peripheral implementation. If there were inhibition in the analyzer receiving the initial stimulus, such a system of fully integrated excitations would have no basis for its appearance.

Consequently, *the inhibition of salivation caused by the inhibitory stimulus develops simultaneously with a biologically negative reflex having all its characteristic peripheral effects.*

The stressful state and the biologically negative reaction of the animal constitute, as we have seen in the preceding chapter, the immediate cause of the intensification of the stronger "inhibitory excitation."

Since the "inhibitory excitation" resulting from an orienting-investigative reaction and a biologically negative reaction appears on the basis of discordance in the action acceptor, the encounter between the negative excitation and the initial alimentary excitation (and, consequently, the origin of the inhibitory process) can occur in those neural structures in which the patterning of the different stages of the conditioned alimentary reaction as a whole takes place. This encounter undoubtedly takes place beyond the cortical area corresponding to the given stimulus, since neither structural nor functional possibilities exist for an encounter of these excitations in the cortical area of the analyzer.

In our first attempt to explain the origin of internal inhibition, we have assumed that it originates "at subsequent stages" of the propagation of "conditioned excitation," without specifying, however, where these stages might be localized (Anokhin, 1932b, 1933a, 1949c). The most probable localization is the *region of the patterning* of the conditioned reaction with all its components as it is represented in the general physiological architecture of the conditioned reflex (see Fig. 6.18c).

This figure, which depicts the moment of discordance in the action acceptor, shows that this noncorrespondence is the initial moment of all the reactions of the organism that appear in response to the nonreinforcement of a well-established conditioned reflex. First there appears an orienting-investigative reaction which always accompanies any deviation from the usual course of events. Its biological purpose lies in the activation of both the analyzer systems and the cerebral cortex, due to which there appears the possibility for a comprehensive and instantaneous increase and greater selection of afferent impulses.

This is a true active selection of afferent impulses by means of which a new afferent synthesis develops, resulting in a reorganization of the complex of efferent impulses which had proved to be inadequate. We already know that any discordance in the case of biologically positive reinforcement transforms this reaction (by way of an intermediate orienting-investigative reaction) into a biologically negative reaction.

As we know, all these processes actually occur—they occupy a certain place in the general physiological architecture of the behavioral act. Consequently, the problem now lies in perceiving all the data of the Pavlovian school on internal inhibition on the basis of the neurophysiological data on the behavioral act.

Naturally, the actual facts and types of internal inhibition established by Pavlov's laboratory constitute a quite definite and significant scientific achievement, but they need a physiological interpretation.

In the next chapter a more substantial attempt will be made to more adequately express these considerations on the basis of the general physiological architecture of the conditioned reflex. Here we shall analyze in detail the interrelations which are established upon the appearance of *different types* of internal inhibition. For this purpose we are introducing a scheme which, even though it does not fully reflect the whole diversity of the phenomena involved in the origin of internal inhibition, can nevertheless

serve as a general model of the interaction of two integrated activities in the case of any type of inhibition of one of them.

Any attempt to formulate a physiological scheme for a more profound study of the problem is useful and justifiable. In analyzing the problem of the mechanisms of unconditioned activity, Pavlov wrote: "Surely these phenomena are much more complicated than we have described them here. But thanks to our new scheme, we are enabled to go forward in the exploration of our subject. This then is the meaning and justification of our plan" (Pavlov, 1904, see Pavlov, 1967, p. 73).

I regard any kind of utilization of the synaptic formations in the explanation of the data of the Pavlovian school without first solving the problems of the physiological scheme pertaining to these findings as being of little use.

Only when we have indicated the exact location of the process under study in our physiological scheme can we, with a knowledge of the detailed neurophysiological mechanisms of this scheme, attempt to transpose the problem to the level of the synaptic interrelations. Without adhering to this rule, all operations at the synaptic level are unsubstantiated assumptions, of which very many can be made. Our hypothesis of convergent coupling shows the most acceptable way of utilizing the data on the synapse when explaining the key mechanisms of the functional system (see Chapter 5). I consider it to be premature to discuss these aspects of the problem without having answered the basic questions concerning the *interrelation of excitation and inhibition* as proposed by Pavlov and other Russian physiologists.

In view of these considerations, it is first of all necessary to represent schematically the characteristic features in the interrelation of two systems of impulses whose

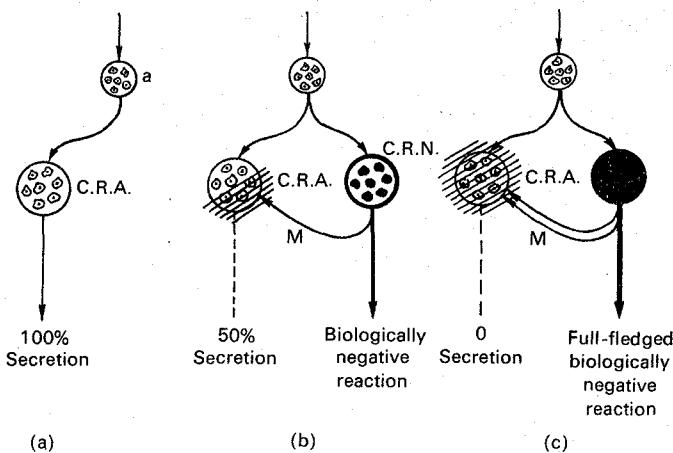


FIG. 15.3. Illustration of gradual extinction of secretory effect based on the concept of an encounter between two systems of excitation. (a) Normal conditioned alimentary reflex; (b) stage of partial inhibition of stimulus being extinguished as a result of the appearance of a biologically negative reaction; (c) stage of complete inhibition of alimentary reaction and disappearance of secretion. C.R.N., cortical representation of negative reaction; C.R.A., cortical representation of alimentary reaction; a, analyzer; M, pathway for collateral inhibition.

encounter results in conditioned inhibition. These diagrams will show in a general form the *spatial interrelations and the localization* of conditioned inhibition in all its known modifications.

First we shall analyze a scheme of the three basic stages in the development of extinction with an evaluation of the vegetative components of the conditioned reaction (Fig. 15.3).

These diagrams illustrate the three most important stages in the development of extinction. Diagram (a) demonstrates the generally accepted concept of the propagation of conditioned excitation during the action of a positive conditioned alimentary stimulus (a bell) in a well-established conditioned reflex. The impulses enter the cortical end of the corresponding analyzer and then proceed over the cortex to the cortical representation of salivary secretion (or the representation of the alimentary reaction as a whole). The normal effect of this conditioned stimulus is conditioned secretion, given a value of 100 per cent.

Diagram (b) illustrates that interrelation of the processes in the cerebral cortex which sets in *after several nonreinforcements* of the conditioned stimulus with food. This diagram shows that stimulation by the same bell and of the same analyzer (a) now leads to a dual propagation of the impulses. On the one hand, a certain fraction of the impulses from the analyzer still proceeds over the old pathway and forms an action acceptor with the afferent parameters of the alimentary reinforcement, which is apparent from the 50 per cent conditioned salivary secretion. On the other hand, due to the same indefinite afferent synthesis, the conditioned stimulus forms an action acceptor which to the same degree reflects the new meaning of the conditioned stimulus, i.e., non-reinforcement. This duality of the central apparatuses of the impulses evokes in the nervous system of the animal a state of conflict manifested by a number of behavioral acts.

However, with systematic extinction as a result of statistical conditions of reinforcement, a quite specific and *single* action acceptor having all the parameters of non-reinforcement is ultimately formed.

As we have already stated, the principal physiological result of extinction is specifically the establishment of a "conflict-free action acceptor," which corresponds to what we previously called "economical inhibition," i.e., "conflict-free inhibition."

How is the inhibition of this activity stabilized, and is this inhibition always active? Most probably this depends, in each specific case, on how the afferent synthesis proceeds and on what kind of action acceptor it forms. Apparently the type of reaction occurring during extinction depends on the extent of discordance in each particular case.

Principal attention should be given to the connecting neuron M. In my opinion, it must be the conductor of "inhibitory excitation" from the system of the negative reaction to the cortical representation of the alimentary reaction. Such a possibility of "secondary inhibition" (Ukhtomskii) is at present physiologically well substantiated. It may occur as a result of various forms of inhibitory interactions, such as the classical Sechenov action of a higher level on a lower one. For integrated reactions, which must inevitably pass through the stage of decision making, this inhibition of an extraneous reaction most probably occurs during decision making, i.e., the selection of the stronger activity,

one of many degrees of freedom. The mechanism of inhibition itself is most probably implemented through various structural connections and especially by means of axonal collaterals.

Indeed, axonal collaterals occur mainly in the efferent neurons that pattern the complexes of effector impulses. It is natural to assume that as soon as the process of patterning a dominant activity has reached the point of decision making and the implementation of a program of action, "secondary" impulses arise through the enormous number of axonal collaterals. It is highly probable that any other reaction is inhibited by means of these collaterals.

Parallel with the intensification of the negative action of the conditioned stimulus being inhibited, there is an increasing inhibitory effect on the residual excitation in the cortical elements pertaining to the conditioned alimentary reaction.

In summarizing all the considerations presented above, one may state as a preliminary conclusion that the "encounter" of impulses patterning different nervous activities can occur on those cortical and subcortical structures which together determine the integration of the conditioned reaction.

If the structure of every system of impulses is based on the "pacemaker" principle, then each activity must in the final analysis be excluded by a mechanism which eliminates *energy* integration in it. What activity is to be eliminated, as well as how and when, is apparently decided by the cerebral cortex, while the actual mechanism of inhibition is most probably effected by means of subcortical interrelations. It may be assumed that mechanisms of the most diverse nature may participate: it may be pessimal as well as presynaptic and electrotonic inhibition, i.e., both depolarizational and hyperpolarizational inhibition.

The principle of the antagonistic interaction of activities of different functional meaning (positive or negative) constitutes the reflex theory. Pavlov formulated this interaction as follows: "... if together with a certain reflex another is produced, the former suffers in strength or is completely destroyed" (Pavlov, 1912a, see Pavlov, 1967, p. 185).

The general principle of the interaction of the two integrated activities shown on the diagram presented above, as applied to extinctive inhibition, fully applies both to other kinds of conditioned inhibition and to unconditioned inhibition, taking into account the difference pertaining to the "conditions of origin" of unconditioned and conditioned inhibition.

These interrelations follow a universal law which could be stated as follows:

1. The organism always operates through integrated activities, for only they determine an adaptive process.
2. The need for inhibition arises precisely because any activity can be well coordinated in all its mechanisms only when it develops without hindrance independently of other activities, i.e., when it leads to a maximum beneficial end effect.
3. An activity can become inhibitory only after the "decision to act." During the stage of afferent synthesis an activity can become inhibitory only by means of the orienting-investigative reaction, which itself is an already established activity.
4. An activity can be inhibitory only if it is dominant, i.e., if it has a higher degree

of excitability than the activity being inhibited. This is evidently determined by the motivational component of the afferent synthesis.

Returning to the diagram of the development and localization of extinction, we must note that the process of extinction is depicted in this diagram up to the appearance of the "first zero" of the secretory effect, which corresponds to the cessation of impulses emerging onto the terminal pathways of the *secretory* apparatuses. At this time, however, those mechanisms of the functional system which pertain to the motor, respiratory, or any other component may still be excited to a certain extent.

In this case there is a *dissociation* between the individual components of the conditioned reaction, similar to the one already discussed using the example of secretory-motor conditioned reflexes. Here we encounter the question of the *function of the conditioned reaction* as an adaptive act of the integrated organism. The next chapter will primarily involve a detailed description of this function.

To further illustrate the mechanisms of the development and localization of cortical inhibition, we will now analyze another diagram of differentiation and conditioned inhibition (Fig. 15.4).

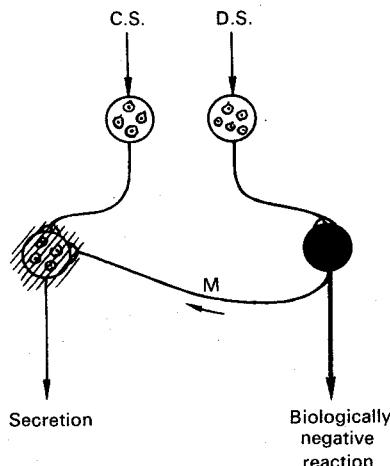


FIG. 15.4. Diagram of elaboration of differentiating inhibition. C.S., conditioned positive stimulus; D.S., differentiating stimulus; M, axon, over which the stronger excitation of the biologically negative reaction exerts an inhibiting influence on the excitations of the alimentary reaction.

It is evident from this diagram that the terminal mechanisms of the origin of differentiation are the same as those of extinction. The initial background for the origin of differentiation is likewise a well-established positive conditioned reflex. The immediate cause of the development of the inhibitory process is also a biologically negative reaction developing as a result of *nonreinforcement with food*. Consequently, the localization of differentiation, which develops as a result of the encounter of the same two systems of impulses, remains the same also.

Along with these similar aspects, differentiation also shows a substantial difference

from extinction, which defines its individual characteristics pertaining to the "conditions of origin."

The difference is this: in extinction the point of origin of both the negative and the positive reflex is *the same cell of the cortical area of the analyzer*, while in differentiation the points of origin of these two reflexes are different cortical cells of the same or different analyzers, or a different number of cells of one specific nature becomes involved (weak tone, strong tone); this circumstance is a characteristic feature of differentiation.

One of these features is the consistently observed initial generalization of the positive effect in response to the first presentations of the "indifferent" unreinforced stimulus. As is known, the first presentations of the indifferent stimulus chosen for the differentiation usually evoke a positive secretory effect.

What is the mechanism of this initial generalization? As was shown by numerous experiments in Pavlov's laboratory, this generalization is based on the process of the spread of excitation evoked by the new stimulus over the given analyzer, ultimately leading to the emergence of impulses onto the nervous pathways of the positive conditioned reflex. Thus, in the case of this initial generalization (Fig. 15.5), the impulses proceed from the cell (b) of the indifferent stimulus toward the cell (a) of the conditioned stimulus and toward the cortical representation of the unconditioned reflex (C.R.U.) (Fig. 15.5 II). This, however, is evidently not the only mechanism of the excitation of the cortical representation of salivary secretion by the indifferent stimulus. An animal that had been accustomed to alimentary reinforcement in the setting of a given chamber for a long time is in a state of *alimentary dominant excitation* from the very moment of its entry into the chamber.

In view of the presence of this dominant, any new stimulus that is more or less close to the conditioned stimuli used may evoke salivary secretion upon first presentation. In this case the excitation propagates from the cortical analyzer cell of the indifferent stimulus directly to the cortical representation of the alimentary center dominant at the given moment, where it increases its excitability up to the level of the effector action according to the principle of the "reinforcement of the dominant" (Ukhtomskii).

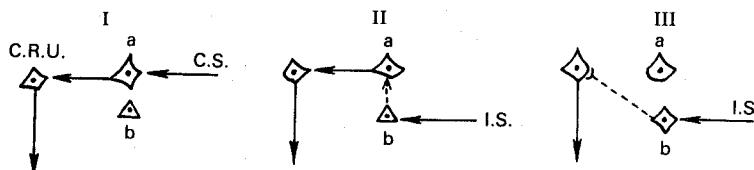


FIG. 15.5. Possible mechanisms of initial cortical generalization of excitation upon first presentation of an indifferent or differentiating stimulus. I, spread of conditioned excitation from conditioned stimulus; II, generalization of excitation from indifferent stimulation over analyzer; III, generalization of indifferent stimulation from its own analyzer directly to the cortical representation of the alimentary unconditioned reflex which is dominant at the given moment. C.R.U., cortical representation of unconditioned reflex; a, analyzer cell of positive conditioned stimulus (C.S.); b, analyzer cell of indifferent stimulus (I.S.).

In part III of Fig. 15.5 this pathway from the analyzer cell of the indifferent stimulus to the representation of the alimentary center is indicated by a broken line. It is most likely that during the first presentation of the stimulus being differentiated both of these mechanisms promote the generalization of the excitation, thus bringing about the secretory effect.

In explaining the mechanism of internal inhibition, we must utilize recent advances in the investigation of the physiology of the reticular formation. In recent years the problem of the conditioned reflex has in fact become the object of intensive study in three independent areas: (a) in the physiology of higher nervous activity, (b) in neurophysiology, and (c) in electroencephalographic investigations. In view of the historical conditions, however, each one of these areas proceeds somewhat independently.

Since the rapid synthesis of these three areas in neurophysiology is effected by physiologists of different specialization, the contradictions resulting from the confusion of terms, concept, and methods become almost unavoidable.

Perhaps demonstrating this proposition most clearly are the contradictions in the points of view elaborated at different times by neurophysiologists and electrophysiologists concerning the process of internal or conditioned inhibition. The contradictions in this problem arose in connection with the development of electroencephalographic investigations and have now become particularly widespread and threaten to multiply, since no efforts are made to overcome them.

By way of example let us take several propositions from Gastaut's recent studies of the electroencephalographic manifestation of internal inhibition (Gastaut *et al.*, 1957b). As is shown by his data, the elaboration of conditioned inhibition is accompanied by the appearance of slow high-amplitude waves of the type known as alpha-waves. Yoshii's studies of natural conditioned reflexes in dogs have also shown that the extinction of the conditioned alimentary reflex leads to the appearance of slow rhythms (Yoshii *et al.*, 1960b). Thus, it gradually came to be thought that the slow high-amplitude rhythm ("archlike rhythm") of electrical activity in the cortical representation of the unconditioned reflex indicates the presence of internal inhibition. But in addition to this, it was also shown in Gastaut's laboratory that similar slow waves in the cerebral cortex appeared at the time the animal was eating.

In one of his publications (Gastaut *et al.*, 1957a, see Gastaut, 1958, p. 271) Gastaut writes :

It is evident that the slow rhythms which appear in the unconditioned region are linked directly to the process of conditioned inhibition. A cat which learns to stop jumping up onto a stool to seek food *when it is sated* or when the conditioned stimulus has been made negative, shows at the same time a rhythm, "en arceau" of high amplitude, in the somatomotor region. In the same way, a rhythm of *similar form and topography* develops in a man when inhibiting a motor conditioned reflex . . . [italics—P.A.]

This excerpt gives the most vivid expression to all the contradictions in the modern electroencephalographic interpretation of the process of internal inhibition.

To begin with, we must eliminate a certain inaccuracy with respect to the interpretation of the "cortical representation of the unconditioned reflex" as generally accepted in Pavlov's laboratory. In Gastaut's experiments the somatomotor area of the cortex cannot be a representation for the cat in which conditioned motor alimentary reflexes are elaborated, since the motor reaction is elaborated as the conditioned reaction in these experiments. Thus, the presence of "archlike rhythms" in the somatomotor area considerably alters the meaning of Gastaut's hypothesis about the localization of internal inhibition.

But even this is not the main point; rather, it is that there are a number of paradoxical propositions in the *fundamental content* of this hypothesis.

What inferences can we draw from Gastaut's aforesaid statements? Slow waves in the cerebral cortex are evoked by taking the signaled food away from the animal by force, but *identical* slow waves appear when the animal is sated. Consequently, on the basis of this electroencephalographic evidence we should say that the two antipodal physiological states of an animal, *nonsatiety and satiety*, are equal. This, of course, is physiological nonsense.

If we take the latter part of Gastaut's conclusion, we shall find another contradiction.

To be sure, according to the electroencephalographic record, the process of internal inhibition in either the motor area of the cat's cortex or in the motor area of man's cerebral cortex is manifested in rhythms identical in "form and topography."

Internal inhibition in man is a result of highly complex differentiations and states of conflict between individual activities and motives almost always of a social nature. And neurophysiologically I cannot conceive of any identity of these complex processes with the processes in the cat's cortex even in their electrophysiological manifestation.

It is clear that for the special study of internal inhibition the value of the slow high-amplitude waves is quite insignificant.

Now, if we approach the problem with regard to the physiology of the reticular formation, the contradictions will become even more evident. From electroencephalographic data we know that any change of electrical cortical activity from rapid to slow waves, including delta-waves, *signifies the transition from an active state to rest, i.e., to the elimination of the activating influence of the reticular formation on the cortical neural elements.*

On the other hand, an intensification of the activating influence of the reticular formation on the cerebral cortex increases the frequency of its waves and brings it into a state of desynchronization, i.e., to the elimination of the slow waves.

Upon comparing these two approaches we arrive at the new paradoxical conclusion that internal cortical inhibition can be expressed by the electroencephalographic manifestation of rest.

Examining the problem from still another approach—the data on conditioned reflexes obtained in Pavlov's laboratory—will reveal the prevalence of other ideas. According to Pavlov, internal inhibition is an active process which, with regards to energy expenditure, costs the organism much more than does excitation. The Vvedenskii-Ukhtomskii school takes the same position. For example, Ukhtomskii believes that inhibition is a "very costly process" (Ukhtomskii, 1927, see Bykov, 1952c). Thus, in this point, too, we have the same perfectly obvious contradictions regarding the

basic concepts of inhibition. The above comparisons clearly show that the electroencephalographic approach to the problem of internal inhibition did not bring us any closer to the knowledge of the true nature of internal inhibition. On the contrary, the difficult and "accursed question"—the relationship between excitation and inhibition—has become more difficult and contradictory.

The experiments of Jasper (1958) show directly that the electroencephalographic index is incompatible with the delicate interactions occurring at the interneuronal level. He has demonstrated, as stated before, that in the same zone some neural elements may be in a state of inhibition. It follows very clearly that the electroencephalographic index cannot be used as a direct indicator of the presence of internal inhibition in the cerebral cortex.

The idea that slow waves are signs of internal inhibition had to lead Gastaut *et al.* (1957b), Yoshii *et al.* (1960b), and Fessard (1960) to conclude that *internal inhibition, similar to coupling, originates in the neural elements of the reticular formation* and that the accompanying slow waves in the cerebral cortex are only a passive result of depriving the cortical elements of the activating influences from the reticular formation.

In our opinion, only one proposition approaches the truth in this concept: the subcortical apparatuses can also be the site of inhibition of an integrated activity. However, we cannot accept the arguments supporting this concept.

Indeed, from the functional point of view, the organization of inhibitory excitation is the active and most important process: it is the essence of the coordinative activity of the brain. As a *process*, however, inhibition is the passive result of an incoming inhibitory excitation. Inhibitory excitation, especially in a behavioral act, almost always originates in the cerebral cortex. The process of integration of a new activity, i.e., of inhibitory excitation, is the main feature in the origin of internal inhibition.

Thus, Gastaut's concept of the primary origin of internal inhibition in the reticular formation lacks a convincing physiological basis. If we assume that internal inhibition results from discordance in the action acceptor, the latter being an exclusive property of the cerebral cortex, then the hypothesis of the subcortical origin of this inhibition will become even more inconsistent (Anokhin, 1949c, 1958a).

The contradictions arising with the acceptance of the thesis about the inhibitory nature of the slow waves cannot be resolved by attempting to characterize the behavior of the *individual cellular elements of the cerebral cortex at the moment the electroencephalograph is recording the slow waves*.

The microelectrode technique has shown that slow waves are in no way equivalent to a complete absence of activity in the nerve cells. Even during highly synchronized waves, i.e., slow waves, each cortical cell continuously discharges corresponding to its individual functional capacities and the nature of its metabolic changes. Essentially, only under these conditions can there be any slow waves in the electrical activity of the cortex.

At the same time we know that inhibition in a cell means a complete cessation of discharges. Apparently, "electroencephalographic inhibition" is a particular form of activity of the nerve cells which, according to its neurophysiological characteristics, does not coincide with our usual ideas of neurophysiological inhibition.

Undoubtedly useful are the electroencephalographic observations at the moment conditioned inhibition is elaborated and under the most diverse conditions of an experiment using conditioned reflexes. They extend our possibilities for evaluating the electroencephalographic data, show the limit of the analysis with inkwriting instruments, and indicate the prospects for their further improvement. But despite this, with electroencephalography in its present condition, it is difficult to hope that inkwriting, which reflects relatively coarse summated electric fluctuation, may help us to analyze the intimate aspects in the origin of internal inhibition.

In this sense I regard as particularly interesting the experiments conducted by my associate Shumilina (1949, pp. 174–185, 1959, 1961), who elaborated conditioned alimentary defense reflexes in the rabbit with a simultaneous recording of the electric potentials from the cortex, medial thalamus, lateral thalamus, and the reticular formation. She has shown that inhibition of the conditioned reflex during extinction and differentiation is actually accompanied by certain changes in the relationship between the cortical and reticular electrical activity. However, from our point of view these changes are of a different nature and require another explanation.

We have yet to discuss what part is played in these processes by the orienting-investigative reaction which, as a rule, appears during the first presentation of a *new* stimulus. The role of the orienting-investigative reaction in these cases is not always the same—it changes in relation to the previous experience of the animal in the particular experimental setting. If the experiments were performed on a given animal only with positive conditioned stimuli, and there had been no nonreinforcement with food, the orienting-investigative reaction to the new stimulus usually intensifies the generalization in the analyzer and the alimentary dominant, and then the secretory effect sets in “on the spot.” If the animal had already been subjected to nonreinforcement, i.e., had there been several differentiations, and had the animal had extinctions of individual positive reflexes, etc., then in such an animal the conditions are present for a facilitated generalization of excitation also toward a negative reaction previously elaborated by experiments with nonreinforcement. In such animals any new stimulus may activate both a positive and a negative reaction *through the orienting-investigative reaction*. Therefore, the final secretory effect under these conditions will reflect some resultant of both indicated reactions. In any case, the secretory effect is in most cases less than in animals in which the experiment was performed only with positive conditioned reflexes.

The influence of the experience of nonreinforcement can be especially striking in cases of frequent trials involving the extinction of conditioned reflexes. In such animals it is sometimes only necessary to carry out just one nonreinforcement of the conditioned stimulus for its second trial to produce a zero secretory effect. Meanwhile it is well known how difficult the first extinction of a well-stabilized positive conditioned reflex is (Anokhin, 1933a).

In the evaluation of the results of the first trial of an indifferent conditioned stimulus, the subtle differentiation is also important. An indifferent stimulus that is qualitatively very close to the positive stimulus will, *with all other conditions equal*, have more favorable conditions for exciting the cortical representation of salivary secretion through the

generalization of excitation in the analyzer than is possible in the case of gross differentiation.

Here, as in all complex processes of the organism, there is a complex of interacting factors. Therefore, a correct evaluation of the end results can be achieved only by strictly considering these factors individually. Unfortunately, this circumstance is sometimes not realized in conditioned reflex experiments. Consequently, substantial errors often appear in the final interpretation of the material.

Everything stated above pertains to the *first presentation* of the indifferent stimulus and to the reaction of the experimental animal to this first trial.

The situation changes radically as soon as the first positive alimentary reaction of the animal to the stimulus to be differentiated is not reinforced with food.

According to our concepts of established conditioned excitation, the process of generalization of the conditioned effect in the first trial of the indifferent stimulus is accompanied by the patterning of an action acceptor, just as in response to the presentation of the usual conditioned stimulus. Therefore, the nonreinforcement of the indifferent stimulus with food also leads to discordance between the reverse afferentation and the action acceptor, as in the first nonreinforcement in the extinction of conditioned excitation. But this means that even the first presentation of the indifferent stimulus during the elaboration of differentiation leads to a certain degree to the patterning of a biologically negative reaction. In fact, the appearance of a secretory reaction in connection with the generalization of excitation may be regarded as an indicator of the presence of alimentary excitation in the animal and, consequently, of the presence of an action acceptor. But the latter circumstance must inevitably end in discordance since the differentiating stimulus is not reinforced. From this moment on the indifferent stimulus gradually begins to assume a specific signal meaning of the *nonreinforcement with food*, a signal of the "stressful conflict state" which evokes a biologically negative reaction of the animal.

As is evident from a description of the sum total of the cortical processes arising in an animal in response to the first presentations of a differentiating stimulus, there inevitably occurs an *encounter* of two systems of impulses. This encounter involves exactly the same mechanism as does extinctive inhibition. In this respect the diagrams presented in Figs. 15.3b and 15.4 almost completely coincide. The only difference is that during differentiation a process of initial generalization and a process of subsequent differentiation of excitations occur at the cortical end of the analyzer. Regardless of this difference, however, the final *mechanisms* of the origin and localization of the inhibitory process during differentiation are the same as during extinction.

A closer examination of other kinds of internal inhibition shows that, *while differing in the conditions of origin*, they develop in the final analysis exactly according to the above-described mechanism.

Let us take as an example the elaboration of a conditioned inhibition. In this case, an indifferent stimulus precedes by 5–10 sec a well-stabilized positive stimulus, and they then act together for 20–30 sec, depending on the general experimental conditions. This combination of stimuli is not reinforced with food. On the other hand, the positive stimulus, *when presented separately*, is reinforced with food as before. After a number of

trials of the unreinforced combination of stimuli, it ceases to evoke a secretory reaction, while the separately presented positive stimulus gives a positive conditioned effect as before.

Since in this case of cortical inhibition the central feature is also the nonreinforcement with food, all mechanisms of its origin and localization in the cerebral cortex develop in the same way as in extinction and differentiation (Fig. 15.6).

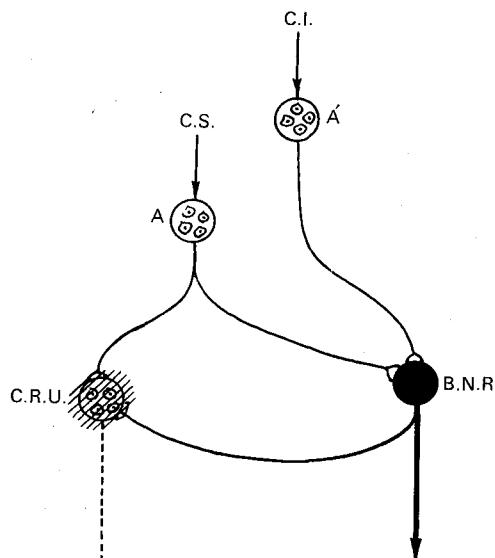


FIG. 15.6. Diagram of formation of conditioned inhibitor. C.S., conditioned positive stimulus; C.I., conditioned inhibitor; C.R.U., cortical representation of unconditioned reflex; B.N.R., biologically negative reaction. The excitation from the indifferent stimulus through the analyzer A' creates a biologically negative dominant before the action of the positive stimulus.

In summarizing the analysis of the whole problem of the localization of cortical inhibition, we may point out that the scheme for the origin and localization of different kinds of conditioned inhibition proposed above is entirely suitable for the explanation of many difficult problems concerning the interrelation of excitation and inhibition. At the same time, this scheme considerably eliminates all those contradictions which appear upon the assumption of a localization of internal inhibition at the cortical area of the analyzer and which, undoubtedly, hinder the final solution of the problem of cortical inhibition.

The first experimental results of our laboratory demonstrating the inadequacy of the concept of the localization of conditioned inhibition in the analyzer were published in 1932 (Anokhin, 1932b).

In 1933, I lectured on the same topic to the Leningrad Society of Physiologists (Anokhin, 1933a). Subsequent to these communications the history of the problem of the localization of conditioned inhibition entered into a new phase, since the propo-

nents and opponents of our point of view had to obtain further, more convincing experimental data.

I shall overlook those objections of some of our opponents which were of a clearly irrelevant nature. They did not provide any resolution of the contradictions existing in this field and did not advance the question at all.

Only in recent years did a number of experimental investigations indisputably contribute to the solution of this crucial problem. For example, in a series of observations on man involving the use of hypnotic suggestion, Korotkin and Suslova (1955) discovered a number of phenomena which do not fit into the generally accepted concept concerning the localization of conditioned inhibition. In these experiments two complex conditioned blinking reflexes were elaborated in a female subject by reinforcement with a stream of air directed at the cornea. The conditioned stimuli were: light + M_{120} , and buzzer + M_{120} . After a certain period of training, both complex conditioned stimuli gave a stable and invariable conditioned reflex—blinking. It was then hypnotically suggested to the subject that after the buzzer + M_{120} there would be no stimulation with air, while after light + M_{120} the stimulation with air would continue.

After this hypnotic suggestion, the reactions of the subject changed considerably: the conditioned reactions to both complex stimuli were maintained, *while no reaction followed the application of the actual stream of air*. This result has shown that the hypnotic suggestion inhibited the unconditioned reflex completely and did not influence the conditioned reflex.

In this interesting experiment one should especially note that buzzer + M_{120} is a signal for the hypnotically suggested “absence of the unconditioned stimulus.”

After the first hypnotic suggestion changes the reaction of the subject to the complex buzzer + M_{120} , the investigators hypnotically suggest that “there will be neither a buzzer nor a light.” By means of this second suggestion they eliminate the conditioned reflex significance of the *first components* of both complexes but leave intact the conditioned reflex significance of M_{120} , which is common to both complexes. The conditioned reflex significance of the stimulus M_{120} after the second suggestion is confirmed by the fact that during the time of isolated action of the buzzer and the light there is no blinking reaction, while during the action of M_{120} the blinking reaction remains unchanged.

An interesting result of this second suggestion is the fact that the light as a conditioned stimulus has now acquired an *inhibitory* significance, whereas in combination with M_{120} it is, as before, a *positive* signal for the unconditioned stimulus. In response to the complex buzzer + M_{120} , just as after the first suggestion, the unconditioned reaction to a stream of air is altogether absent, while in response to the complex light + M_{120} this reaction occurs as before.

Thus, an already familiar relation is established: the *same* conditioned agent, light, is *at the same time* an inhibitory signal for the blinking effect proper and a positive agent in a complex with M_{120} for the appearance of the unconditioned stimulus. If one proceeds from the indubitable premise that the same external agent—light—always stimulates the same cortical cells, there arises a clear contradiction to the concept of the localization of conditioned inhibition in the cortical area of the analyzer.

In fact, if light would evoke the inhibitory process already at the stage of its action

in the cortical area of the analyzer, its action on the unconditioned reflex would be impossible. Thus, we see that as a result of the experiments described above the authors had to come to the conclusion which we had formulated in 1932 on the basis of the experiments analyzed above. It is therefore quite natural that Korotkin and Suslova (1955) formulate their conclusions in the form of the following question: "... does the inhibition of the conditioned reflex to the stimulus 'eliminated' by hypnotic suggestion originate, not in the primary cortical elements receiving the impulses from the conditioned stimulation, but in the subsequent cortical components of the complex reflex arc?"

Similar results have emerged more clearly from the investigations of Khodorov, who, in special experiments, reproduced those interrelations in the cerebral cortex which we had ascertained on the example of secretory-motor reflexes. Khodorov's experiments were designed according to the same plan: in accord with the intention of the experimenter, the same conditioned stimulus was to have at the same time both an inhibitory and a positive meaning, which for us was the principal evidence against the concept of the localization of conditioned inhibition in the cortical area of the analyzer.

He elaborated the following positive and inhibitory conditioned reflexes: a continuous ringing was a conditioned defense stimulus for a front and a hind paw simultaneously, while an interrupted ringing (differentiation) was reinforced only at the front paw. As a result of these combinations of stimuli, a stable differentiation was established so that the "positive" bell produced a simultaneous lifting of *both* paws, while the "inhibitory" bell resulted in inhibition at the hind paw and in lifting of the front paw.

Thus, just as in previous cases, the same conditioned stimulus produces a dual effect: excitation of the front paw on the one hand and inhibition of the hind paw on the other. It follows that *the interrupted ringing cannot evoke conditioned inhibition in the cortical cells of the auditory analyzer*.

Khodorov (1955) correctly concludes: "One is compelled to admit that the internal inhibition evoked by nonreinforcement of the conditioned reflex initially originates somewhere *beyond the cortical area of the conditioned stimulus*. The cortical cells of the inhibitory stimulus are clearly in an excited state at this time."

In addition to the recently published findings we have presented, many more examples can be given which also correspond to the same experimental pattern. For example, in the experiments of Rokotova (1956), it was repeatedly found that a stimulus to which conditioned inhibition is elaborated may lead at the same time to the inhibition of one reaction and the excitation of another form of reaction. In the work of Skipin (1956) we see the same result which confirms in another way the concept of the impossibility of a *localization of conditioned inhibition in the cortical area of the analyzer*.

Summarizing the material presented in this section, we can say that the first stage of the problem of the localization of conditioned inhibition is quite definitely solved by proving the inadequacy of the former concept. On the basis of physiological data and considerations, the complete impossibility of a localization of the process of conditioned inhibition in the cortical area of the analyzer has been demonstrated.

This important proposition undoubtedly advances our understanding of the physiological mechanisms of higher nervous activity. Unfortunately, it took 35 years from the time of its first publication by us for it to become obvious and receive extensive experimental confirmation.

The impossibility of a localization of conditioned inhibition in the cortical area of the analyzer is becoming more and more evident now. In view of this, various investigators are attempting to determine this localization at other points of the conditioned reflex arc.

Previously (Anokhin, 1932b, 1949c), in speaking of the impossibility of a localization of internal inhibition in the cortical area of an analyzer, we have, as has already been mentioned, suggested its possible localization "at subsequent stages of the propagation of conditioned excitation," including herein, of course, also the cortical representation of the unconditioned reflex. Some investigators (Korotkin, Suslova, Khodorov, Rokotova, Skipin, and others) have presented sufficiently convincing data confirming this concept.

At the same time certain investigators (Asratian, 1955) made an attempt to localize internal inhibition somewhere "between" the cortical area of the analyzer and the cortical representation of the alimentary center.

All these points of view, which are modifications of our initial hypothesis, are based on the absolutely *certain* proposition of the impossibility of maintaining the opinion of a localization of internal inhibition in the cortical area of an analyzer. We consider this to be the most important result of our investigations begun in 1930.

This becomes even more apparent if we consider the historical role of the concept of the localization of internal inhibition in the analyzer area. The persistence of this hypothesis for such a long time, even though it was in frequent disagreement with results from actual experimental work, is very significant in itself. It indicates first of all that, while closely adhering to the main idea of the reflex theory, only one *linearly* related effect is evaluated, and the possibility of comparing many components of a conditioned reaction (secretion, heart and respiration rate, movement, etc.) was eliminated. On this basis the concepts of "conditioned cardiac reflexes," "conditioned vascular reflexes," etc., have developed.

It seemed entirely natural to conclude that if the *selected isolated indicator of the conditioned reflex* is absent, the reflex arc can be inhibited in the first stage of the action of the conditioned stimulus on the brain. In addition, the localization of internal inhibition in the analyzer area made it easier to accept the concept of an *irradiation of inhibition over the cerebral cortex*. Thus, all the stages and aspects of the development of the concept of internal inhibition have been incorporated into this general concept. It is therefore understandable that it is impossible to change even one aspect in this concept without an immediate change in its other aspects too. This has become especially apparent now that we have recognized the conditioned reflex as a complex physiological structure in which every key mechanism has acquired its own specific, but not linear, significance.

In Chapter 6, dealing with the functional system and the analysis of all the key mechanisms of the patterning of the behavioral act, it became clear that in principle

it is possible to "inhibit" a conditioned reflex by acting on any one of its constituent mechanisms. For example, any interference with the processes of afferent synthesis inevitably affects the conditioned reaction itself. Disturbances resulting from any type of new setting, situation, etc., probably operate in this manner.

On the other hand, any nonreinforcement *becoming effective at the moment of discordance* must affect "decision making" and the patterning of the efferent complex, i.e., the "program of action." It follows that nonreinforcement with food, and the resulting discordance, is only one of many possible cases of the appearance of inhibition of the conditioned salivary reaction.

Experimental results justify assuming that the restructuring and the inhibition of the behavioral act depend directly on the extent to which the behavioral act can be altered: (a) if the purpose of the behavior is retained, the restructuring, and consequently inhibition, is limited to the complex of the efferent impulses; (b) if the discordance leads to a change in the purpose of behavior, all mechanisms of the afferent synthesis must operate again.

Without question, the understanding of the whole physiological basis of these changes in behavioral acts is not an easy task. But it has been considerably simplified upon the acceptance of the physiological architecture of the behavioral act as described in Chapter 6.

CHAPTER 16

The Mechanisms of the Patterning of the Conditioned Reaction as an Integrated Activity of the Organism

IN proposing the concept of the "zone of patterning of the conditioned reaction," we wanted to emphasize that the two most important mechanisms of higher nervous activity—the patterning of the conditioned reaction and the inhibition of specific components of the reaction—are most intimately related *in time and space*.

If one bases the interpretation of the behavioral act on the traditional concept of the reflex, it seems rather easy to determine the zone of patterning of the conditioned reflex. Possibly this zone is located immediately after the afferent part of the reflex arc. As we have seen, however, the solution to this problem is not as unequivocal if we base the behavioral act on the functional system. Because an integrated reaction is highly complex, every one of its key mechanisms can, in principle, be affected separately.

It must be kept in mind that all known integrated reactions (the alimentary, the biologically negative, and the orienting-investigative reaction) are manifested as complexes of effects involving nearly all systems of the organism. Consequently, the interaction of these integrated activities is actually much more complex than its representation in my simplified diagram of one axonal collateral and one internuncial neuron. Thus, the most important task in the investigation of higher nervous activity consists of revealing the composition of the conditioned reaction, performing a physiological characterization of its components, and determining the most plausible sites of interaction of two specific activities of the integrated organism. Only under this condition can we satisfactorily explain that physiological mechanism by means of which *specifically the motor or the secretory component, for example, is inhibited, and not the other components of the conditioned reaction*.

In order to formulate this question more distinctly, we shall analyze a specific case of the inhibition of a conditioned alimentary reaction by excitation from a stronger biologically negative reaction, which is a typical case of the origin of conditioned inhibition. The conditioned alimentary reaction has, in addition to the secretory component, a number of other components, such as the respiratory, cardiovascular, etc.

But the biologically negative reaction also has *all these components* (except for the secretory). Therefore, the question arises: by means of what specific mechanisms are the vegetative components of the alimentary reaction eliminated and the same components, only in a different qualitative and quantitative form characteristic of the biologically negative reaction, evoked?

Is each component of the alimentary reaction inhibited separately, or does the form of these components change automatically through the incorporation of some *integrated nucleus* of the dominant reaction? If the propagation of the impulses of the dominant reaction to the effectors proceeds according to the second type, the problem of the localization of the conditioned inhibition becomes different. It must then be assumed that there is an interaction of two highly integrated neural formations which are a kind of "condensation" of all the processes that subsequently develop as specific reactions—the alimentary and the biologically negative. Thereafter, subject to the dominant "integral," all the effector mechanisms receive a prepared pattern of impulses which correspond to the specific character of the activity of the organism dominant at the given moment.

Our discussion of the problem of the localization of inhibition in the cerebral cortex has brought us to one of the key questions in the physiology of the conditioned reflex: *where and how* does the patterning of the integrated conditioned reaction, which has such diverse effects, occur? Since this question is directly related to the problem of *where and how* the process of cortical inhibition arises, we shall give it special attention.

That the conditioned reaction consists of a number of specific effects was well known in Pavlov's laboratory, even though the necessary conclusions were not drawn from it. Pavlov quite clearly defined this complexity of effects of the conditioned reaction when he said: "Usually our behaviour consists not of isolated, but complex reactions, corresponding to the constant complexity of the surroundings" (Pavlov, 1933b, see Pavlov, 1957, p. 530).

In accordance with this concept, Pavlov fully characterized the interrelation of the two principal components of the conditioned alimentary reflex, the secretory and the motor component.

We must agree that the conditioned alimentary reaction of an animal is an expression of its *general* alimentary excitation. Precisely for this reason it outwardly appears as a complex of harmoniously related effects which impart to the reaction as a whole a specifically alimentary character.

As I have already indicated, in addition to the secretion, which is a specific component of alimentary excitation and traditionally serves as an indicator of cortical processes, there also is in the animal a number of other manifestations of the same alimentary reaction: movement toward the food, a change in heart and respiration rate, initiation of the secretory and the motor function of the intestinal tract, activation of the function of the endocrine systems, etc.

In attempting to understand the physiological nature of this integrated activity of the organism, we encounter an important characteristic of the complex of effects of the conditioned reaction. Any one of the components of the conditioned alimentary reaction, as well as of any other reaction, regardless of the number of components, is not isolated and independent of the nature of the general reaction. All the components of the conditioned alimentary reaction are manifested in such a composition and to such an extent as is necessary to ensure specifically the alimentary reaction. In other words, the respiratory component of the conditioned alimentary reaction is not just respiration, but respiration which in its volume, rhythm, and intensity is adapted to

the nature and intensity of the integrated *alimentary* reaction. On the other hand, the respiratory component as part of the complex of effects of another integrated conditioned reaction, e.g., the *defense* reaction, will be different, but again in complete accordance with the biological nature of the given reaction. Similar analyses may also be performed for other components of the complex conditioned effect.

These considerations compel us to assume that *the harmonious coordination of all components of the conditioned effect ensuring the success of the conditioned reaction as a whole must result from an organic synthesis of the central nervous processes appropriate to all the components of the given reaction*. Presently we shall attempt to elucidate this most important mechanism of neural integration.

In discussing the problem of the interrelation of the motor and secretory components of the conditioned reaction, Pavlov said:

We now have sufficient data to show that the two components of the conditioned alimentary reflex are represented at two different points of the cortex: one in the motor region, and the other elsewhere [Pavlov, 1949c, pp. 552-553].

These two points must substantially differ from each other in their functional characteristics. The motor region is concerned with voluntary activity and has constant training in inhibition and excitation and their alternation. The salivary reaction, although its cortical representation must be acknowledged, is evidently set up in a different way—it is an involuntary activity: we cannot control salivary secretion, we cannot cause our saliva to flow [Pavlov, 1949c, p. 180].

It is easy to imagine how complex the synthetic process must be, combining all the components of the conditioned reaction into a harmonious whole. These components are *differently located* in the subcortex and cortex, have *different physiological characteristics*, a different degree of "voluntary" control, etc. Nevertheless, as soon as the conditioned stimulus begins to act, the cortical nervous processes of all these effects immediately form an organized system of excitations which ensures the appearance at the periphery of an integrated adaptive act having an appropriate proportion of each component.

How and where does this decisive process, which unites all the components, occur? One may think that the cerebral cortex determines the appearance of one or some of the most important components of the conditioned reaction with the rest, such as the respiratory and the cardiovascular component, being "connected up" somewhere in the subcortex on the pathway of the impulses evoked by a conditioned stimulus from the cortex to the lower parts of the nervous system.

However, the data regarding this question indicate something quite different. One must rather assume that the process of integration of the conditioned reaction as a whole already occurs in the cerebral cortex on the basis of the cortical representations from the corresponding organs, and that here *all components of the conditioned reaction must be harmoniously coordinated with the general interests of the given conditioned reaction*.

As conceived by Pavlov, ". . . the entire organism with all its components reflects itself in the cerebral hemispheres."

According to this view, any one of the components of a conditioned reaction, regardless of how insignificant it may be, must have its afferent representation in the cerebral cortex, thus influencing the development of the cortical processes. Consequently, the system of excitation, which constitutes a conditioned reflex, must involve practically all sections of the cerebral cortex. As a result of such a mechanism of the patterning of the conditioned reaction, the respiratory and the cardiac centers of the medulla oblongata participate only *passively* in a given conditioned reaction which has completely formed already at the level of the cerebral cortex, i.e., long before the arrival of the impulses in the medulla oblongata. Probably this constitutes one of the "creative" roles of the cerebral cortex as an afferent organ according to Pavlov's views.

Two possibilities of integrating both somatic and vegetative components into an integrated conditioned reaction are conceivable. The cortical synthesis of all the diverse stimuli from the external and internal world leads to the patterning in the cortex of the *synthetic nucleus* of the entire reaction in the form of a definite system of cortical excitations. Only then is this system of excitations implemented at the periphery via the subcortical, bulbar, and spinal centers.

But another mechanism is possible too. Cortical afferent synthesis, as we have seen, occurs with the inevitable participation of all the numerous impulses ascending from the subcortex. There is reason to believe that this connection with the cortex is effected by a continuous cortico-subcortical reverberation of excitations. Thus, the actual decision making about the patterning of one particular reaction is a result of this extensive cortico-subcortical complex of excitations in which the cortex fulfills the role of differentiation and choice, and the subcortex that of activating a definite complex of always integrated excitation.

It is known that after the removal of the cerebral cortex, subcortical structures are able to accomplish reactions in a fully integrated way. Therefore, the most important function of *when, how, and where* to direct the action of these integrated complexes belongs to the cerebral cortex.

Just how closely the individual components of a reaction of an animal are adjusted to each other and how much they serve a single task—that of adapting the animal to certain conditions—can be seen from the following example. Let us assume that in the usual setting of a stereotypic experiment a strong and new auditory stimulus has suddenly acted on the animal. As is shown by special experiments considering the respiratory and the cardiac component, in response to this action of an unexpected stimulus, the respiration assumes an inspiratory, tonic character, and the cardiac contractions become *more frequent*. In this respect the adaptive nature of the change of the individual components is clearly evident. The *holding of the breath* is a necessary consequence of the increased tonus of the analyzers during the orienting-investigative reaction, and the *increased frequency of the cardiac contractions* is a compensatory adaptation to the deficiency in the oxygen supply to the brain and other organs. This adaptation has naturally developed since during strenuous activity the organs require a greater oxygen supply, and, moreover, after a temporary holding of the breath there usually follows a deep compensatory inspiration. Consequently, the entire reaction is indeed of an integrated nature that is appropriate for the given conditions.

In regard to this it is essential to discuss the following questions:

1. How is that "synthetic nucleus" of the reaction constituted which undoubtedly is formed before it becomes active in some combination of peripheral effectors which is characteristic of a given reaction?
2. Does it consist only of neural elements of the cerebral cortex, or do certain elements of the "nearest subcortex" (essentially, of the hypothalamus, the thalamus, and the reticular formation of the brain stem) also enter into it on a basis of equal participation?
3. If these formations are components of this integrative mechanism of the reaction, what part of the reaction or, to be more exact, which of its aspects and properties do they determine?

Even a few years ago we could fail to answer these questions completely and be satisfied with the concept that all aspects of a conditioned reaction are determined by cortical processes. Now, however, since it has been shown in numerous direct experiments that there is not a single cerebral process in which the cortex and the subcortex are not acting as an organic unit, we must attempt to discern which aspect or which characteristic of a conditioned reaction is ensured by the cortical and which by the subcortical level of the brain.

Only after answering all these questions will we be able to understand why identical series of impulses emerge onto the final nervous pathways of different vegetative organs. The present state of the physiology of higher nervous activity is, however, still very far from elucidating the physiological nature of cortico-subcortical interrelations.

Without doubt, all the impulses intended for the peripheral organs taking part in a given reaction are patterned into an integrated unit *simultaneously*, and they leave this integrative apparatus simultaneously, too. But at the same time we are well aware that the *nervous pathways* over which the individual series of impulses then propagate and reach the corresponding peripheral apparatuses are entirely different. These individual pathways have their own specific physiological characteristics and their own specific spatial distribution, since all the impulses are directed toward different organs which are often very remote from each other.

As an illustration we shall attempt to analyze a well-known motor reaction that is very frequently used in conditioned reflex experiments: the *local flexion* of a hind leg upon electrocutaneous unconditioned reinforcement.

It is known that the movement of an extremity or of any one of its sections is implemented via specific pathways of the central nervous system, i.e., via the pyramidal tract. The impulses causing these local movements start in the cerebral cortex and emerge onto the pyramidal tract, ultimately reaching the terminal motoneurons of the appropriate segments of the spinal cord without being transmitted via any synaptic relays along the way.

True, in recent years the very concept of the "specificity" of impulses propagating along the pyramidal system has quite legitimately been subjected to extensive discussion. In a number of articles that were subsequently organized into a special monograph, Walshe (1948) refutes the generally accepted concept of the local nature of movements which are effected by the pyramidal tract. To a considerable extent these

concepts coincide with our point of view concerning this question which will be substantiated below. Here it is important to emphasize that the pyramidal component of any local movement, maintaining its relation to the integrated act on the basis of which it has developed, nevertheless has its own individual physiological character.

This is first manifested in the fact that any local movement can be carried out only if the general distribution of impulses *over the musculature of the whole body* has shifted its center of gravity and brought about a posture of the animal which permits the actual implementation of the appropriate local act.

As was shown by some of our experiments, these interrelations of the general or *postural excitation* and the *local excitation* actually develop at the corresponding segments of the spinal cord in a definite and strictly coordinated sequence. In contrast to the pyramidal impulses, the impulses of general motor excitation, which provide for the adaptive change of the posture of the animal in accordance with the given local motor act, pass through a number of subcortical centers. Thus, before coming out to the same motor elements of the spinal cord, they pass through several synaptic relays.

The impulses which, in this same conditioned reaction, provide for the adaptive changes in the respiratory, cardiac, vascular, and other vegetative functions, have an even more specific path. They pass through several synaptic relays and therefore are considerably delayed before reaching the working organs. In addition, the actual paths of propagation to the different components of a conditioned motor reaction have their own specific physiological properties.

By what physiological means does the nervous system, with such a fundamental difference between the individual series of impulses that constitute an integrated conditioned reaction of an animal, achieve the coordinated participation in time and space of all the components of this reaction?

This question opens broad perspectives in the physiological analysis of the interaction of diverse cortical and subcortical impulses which is established during the patterning of an integrated conditioned reaction. Unfortunately, this question has never yet been the object of systematic investigations. However, individual investigations involving, for example, the *composition* of the conditioned motor defense reflex, shed light on the characteristics of this extremely interesting synthetic process.

Shumilina and Kas'ianov performed, in our laboratory, kymographic and oscillographic analyses of the rates of development of postural and local excitation in different groups of muscles in animals and man during the occurrence of the conditioned defense reflex.

In an animal on a stand an electromyogram was recorded along with a kymographic registration of the conditioned defense movement of the hind leg (Shumilina, 1949, pp. 174-185; Kas'ianov, 1950a). The electric potentials were recorded simultaneously from the flexors of the hind leg which is flexed and from the extensors of the contralateral hind leg. A similar setup was used also in man (Kas'ianov, 1950b). In the experiments on animals, in response to a conditioned defense stimulus, the animal lifted the appropriate hind leg. In a standing human subject, verbal instruction to raise the right leg served as the stimulus.

In both kinds of experiments, similar results were obtained. As soon as the conditioned stimulus began to act, there immediately and *first of all* occurred a considerable

increase or a reappearance of the electric potentials in the *extensors of the opposite extremity*. Only then, after several fractions of a second, did electric potentials in the flexors of the extremity being raised appear. This result was the same in all forms of the experiment, and there was a difference only in the length of the interval between the first and the second electrical phenomena. It is interesting that this interrelation of the generalized and the local excitation exists also when the human subject raises one of his legs voluntarily, i.e., without any *direct* instruction.

As is shown by accurate oscillographic measurements, the impulses from the generalized or postural motor excitation reach the lumbar motor elements and the muscles of the corresponding extremities 0.2–0.4 sec earlier than do the pyramidal impulses that provide for the local flexion of the extremity.

The physiological significance of this “overtaking” is clear: by means of it, such a new form of equilibrium and such a distribution of the points of support of the animal’s body are created first of all as to fully provide for the animal’s ability to carry out the given *impending* local act (Shumilina, 1949, pp. 174–185; Kas’ianov, 1950a, 1950b).

What physiological mechanisms cause the postural impulses (as a *component* of the conditioned motor reaction) to arrive at the lumbar segments *before* the impulses traveling along the direct pyramidal tract, if they arose in the cerebral cortex simultaneously? The answer must be sought in the exceptionally high rate of propagation of those impulses which ensure the stability and equilibrium of the animal’s body. According to the latest investigations, this rate is almost 120 m/sec, while the rate of propagation of impulses over the pyramidal tract is only about 80 m/sec.

In view of these special features, the two kinds of impulses, the postural and the pyramidal, *after having started simultaneously in the cortical complex of the conditioned motor reaction*, reach the effector segments of the spinal cord at different times. As a result, the animal is able to shift the center of gravity of its body in such a way that *it becomes physically possible* to raise one of the hind legs.

The purposefulness of this physiological architecture of the conditioned motor reaction is obvious: an animal or human being cannot move any of its extremities without a shift in the center of gravity of its body; consequently, this must be provided for *first of all*.

This example illustrates well the great importance of the *moment of patterning* of a conditioned reaction in the cerebral cortex for the understanding of the dissociation between its individual components and consequently for the understanding of the role of the inhibitory process in this dissociation. One can surmise two possibilities of such a harmonious union of the generalized motor activity and the local impulses pertaining to the pyramidal system of the cortex.

The first possibility could be that the impulses resulting from the action of the conditioned stimulus may proceed *solely* to the cerebral cortex. Here the impulses evoke a complex which in some form contains “seeds” of both forms of future impulses that ensure at the periphery a coordinated distribution of the generalized and the local impulses. Naturally, this complex must be a synthesis of all that previous experience of the animal in which, on the basis of conditioned reflex connections, the given form of its movements was created.

Such an assumption of the patterning of the integration of both forms of impulses already in the cerebral cortex is entirely feasible since, on their afferent pathway, these impulses may dissociate and proceed to different conducting pathways having a different rate of propagation. In this manner they could ensure in the motoneurons of the spinal cord the temporal relation essential for guaranteeing the coordinated act at the periphery.

There is a second possibility, however. The impulses evoked by the conditioned stimulus may propagate not only toward the cerebral cortex but at the same time they may, at the level of the *subcortical* structures, excite those neural complexes which themselves have been created during the acquisition of motor experience under the influence of the cerebral cortex and in close interaction with it. As a result of such a propagation of the impulses evoked by a conditioned stimulus, two complexes (the cortical and the subcortical) could be excited almost simultaneously and could, with the aid of connecting neurons, form a functional unit. In this case a system of two series of motor impulses would arise in which, in spite of the functional unity, each series would, under certain conditions, have a certain degree of independence of origin and propagation. If the second hypothesis is true, the individual behavior of the series of motor impulses during their temporally dissociated propagation toward the peripheral working mechanisms would be more understandable. Actually, both hypotheses deserved discussion and further experimental verification, which was carried out by my collaborators Shumilina and Kas'ianov.

The form of experiment which will enable us to examine these two possibilities will become apparent if we carefully consider the pathways of propagation in Fig. 16.1.

Let us assume that the animal has well-established conditioned defense reflexes and that a dissociation between the postural and the local excitation is apparent. If now an extirpation of the motor analyzer with a considerable inclusion of the limitrophic cortical formations is performed, the conditioned excitation would, according to the first hypothesis, be completely deprived of *both the generalized and the local excitation*. According to the second hypothesis, it would be deprived of only the *local component*, but would preserve in some form the generalized postural excitation.

It turned out that presentation of the conditioned stimulus several days after the operation produced only negligible changes in the postural excitation, while the local defense component of the conditioned reaction was entirely absent (see below).

These results provide a definite answer to the above question. They convince us that during the elaboration of the conditioned defense reflex an extensive system of interrelated impulses is established to which each section of the central nervous system contributes its specific share.

Could it be any different? How could there be a redistribution of the tonus in the entire musculature of the body without the participation of the vestibular system? Consequently, the whole point is that the mechanisms of the vestibular system establish *during the process of elaboration* a functional unity with the cortical processes that fulfill the decisive coupling role in this extensive system of impulses. This problem was the object of Koriakin's research for several years.

In addition to the questions discussed above, Koriakin attempted to more fully

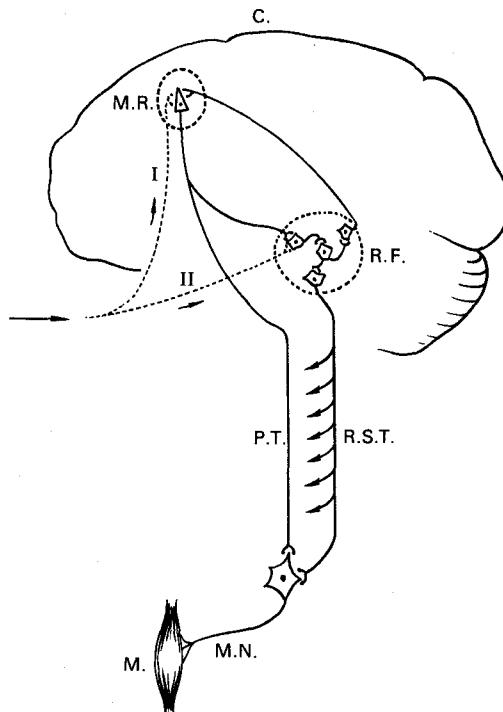


FIG. 16.1. Two possible pathways for the spread of conditioned excitation during the formation of a conditioned motor defense reflex. I, pathway connected with the cortical integration of the postural and of the local excitation; II, pathway permitting the inclusion of the postural excitations already at the level of the subcortical apparatus (reticular formation); C., cortex; M.R., motor region; R.F., reticular formation of the brain stem; R.S.T., reticulospinal tract; P.T., pyramidal tract; M.N., motoneuron; M., muscle.

characterize the patterning of the first phase of development of the conditioned motor reaction, i.e., the patterning of the generalized or postural excitation itself. This process interested us in two respects. First of all, it follows from the very nature of postural excitation that it must excite the corresponding segments of the spinal cord in a definite sequence. But it is this sequence that must become the index of the degree of dependence of the postural excitation on the cortical nervous processes in the motor analyzer, i.e., on the mechanisms of the local component of the conditioned reaction as a whole.

Naturally, this new purpose also demanded a new method of investigation. Since the animal on the stand has, as usual, four points of support (the four legs) and shifts to three points of support upon lifting a leg, it was necessary to examine what happens during this interval to all four legs. It is clear that any change in the distribution of the tonus over the segments of the spinal cord must immediately affect the magnitude of the weight load on each leg. This served as a starting point in the development of a

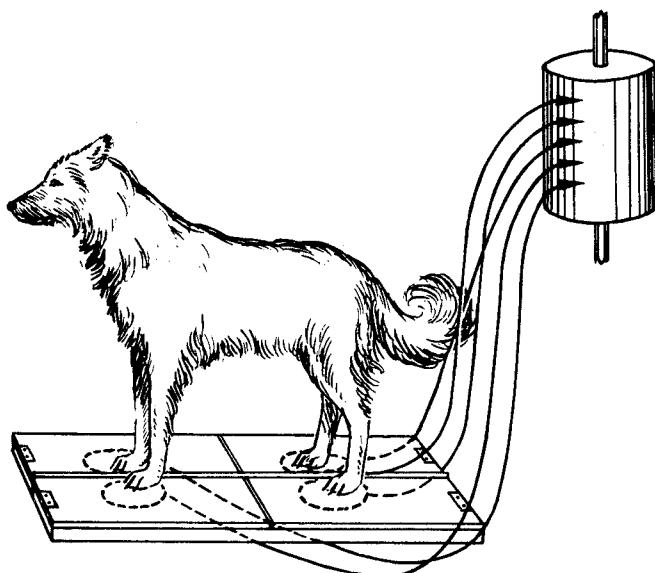


FIG. 16.2. Representation of stand with four platforms for recording movements of extremities of dog.

procedure for recording the propagation of postural impulses over the segments of the spinal cord.

This was achieved with the following equipment. The foundation of an ordinary stand consisted of a solid board, on which four mobile platforms for the four legs of the dog were mounted. The pressure applied to each one of the platforms was recorded on a kymograph by way of pneumatic transmission (Figs. 16.2 and 16.3). Thus, we

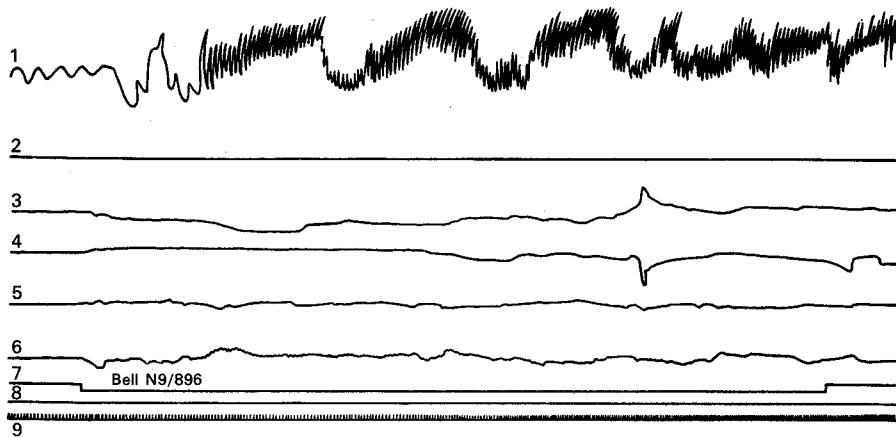


FIG. 16.3. Actogram recorded on stand with four platforms. Recording made after extirpation of both motor regions of cerebral cortex. 1, respiration; 2, local movement of paw (left hind); 3, general (postural) movement of left hindpaw; 4, right hindpaw; 5, left front paw; 6, right front paw; 7, conditioned stimulus; 8, recording of unconditioned stimulus; 9, time in 0.2 sec.

were able to trace in time how the impulses from the generalized excitation propagate over the spinal cord and what the relations of the local movement to each stage of development of the postural impulses are.

Koriakin's investigations yielded many interesting results. Here we shall note several propositions which follow from his work (Koriakin, 1958, 1959).

1. The nature of the distribution of the postural impulses preceding the appearance of a local act is constant, standard, and specific with respect to the given local act. It does not immediately become such, however. A certain period of *elaboration* of this standard distribution of efforts over all four legs is needed.
2. During the switching of the conditioned defense reflex of one leg to a conditioned reflex of another leg, the *local* conditioned reflex is switched rapidly, whereas the postural standard of the first conditioned reflex is switched with great difficulty.
3. During the elaboration of differentiation to a conditioned defense reflex, the local motor reflex is inhibited with comparative rapidity, whereas the postural component of the positive conditioned reflex still continues for a long time (Fig. 16.4).

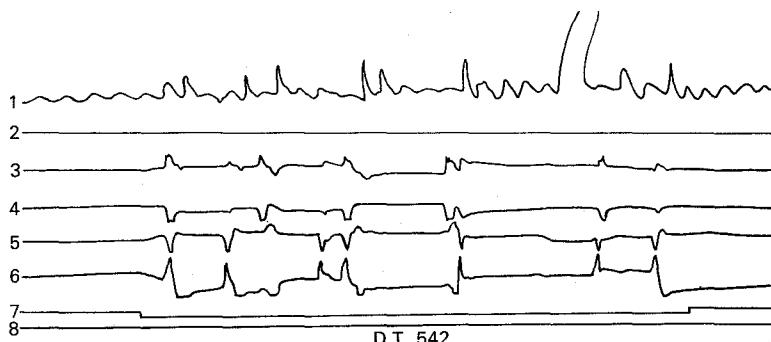


FIG. 16.4. Actogram after complete differentiation of conditioned defense reflex: presentation of differentiating tone (D.T.) No. 542. Designations same as in Fig. 16.3. The complete absence of local jerking away of the left hindpaw can be seen (second line from top). The postural excitation has survived intact.

Upon comparing all these properties of the local and the postural impulses, we see that the stability and inertness of the latter reflect the most characteristic features of the function of subcortical structure.

Especially interesting in this respect are the data obtained during the elaboration of differentiation. The invariable "overtaking" of the local impulses by the postural impulses and the extreme stability of the specific architecture, i.e., of the conditioned nature, of the postural impulses make the second possibility (the cooperation of cortex and subcortex) highly probable (see Fig. 16.1).

At this point we should call attention to several other data which appear to have the same physiological characteristics.

Two interesting phenomena were observed in our laboratory for which we were

unable to find a suitable explanation for a long time. We have named the first of these phenomena the "reaction of the first second." The first second of the isolated action of a conditioned stimulus evokes a conditioned *motor* reaction of the animal which is of exceptional stability and inertness during the elaboration of differentiations, during switching, etc. (Anokhin and Artem'ev, 1949).

This brief conditioned motor reaction persists even when the conditioned stimulus has not been reinforced many times. But even if it finally does disappear, as, for example, after prolonged switching of the conditioned motor reflex, the animal has only to doze for a while, and this "reaction of the first second" reappears. As early as that, we had the impression that this reaction resembles in all its characteristics a reaction of subcortical nature, even though it undoubtedly develops under the influence of cortical processes. What, then, is the meaning of this reaction of the "first second," which in all features resembles those conditioned reflexes which Pavlov had said "compete in their persistence with the unconditioned reflexes"?

Its meaning became clearer when it was discovered in our laboratory that the respiratory component of a conditioned reaction is generally manifested before all the other components (Balakin, 1935; Kas'ianov, 1947).

As we already know, Gantt (Robinson and Gantt, 1947) concluded that the cardiac component of a conditioned reaction is manifested even before the respiratory component. This, however, does not change the fundamental essence of the "overtaking" of the basic components (the secretory and the motor components) by the vegetative components. What is important is that all the phenomena described above, which develop as soon as the impulses from the conditioned stimulation reach the first integrative structures of the subcortex, have certain common properties: *they reflect the initial propagation of impulses evoked by a conditioned stimulus over the subcortical structures that have coupled with the cortex during the elaboration of the conditioned reaction.*

What mechanisms cause the early emergence onto the spinal cord of postural impulses, the impulses of the "first second," the impulses of the respiratory and the cardiac center, etc.?

Our first assumption was that this "overtaking" is most probably brought about by means of the reticular formation and its descending pathways (Shumilina and Anokhin, 1939). Only in recent years, however, was this assumption fully confirmed by the rapidly developing physiology of the reticular formation (Moruzzi and Magoun, 1949; Magoun, 1952a, 1952b; and others).

As was shown by investigations of the reticular formation, it is reached by collaterals from all the ascending afferent pathways. This functional position of the reticular formation enables it to receive all afferent impulses before they reach the cerebral cortex by way of synaptic relays at the thalamic level.

It is therefore difficult to suppose that these afferent impulses, arriving by collaterals into the reticular formation, would not become involved in the elaboration of conditioned reflexes. Undoubtedly, every conditioned stimulation evokes first of all an excitation of the reticular formation, and this manifests itself in those functional systems of the organism which are directly connected with this structure. We believe that because of this the respiratory component precedes all other components of the conditioned

reaction. The generalization of the conditioned excitation in the region of the reticular formation occurs before this excitation has encompassed the most differentiated cortical component of the conditioned motor reaction. This means that the system of the respiratory center, the cardiac center, and the vestibular centers can be excited during the action of a conditioned stimulus in the manner of a generalization of excitation *already at the level of the reticular formation and the region of the hypothalamus and thalamus.*

If this assumption is accepted, much that is not understood in the behavior of the vegetative components of a conditioned reaction will become sufficiently clear. It must, however, be specially noted that this assumption does by no means deprive the conditioned reaction of its integrity and unity as a cortical functional formation, since in higher animals the specific feature of the conditioned reaction, its signaling adaptive nature, is a function of the cerebral cortex. The only thing involved in the assumption is the manifestation of specific components of the conditioned reaction which, in accordance with its general physiological architecture, must arrive at the peripheral effectors before the conditioned reaction as a whole has been patterned.

For example, if, in the specific case of the conditioned defense reaction, the animal were to raise a hind leg before the tonus of the axial musculature has become distributed in accordance with the impending local movement, it would immediately fall down, just as does a bronze figurine with a broken-off leg.

Therefore, we see that our laboratory data obtained over a period of more than 25 years are now being more precisely explained. The above interpretation of the phenomena of "overtaking" with respect to the respiratory, cardiac, postural, and other components of the conditioned reaction was considerably promoted by recent investigations of the reticular formation. Only slight progress has as yet been made concerning the role of the reticular formation in the patterning of integrated behavioral acts. A comparison of the data from higher nervous activity with the general physiological characteristics of this neural formation can undoubtedly lead to positive results.

During the discussion of the interrelation of the cortex and the subcortex, the most outstanding features of this new neurophysiological trend will receive special consideration. Now it is important to emphasize that the mechanisms of *the patterning of the conditioned reaction* as an integrated act can be understood on the basis of the properties of the integrated architecture of the functional system. Any purely verbal formulations of the "integrity" of the conditioned reflex will satisfy the investigator less and less.

In this regard we shall attempt a deeper analysis of the processes that accompany the appearance of the conditioned defense reaction exemplified by the raising of the right hind leg.

The weight of an animal standing on four legs is uniformly distributed over four points of support. Consequently, each leg takes a definite part in maintaining the body in a horizontal position.

What happens when the conditioned defense stimulus begins to sound? As is shown by the experimental data discussed above, there first of all occurs a redistribution of the postural impulses, as a result of which the animal's body weight is distributed over three points of support. This means that already during this phase of the patterning of the

conditioned reaction, the hind leg which will implement a local reaction is freed from the postural impulses.

Consequently, we must admit that in the central complex of the motor impulses which ensures the maintenance of the normal posture of the animal *inhibition* of a certain part of this complex that pertains to one hind leg has already occurred. *Even though this leg has not yet been lifted, its spinal elements are free to receive the local impulses of the pyramidal tract.* Oscillographic analysis shows that this whole process of ensuring the local act takes place within 0.1–0.2 sec.

From all this it is evident that the inhibition of individual components of an integrated conditioned reaction can take place only *during* the patterning and in the *area* of the patterning of the entire central complex of the impulses ensuring the appearance of the conditioned reflex.

Returning once more to the example of the differentiation of a conditioned alimentary reflex, let us assume that it appears in the cortical representation of the unconditioned reflex as a result of the action of the stronger excitation of a biologically negative reaction on the excitation of this representation. But we already know that the conditioned alimentary reaction taken as a whole includes not only the secretory response but also consists of a number of other components *which may enter into the negative reaction in their own specific form.* Among such components are general movement and respiration. Respiration as a component of the conditioned alimentary reaction has its own specific features: there is a deep expiration, a definite rhythm, but no significant increase in frequency. Respiration as a component of the biologically negative reaction, on the other hand, is frequent, arrhythmic, and, what is especially characteristic, it always has a very high inspiratory tonus.

From this comparison of one of the components of two competing systems of excitation, we must conclude that *a developing biologically negative reaction not only inhibits the cortical representation of salivary secretion, but changes the nature and intensity of all the other components of the conditioned alimentary reaction as well.*

Could there be such a diversity of interactions between the biologically negative and the alimentary reaction if inhibition arose in the cortical area of the analyzer of the differentiating stimulus? Of course not. In addition, the assumption of a localization of the inhibition in the cortical area of the analyzer altogether precludes the possibility of a deeper analysis of all the above-described mechanisms which provide for both the diversity of the integrated reactions of the organism and their interaction which terminates in the inhibition of some components of these reactions and in the appearance of others.

Here it will be appropriate to point to the investigations of the conditioned reaction by Ricci *et al.* (1957), who used the microelectrode technique. While observing the behavior of different elements of various cortical layers, they found an extreme diversity in the processes occurring in them at the moment of presentation of the conditioned stimulus.

While some cortical nerve cells begin to become excited, others lapse into a state of inhibition. Some cells prove to be excited throughout the entire period of action of the conditioned stimulus, while other cells at times become excited and at other times lapse

into inhibition, etc. All this indicates that the conditioned reaction taken as a whole has a very complex physiological architecture.

In this respect recent data of Jasper (1963) are especially significant. In special experiments involving conditioned reflexes he showed that there is a great difference in functional specificity between different cortical cells. Some of them can become excited at the beginning of the action of the conditioned reflex, others at the end, etc. Apparently there are even cells that become specifically excited or specifically inhibited at the moment of elaboration of the differentiation. In all cases, however, the excitation and inhibition comprise a certain integrative system which acquires functional meaning because of its diversity. In summarizing his results, Jasper writes :

Changes in temporal and spatial *pattern* of firing of individual units, with inhibition of some units simultaneously with facilitation of others, seemed of greater significance than was any process which could be adequately described in general terms for the population of neurones as a whole [Jasper, 1963, p. 283].

Such complex effects of unspecific activation can be understood if we abandon the hypothesis that "activation" is a relatively undifferentiated, unstructured, non-directional, or unspecific general energizing process, turning up the "volume control" so to speak. If it is conceived of as a highly integrated process of control or "setting" of neuronal systems for coordinated functions, inhibition playing at least as important a role as facilitation, then the complex changes in unitary behavior would be expected. The integrative functions might, however, be lost or diminished during excessive massive supraliminal activation, as in states of extreme emotional stress [*ibid.*, pp. 284-285].

This conclusion indicates with sufficient clarity that our attempts to understand the true meaning of integrative activity on the basis of electrical phenomena are still very remote from the true neuronal interactions.

Thus, all data lead us to the conclusion that the encounter of "inhibitory" excitation with excitation "being inhibited" in the cerebral cortex and subcortex is highly versatile and occurs during the patterning of the cortical complex of conditioned excitations on the cellular territory of almost all "cortical representations." This encounter is what determines *which components of the conditioned reflex will remain unchanged, which will be altered or replaced by others, and which will be completely inhibited*. As can be seen, such an "encounter" can in fact only be an encounter of systems of impulses, and not of elementary individual impulses.

Does not this concept of the mechanisms of the patterning of the conditioned reaction depreciate that "creative" role of the afferent part of the central nervous system, i.e., of the cerebral cortex, of which Pavlov had spoken? Not at all. One only needs to ask what factors determine the *direction and final results* of the encounter of two systems of impulses in order to see that the afferent function not only is not lessened, but, on the contrary, *moves to the foreground*.

The processing of all the diverse external and internal influences on the organism

by the cerebral cortex during the stage of afferent synthesis determines which of the components of the conditioned reaction will be inhibited at the moment of its patterning and which ones will be adopted. During the patterning of the conditioned reaction nothing can occur without constant influence and control by those afferent impulses which are continuously fired by the analyzer areas of the cerebral cortex.

Only the cortical analysis and synthesis of the afferent impulses, from both the present and past experience of an animal, can determine the adaptive significance of the distribution of excitation and inhibition over the individual components of a given conditioned reaction at the moment of its patterning. The fundamental scheme of this distribution of both processes over the components of the conditioned reaction does not differ from the one we discussed in connection with the elaboration of differentiation or of extinction. There is only an increase in the number of participating cortical representations from different organs and functions.

Let us now attempt to visualize the interaction of the processes of excitation and inhibition during the patterning of the conditioned secretory-motor reaction in the case that is most difficult to explain, namely, the dissociation between the secretory and the motor component of the reaction.

As was already indicated, in our experiments the conditioned secretory reaction of the animal occurs in response to the application of all conditioned stimuli, since they all are consistently reinforced with food, regardless of which side a given conditioned stimulus signalizes. The *motor* component of the conditioned reaction, on the other hand, is in a special situation: the entire differentiation of the behavior of the animal is dependent upon the motor analyzer. This is manifested first of all by the appearance of the secretory component of the conditioned reaction before the establishment of

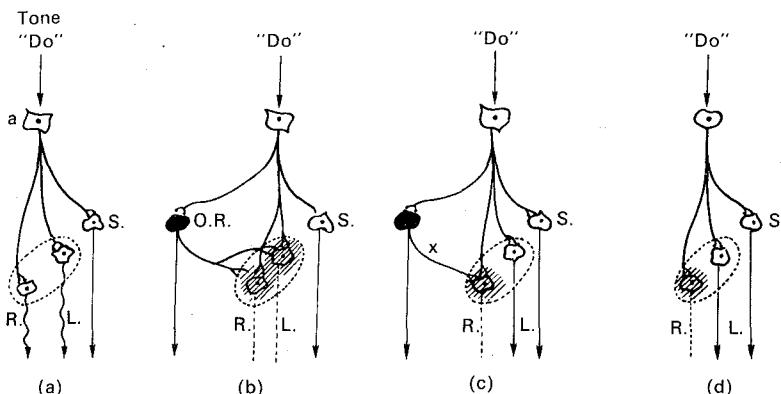


FIG. 16.5. Gradual differentiation of side of reinforcement under conditions of work with bilateral stand. (a) First presentations of differentiating stimulus, mixed reactions; (b) appearance of orienting-investigative reaction (O.R.) and of inhibition of both motor reactions; (c) beginning of differentiation; (d) final and trained differentiation of choice of side without participation of orienting-investigative reaction. The diagram shows the phasic role of the orienting-investigative reaction in the elaboration of the differentiation implemented by the collateral inhibiting connection. a, analyzer; S., secretory component of the conditioned reactions; R., movement toward the right; L., movement toward the left.

differentiation of the motor component with respect to the side of reinforcement. It is for this reason that the animal exhibits a pronounced orienting-investigative reaction during this period.

Let us assume that the tone "do" is reinforced on the left side of the stand and the tone "mi" on the right side of the stand. Let us follow the course of the differentiation of these stimuli with respect to the place of reinforcement. The nervous processes characterizing the individual stages of development of the differentiation are shown schematically in Fig. 16.5.

Diagram (a) shows that the impulses evoked by the tone "do" enter the cortical cell of the auditory analyzer *a*. From here the impulses are directed to a number of cortical representations on the basis of which the conditioned reaction is patterned. These are: the cortical representation of salivary secretion *S* and, corresponding to the two complexes of impulses in the motor analyzer for the right and the left side of the stand, the cortical representations *R* and *L*. Being located within the motor analyzer, the two latter complexes inevitably enter into reciprocal relations with each other, i.e., when one is in a state of excitation, the other must enter into a state of inhibition, as the dog cannot be on both sides of the stand at the same time. In diagram (a) the undifferentiated reaction of the animal is shown for both motor complexes by wavy lines: in response to the conditioned stimulus, tone "do," reinforced from the left feeder, the animal moves both to the right and to the left feeder. Soon, however, the next stage appears in which to the tone "do" (left side) and to the tone "mi" (right side) the animal responds only with the secretory and other vegetative components; *the motor component of the conditioned reaction (a movement of the animal toward the feeder) is completely inhibited*. These relations are represented in diagram (b) by broken lines.

It is thus evident that the interrelation of the processes of excitation and inhibition in the case of the dissociation between the secretory and the motor component of the conditioned reaction (diagram b) is *fundamentally* the same as that in all the other cases of the development of internal inhibition we have discussed. This once more emphasizes the correctness of Pavlov's basic postulate that all forms of cortical inhibition are of the same physiological nature and differ only "in regard to the conditions of their origin."

What serves as the "inhibitory excitation" in the given case, i.e., what leads to the inhibition of the motor components of the conditioned reaction both for the left and for the right side in the presence of conditioned alimentary excitation manifested in conditioned salivary secretion?

Since in our experiments all conditioned stimuli are reinforced with food, it is natural to assume that "nonreinforcement" and the resulting appearance of strong excitation of the biologically negative reaction of the animal cannot in this case be the impetus for the development of inhibition in the motor analyzer, as had been the case in all the previously discussed cases of internal inhibition.

This question is easily resolved if one carefully observes the behavior of the animal during the stage of complete inhibition of both motor components of the conditioned reaction. During the action of the conditioned stimulus the animal exhibits an extraordinarily pronounced orienting-investigative reaction: it alternately and intensely stares at both sides of the stand, glances toward the conditioned stimuli located under

the center of the stand, etc. In some animals this orienting-investigative reaction develops with such distinctiveness and force that they jump off the stand and rush off to "investigate" the source of the stimuli that are difficult for them to differentiate. Thus, the fundamental scheme of the origin and localization of cortical inhibition, *the inhibition of the cortical representation of salivary secretion through the development of a stronger "inhibitory excitation,"* remains in force. However, the role of the biologically negative reaction was assumed in our experiments by the strong excitation from the orienting-investigative reaction. Rather than the excitation of the cortical representation of salivary secretion S, the excitation of the two not yet differentiated complexes of the motor analyzer (see Fig. 16.5b) is inhibited.

Thus, the special features of the procedure involving reinforcement with food from two feeders located at opposite sides of the platform result in the entire cortical energy of the animal being directed at the differentiation of the two reciprocal complexes of the motor analyzer, while the secretory component, which is always reinforced, occurs throughout almost the entire period of this differentiation.

In all the presented data and considerations the selective inhibition of only the motor component of the conditioned reaction was discussed. This, of course, is not equivalent to inhibition of the motor analyzer as a whole, since the animal, while continuing to sit in the middle of the platform, is by no means deprived of the ability to move: during the action of the conditioned stimulus it alternately turns its head toward the right and left feeder, sniffs the air, assumes a posture of attention, etc. But at the same time a quite well-defined form of movement is inhibited, namely the *conditioned motor reaction toward the feeders*.

Pavlov noticed this ability of the motor analyzer to functionally fractionate its individual components, enabling the animal to regulate its motor adaptation to the external environment in the most diverse combinations of muscular contractions. In describing the characteristics of the "reflex of biological caution" Pavlov noted:

At the same time that its body is immobile, the dog investigates the setting by turning its head, i.e., its receptors, nose, ears, and eyes, in various directions. . . . Its main features [those of the reflex of biological caution—P.A.] are: immobility of the entire body together with continuing activity of the receptors and movement of the head [Pavlov, 1949c, p. 587].

As can be seen in this description of the reflex of biological caution, the ability of the motor analyzer is fully characterized which we also encountered in the experiments involving the dissociation between the secretory and the motor components of an integrated conditioned reaction.

Elsewhere, speaking directly of the selective spread of inhibition over the cerebral cortex, Pavlov wrote:

As for the extent of inhibition, one observes functional fractionation and dissociation of both the cortex and the rest of the brain into larger or smaller segments. Especially in the cortex, the motor region is often isolated from the remaining part of the

hemispheres, and a functional dissociation within the motor region itself is also quite clearly revealed [italics—P.A.] (Pavlov, 1933b, see Pavlov, 1951b, p. 200).

This statement clearly emphasizes how fractional can be the inhibition of the individual components of the always complex conditioned reaction.

However, the question arises: could there be such a minute functional fractionation of the motor analyzer of the cerebral cortex if the inhibition arose *directly* in the cortical analyzer of the given conditioned stimulus, e.g., in the cells of the auditory analyzer that correspond to the tone "do"? At this time we do not see any way to provide a physiological explanation of such a fractional localization of conditioned inhibition.

We know from the great wealth of experience of Pavlov's laboratory that in almost all cases of the effect of external inhibition, the *sudden* effect of certain external or internal agents on the animal is involved. Because of the "novelty" of these agents, they evoke a pronounced orienting-investigative reaction. The excitation from this reaction is, in the final analysis, that "inhibitory excitation" which causes the appearance of the process of inhibition both in the subcortex and in the cortical representation of the alimentary center, i.e., which inhibits the existing alimentary activity of the animal by the mechanism already familiar to us.

In discussing the origin of external inhibition in his third lecture, Pavlov stated the conditions of its appearance as follows:

Any such new stimulus immediately leads to the appearance of an investigative reflex, i.e., the appropriate receptor is turned towards the new stimulus, the dog listens, looks, and sniffs attentively, and this investigative reflex inhibits the conditioned reflex . . . all cases of external inhibition . . . are characterized . . . by the fact that as soon as another, extraneous nervous activity appears in the central nervous system, it immediately makes itself known by the decrease or disappearance of the conditioned reflexes . . . [italics—P.A.] (Pavlov, 1927, see Pavlov, 1947, pp. 52, 55).

These quotations of Pavlov reveal one essential point: in his evaluation of competing activities, he speaks consistently of the inhibitory action of the *investigative reflex that has already developed in all of its components*. I would like to call special attention to the fact that this is in accordance with the schemes of the origin of internal inhibition presented above.

Proceeding from the principle of the functional system, we can also formulate the difference between internal and external inhibition. Internal inhibition always results from discordance in the action acceptor, since *nonreinforcement* is a necessary condition in this case.

In the case of external inhibition, however, the inhibitory excitation from an extraneous activity may interfere with any phase in the development of the mechanisms of the functional system of a conditioned reflex. Moreover, external inhibition sets in immediately at the time of action of the inhibitory excitation. Internal inhibition, on the other hand, develops gradually after the second and third nonreinforcement as a

result of the patterning of a new action acceptor, which corresponds to the state of dissatisfaction. The conditioned stimulus then becomes the signal of this dissatisfaction.

By looking at the fundamental scheme proposed above (see Figs. 15.3 and 15.4) for explaining the origin of all types of internal inhibition, one can see that the "inhibitory excitation" from the orienting-investigative reaction inhibits the current activity of the cortical representation of salivary secretion *by the same fundamental physiological mechanisms* as does the "inhibitory excitation" from the negative reaction of the animal evoked by nonreinforcement with food in internal inhibition.

This completes our arguments concerning the origin and localization of all types of cortical inhibition, both external and internal, in all its modifications. In the final analysis they all are *a result of the action of a stronger excitation from another, nonalimentary reaction on the cortical representation of salivary secretion, although the conditions for the onset of these other reactions may differ in their most diverse details*. This was clearly shown in the three comparative schemes for extinction, differentiation, and conditioned inhibition.

The only difference is that in all types of conditioned inhibition the "extraneous activity" results from discordance and is initially an *orienting-investigative* reaction and afterwards a *biologically negative* reaction, while in all cases of external inhibition it is any other, *nonalimentary* activity. This other activity may be an orienting-investigative reaction, a nociceptive reaction, an aggressive reaction, a sexual reaction, etc.

Structurally, both types of inhibition result from the inhibitory effect of some stronger, new activity of the organism on an existing conditioned activity of the cerebral cortex. By their intimate nature they can be caused by either pessimal, i.e., depolarizational, inhibition, which develops in the cortical and subcortical apparatuses, or by hyperpolarizational inhibition.

The question remains: when is this actual "inhibition" of an activity brought about by *constitutional* inhibition that develops at specific postsynaptic membranes by means of Renshaw cells, and when is it brought about by pessimal (Vvedenskii) inhibition? It is quite possible that the latter kind of inhibition, too, is brought about by the incorporation of internuncial inhibitory neurons having a high threshold of excitability.

In summarizing all that has been said on the general physiological architecture of the conditioned reaction as an integrated activity of the organism in relation to the localization of conditioned inhibition in the cortical cell structures, we can state the following conclusions:

1. The basic unit of activity which adapts the organism at a given moment is the functional system (see Chapter 3). The organism continuously changes its activities; consequently, *any form of inhibition is a means of eliminating superfluous activities from the organism* in accordance with the exclusion principle.
2. Conditioned inhibition can occur only when the conditioned reaction subject to inhibition (or its components subject to inhibition) *has already been patterned*. In the absence of a conditioned reaction, there is naturally no physiological basis for the implementation of an inhibitory action of a stronger, i.e., dominant, nervous activity. Inhibition of a conditioned reaction is possible in the stage of incomplete afferent synthesis as well.
3. The systemic approach to the explanation of internal inhibition is inevitably based

on interpreting the nonreinforcement with food to be *discordance*. In all cases, this inhibition is the result of an already established conditioned reaction. Therefore, internal inhibition might be based on conflict, at least after the second presentation of the stimulus being extinguished.

As is evident from the data presented, the stage in the development of the conditioned reaction during which the conditioned excitation has reached the *terminal neurons* of the working mechanisms of the given reaction by no means occurs in the zone of patterning of the conditioned reaction. This zone is located before the terminal neurons and constitutes an integrative formation which corresponds to the area of decision making, in which patterning of a quite definite action occurs through the complete inhibition of all the other numerous degrees of freedom. Therefore, the terminal neurons receive impulses which are evoked by the conditioned stimulus and are clearly manifested in the end effect of the entire conditioned reaction. In connection with this, it is unlikely that the conditioned inhibition would be able to act at the level of the terminal neurons, since here the process has been irreversibly patterned.

Possibly only in individual and special cases, which will be referred to below, can the cerebral cortex send its inhibitory impulses to the periphery, selectively inhibiting isolated components of the conditioned reaction.

In the examples of conditioned reactions which were analyzed above, we were dealing with an effector apparatus having the seeds of all components of the *future* conditioned reaction in an integrated form. It is important to note that, in addition to the cerebral cortex, the subcortical structures also actively participate in this stage of the patterning of the conditioned reaction. The extraordinary inertness and the rapidity of the development of certain components of the conditioned reaction, such as the respiratory component, emphasize its heterogeneous qualitative composition.

If we consider that these components may be inhibited either simultaneously, successively, or in various combinations, it will become quite obvious that, as applied to the origin of conditioned inhibition, the concept of "localization" must assume some kind of different, "systemic" meaning. I would assert that in the further search for the "localization" of conditioned inhibition, the study of the architecture of the conditioned reaction and its patterning must be given priority. Only by a thorough study will it be possible to determine the actual place of the hypothetical "foci of inhibition" in the integrated adaptive act.

Special attention must be given to the commonly used concept of the "cortical representation of the unconditioned reflex." Can any newly developed integrated activity of the organism, causing a strong excitation in a specific cortical area, exert an inhibitory effect on the "cortical representation of the unconditioned reflex"? After demonstrating the inadequacy of the concept of the localization of inhibition in the cortical area of the analyzer, beginning with 1932 we adhered to this point of view. At that time we had no other bases for explaining the mechanisms of the patterning of the conditioned reaction as a whole, and therefore used the "cortical representation of the unconditioned reflex" as a possible formation in which conditioned inhibition may arise. I must admit, however, that we did not have any especially convincing reasons and physiological premises for doing so. Essentially, the only justification for

this new point of view was merely the impossibility of maintaining the former and generally accepted point of view concerning the localization of conditioned inhibition, as it did not agree with experimental data.

On the basis of their own original experiments, a number of other authors (Korotkin, Khodorov, and others) have subsequently also accepted our point of view.

However, our current concepts of the mechanisms of the *patterning* of the integrated conditioned reaction suggest that our previous point of view can no longer be accepted without some reservations. Even less convincing are the claims that conditioned inhibition is localized somewhere between the analyzer and the "cortical representation of the unconditioned reflex" (Asratian, 1955). As a matter of fact, there are no physiological reasons for such an assertion, and it is even doubtful whether there could be any if the characteristics of the above-discussed architecture of the conditioned reaction itself are taken into consideration (see Chapter 4).

It is quite evident that all our concepts of the localization of conditioned inhibition directly rely on our understanding of the physiological and morphological nature of the "cortical representation of the unconditioned reflex." Strange as it may seem, we have not discussed this representation with regard to its place in the system of the integrated conditioned reaction.

Using Pavlov's initial ideas concerning this problem, one must conceive of the "representation" of any organs, tissues, and functions in the cortex as an *afferent* formation. This means that it must necessarily participate in the afferent synthesis of all the impulses arriving from the periphery during the action of the unconditioned stimulus. This is what determines the decisive role of the unconditioned stimulus as reverse afferentation in the establishment of the action acceptor. Consequently, the *afferent* nature of the representation of the unconditioned stimulus in the cerebral cortex determines also its role in the establishment of a new afferent mechanism of the conditioned reflex, which, as we have seen, is absolutely essential for modifying the reflex action according to the results.

This concept of Pavlov concerning the cortical representation of the unconditioned stimulus completely agrees with his views regarding the cerebral cortex as an "isolated afferent section" of the central nervous system. This, of course, does not mean that the cortex is completely without an efferent function, as certain investigators believe. There are neural elements in the cortex responsible for the firing of integrated series of impulses to the working centers, but this by no means contradicts the idea that the cerebral cortex functions principally as an afferent organ.

As we have seen, the role of afferent synthesis in the cerebral cortex consists in determining what type of reflex act must be patterned at a given moment, according to the most diverse afferent signals from the external and internal receptors. The actual response, however, must be patterned subsequent to the afferent synthesis, both spatially and temporally.

The problems concerning the localization of the inhibitory processes which impede the development of the conditioned reflex can be analyzed on the basis of the general fundamental architecture of the conditioned reflex. As is evident from Fig. 6.18, the cortical representation of the unconditioned stimulus may be spatially united with

other afferent signals in the "zone of afferent synthesis." At this stage in the patterning of the conditioned reaction, i.e., during afferent synthesis, the efferent mechanism of the conditioned reaction has not yet received any organized excitations; therefore, the patterning of the conditioned reaction with regard to the composition and distribution of its effectors has not yet begun.

Probably many aspects of the conditioned reaction are still not considered in Fig. 6.18. However, with respect to the present problems concerning the localization of conditioned inhibition, this scheme undoubtedly clarifies *precisely what we cannot accept in the existing concept of localization and what we have yet to investigate in order to solve this difficult problem.*

At present it is important that through this composite diagram of the conditioned reflex, we can further examine those questions which had remained unanswered in the preceding chapters, particularly the question *of the development of internal inhibition in two stages.* At what point of this scheme, or rather, at what stage in the development of the conditioned reflex is it possible to intervene so that it cannot be patterned? In other words, *in what part of the physiological architecture can the inhibitory excitation of a stronger activity interfere with the patterning of the conditioned reaction, i.e., inhibit it?*

The physiological architecture of the conditioned reaction lends itself to interference in the patterning of the reaction at several crucial points in its development. First of all, the inhibitory excitation can interfere with the afferent synthesis, thus making impossible the patterning of the efferent mechanism of the conditioned reaction. If, however, the afferent synthesis has already been completed, the intervention of inhibitory excitations during the span of time that elapses between the moment of completing the afferent synthesis and decision making (the moment of patterning of the efferent part of the reaction) may also interfere with the appearance of both the conditioned reflex as a whole and any one of its individual components.

From a comparison of these two possibilities of inhibitory action on a current conditioned reflex activity, it is evident that each one of them is fundamentally possible. Actually, inhibition can probably set in during both of these stages, and yet to the experimenter, who usually records the end effect of inhibition, *the absence of some indicator*, this fine distinction between stages is not apparent.

A careful study of the experimental material from both Pavlov's laboratory and the laboratories of his students will disclose many examples of different types of inhibitory action of extraneous excitation depending on the stage of patterning of the conditioned reaction.

It has been known for some time that it is by no means irrelevant during what stage of the patterning of a conditioned reaction the external inhibition occurred. If the new stimulus has acted shortly before the *beginning* of the action of the conditioned stimulus, there will be one kind of inhibitory effect, since the orienting reaction as an inhibitory system is dominant by the time of presentation of the conditioned stimulus. If, however, the new stimulus acts during the stage in which the conditioned salivary secretion has already started, i.e., when the conditioned reaction as an integrated act has already been patterned on its efferent pathways, the interrelation of the processes will be reversed and, consequently, the final inhibitory effect will also be different.

In the former case, the suddenly acting new stimulus has produced an orienting-investigative reaction before the afferent synthesis evoked by the conditioned stimulus has occurred. In the latter case, the stage of both the afferent synthesis and the patterning of the efferent complex of the given conditioned reaction has passed. Thus, the new stimulus must enter some kind of relationship with the already present alimentary dominant. It is clear that the final resultant in this latter case will depend on the interrelations of the strengths of the orienting reaction and the alimentary dominant.

Interrelations of this kind were repeatedly studied in our laboratory. We made use of the special features of our secretory-motor method with bilateral feeding and systematically evoked the collision of two positive conditioned motor reflexes.

As was established during the early experiments, the *simultaneous* presentation of two conditioned stimuli which signalize feeding from opposite feeders creates specific interrelations in the cerebral cortex. Since each one of the stimuli was reinforced by the same amount of bread crumbs, the signal meaning of the stimuli was identical. Consequently, in the simultaneous stimulation, only the characteristic feature of the conditioned stimulus itself could be apparent.

It was found that in any pair of conditioned stimuli, the bell is the first to pattern its appropriate conditioned reaction (movement to the feeder). If a bell and light are presented simultaneously, the animal, as a rule, runs to the side signaled by the bell and not by the light, which had been reinforced from the opposite feeder. This predominant reaction to the bell is maintained even when the bell is reinforced with bread crumbs and the light *with meat*. Consequently, the signal meaning of the conditioned stimulus (light) is less effective than the signal meaning of the bell, which again patterns the secretory-motor reaction appropriate for it prior to the light.

The first explanation of this phenomenon was based on the different degrees of corticalization of the visual and the auditory stimuli. To the extent that the auditory stimuli are considerably less corticalized than the visual ones, it could be expected that the two stimuli, the bell and the light, *simultaneously* beginning to spread over the central nervous system, i.e., the subcortical mechanisms, then have a different fate: the light, having the maximal corticalization, patterns the reaction appropriate for it only by way of the cortex, while the bell patterns its appropriate reaction *already at the level of the subcortical mechanisms*. This can explain why the conditioned reaction to it appears so rapidly. The very same thing, probably, explains also the previously discussed phenomenon of the "first second" in the patterning of the conditioned motor reaction, since it appears mainly in response to an auditory stimulus.

If the relations between the two simultaneously applied conditioned stimuli in our method turn out precisely as assumed above, then we have a very convenient model for the physiological characterization of the different stages of the patterning of the conditioned reaction.

The experiments were set up in such a way that the visual stimulus in the pair increasingly preceded the bell until its own reaction began to be patterned in response to it before the bell would go into action. In this way we endeavored to apply the bell after the impulses from the visual conditioned stimulus emerged onto the efferent

pathways. The experiments have shown that this procedure is extremely important to discern the stages in the patterning of the conditioned reaction.

If the conditioned reaction to light has already been completely patterned, i.e., if the animal has run to the appropriate side and conditioned salivary secretion has begun, the bell does not so easily interrupt the effect of the light, and evokes only with difficulty and with great delay the appropriate conditioned reaction (Anokhin and Strezh, 1934; Zachiniaeva, 1949).

Never, at the beginning of the elaboration of internal inhibition, could the biologically negative reaction set in before the presentation of the conditioned stimulus, before the moment of afferent synthesis, or during the patterning of the efferent component of the conditioned reflex. Internal inhibition *arises only as a result of the nonreinforcement with food of a conditioned reaction that has already established and manifested all of its components*. In other words, in this case in response to the action of the conditioned alimentary stimulus, the afferent synthesis is fully completed, the efferent component of the conditioned reaction is being patterned, and finally all its peripheral components are manifested. Only on this background does the new stimulus, the nonreinforcement with food, act, subsequently patterning the biologically negative reaction. Later on, when the biologically negative reaction becomes the dominant negative reaction of the animal as a result of a number of nonreinforcements with food, any subsequent presentation of the conditioned stimulus inevitably occurs on the background of the preexisting negative state of the animal. This is precisely that stage of conflict in the development of internal inhibition which we analyzed in detail in previous chapters.

With this general scheme of development of the conditioned reflex, we can ask: at what point in this cyclic process will the inhibitory influence from the other, stronger activity be first exerted?

The experience of our laboratory convinces us that where conditions for the nonreinforcement of a well-established conditioned reaction have arisen, its switching or gradual inhibition begins always *at the end of the action of the conditioned stimulus*, which is precisely that moment when there appears for the first time a disruption of the cyclic structure of the conditioned stimulus, i.e., a discordance between the reverse afferentation and the action acceptor (Anokhin and Artem'ev, 1949).

Figure 16.6 is a diagram of the course of the switching of the conditioned motor reflex, constructed on the basis of a number of experiments performed in our laboratory. As can be seen, the first indications of a switching of the initial relations, i.e., an inhibition of the former system of excitations, appear at the end of the isolated action of the conditioned stimulus. In connection with this it is important to remember that by the given moment the efferent component of the conditioned reaction is completely patterned.

In addition it is known that during the extinction of a conditioned reflex, just as during the elaboration of all types of internal inhibition, the secretory effect in response to the inhibitory stimulus may be present for a long time after the beginning of nonreinforcement. This secretory effect, regardless of its magnitude, indicates a certain residual alimentary excitation and, most importantly, *the arrival of impulses at the effector components of the conditioned reaction*.

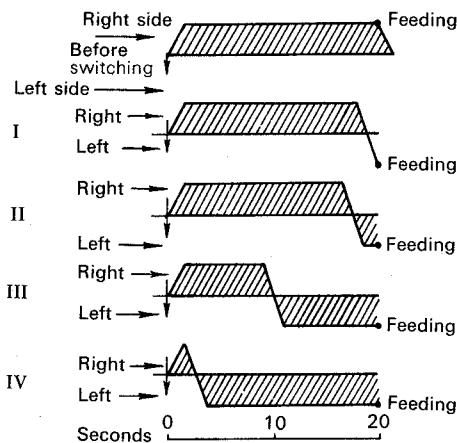


FIG. 16.6 Switching of conditioned motor reflex, formerly reinforced on the right. The diagram shows that the switching of the conditioned reflex begins with the moment of reinforcement.

Recording the respiratory component of the conditioned reaction throughout the entire elaboration of conditioned inhibition proves that the vigorous respiration characteristic of conflicting interactions of the biologically negative reaction and the positive alimentary reaction sometimes appears also during the second phase of extinction *only if conditioned salivary secretion has appeared*.

These observations support the assumption that the first conflicting interactions of the positive alimentary reaction being extinguished and the continuously intensifying biologically negative reaction occur in the area of the patterning of the efferent component of the conditioned alimentary reaction. At this stage of the elaboration of internal inhibition, the conditioned stimulus being extinguished patterns as before the afferent synthesis specific for the conditioned alimentary reaction.

It seems that the moment at which a state of conflict can no longer be detected from the respiratory and the secretory components of the conditioned reaction corresponds to that stage in the development of internal inhibition when the stimulus being extinguished or the differentiating stimulus immediately patterns the afferent synthesis of its specific negative reaction. This, indeed, is the conflict-free, "economical" stage in the development of internal inhibition, whose explanation we have postponed until this chapter.

Thus, the above-analyzed material and considerations make it possible to explain to a certain degree the existence of two stages in the development of extinctive inhibition, as had been proposed in the chapter on the mechanisms of the origin of internal inhibition (Chapter 12).

Briefly summarizing our views on this, we can propose the following for discussion:

Any conditioned reaction can be patterned as an integrated act only after an appropriate integration of the entirety of external and internal stimuli (situational

stimuli, motivation or the unconditioned reflex, attitudinal drive, triggering stimulation in the form of the conditioned stimulus, memory, etc.).

According to the cyclic architecture of the conditioned reflex the inhibitory action of any other stronger activity of the organism on it can in principle be exerted during the two main stages of its development: during the stage of afferent synthesis and the stage of the patterning of the efferent component of the conditioned reflex.

Experimental evidence strongly indicates that any well-established conditioned reaction begins to be switched at the end of the conditioned reflex action, when its efferent component has already been completely patterned. This, from our point of view, is the first stage of conflict involved in the patterning of internal inhibition.

In the second and later form of inhibition of the conditioned reflex in the elaboration of specifically internal inhibition, the afferent synthesis, essential for the patterning of the efferent mechanism of the reaction, becomes incomplete or is entirely changed. This form of inhibition of the conditioned reflex *is not of a conflicting nature*, since a new action acceptor has already been patterned for which nonreinforcement is an appropriate reverse afferentation. Characterizing this second stage of development of internal inhibition is the absence of major changes in the vegetative components of the conditioned reaction. Evidently, this "economical" stage completes the acquisition of any inhibitory experience.

All the material presented above represents the most acceptable postulate concerning the mechanisms of the development of internal inhibition in two stages. Since this postulate agrees most fully with a number of experimental results, it should be regarded as a point of departure for further investigations.

CHAPTER 17

The Inhibitory Effect of the Cerebral Cortex on Subcortical Activity

UNTIL now we have been examining those forms of internal inhibition which had been well studied by Pavlov and his students. One more very important form of cortical inhibition was justifiably called "higher inhibition" by Pavlov: *the inhibitory effect of the cerebral cortex on subcortical activity*. To a considerable degree, the mechanism of the origin and the localization of this form of inhibition are interpreted on the basis of the characteristics of extinction, differentiation, and other kinds of internal inhibition.

This inhibitory effect of the cortex on the subcortex is one of the most obvious adaptations of higher animals and especially man to the environment. Pavlov had fully defined its physiological meaning. Inhibition of this kind either *entirely eliminates* any complexes of cortical and subcortical activity which are inappropriate to the environment or *corrects* this activity so that it precisely adapts to the new conditions.

This inhibition is intended to correct all the primitive, and even purely animal, impulses of man in accordance with his social environment. The role of higher inhibition is enormous, especially in the upbringing of a child, which upon birth has only biological needs, while subsequently under the influence of the environment it becomes a social being by the gradual suppression of its original inclinations. This form of inhibition provides man with the greatest possibilities of governing his passions and inclinations in accord with high social motives.

Pavlov described the complex inhibitory influences of the cerebral cortex on the subcortical functions in the following way:

Does not the development of our personality consist in the fact that under the influence of education and religious, social and civic requirements, we gradually learn to inhibit, to repress that which is prohibited by the factors just mentioned? . . . Do we not constantly encounter the fact that in fits of passion, *which overcome the cortical inhibition*, men speak and act in a manner which they regard as inadmissible when they are calm? And do they not bitterly regret such behaviour when the fit of passion recedes? [italics—P.A.] (Pavlov, 1933b; see Pavlov, 1957, p. 539).

These sentences reflect man's entire age-old struggle with his biological passions and motives. They express the true struggle of man for the right to be called man.

The distinguishing feature of this "higher inhibition" is that it originates on the basis

of somewhat different physiological mechanisms than do all the previously discussed types of internal inhibition. Elucidating the physiological characteristics of this particular type of inhibition will considerably clarify the characteristics of its establishment in man. Therefore, special attention must be given to this type of inhibition.

Fundamentally, the origin of higher inhibition is the same as in the previously discussed types of cortical inhibition: it sets in as a result of the dominance of the excitations of a stronger activity. In accordance with the architectural characteristics of the interrelation of the cortex and the subcortical structures, however, this dominance must, in our opinion, be established in a somewhat different localization.

It has been shown that all the other analyzed types of internal inhibition are basically localized at the level of the cerebral cortex, or more precisely, in that zone of the development of the conditioned reaction in which it is patterned as a whole with all its effector components. The inhibition of *subcortical activity by the cortex*, however, obviously cannot proceed by this mechanism, since we know from everyday laboratory results that a more or less extensive inhibition of the cerebral cortex *releases*, i.e., disinhibits, the subcortical activities. Consequently, the study of the mechanisms of this form of inhibition confronts us with a more general problem of the theory of higher nervous activity, namely, with the problem of the *interrelation of the cortex and the subcortex*.

In order to clearly see the path of the further study of this highly important problem, we shall start first of all with a presentation of Pavlov's concepts regarding this form of higher inhibition.

In pointing out that the cerebral cortex is capable of inhibiting subcortical "tendencies," Pavlov emphasized especially the inhibition by the cortex of all that pertains to the complex unconditioned reflexes of the subcortex (the "emotional reserve"). Since he developed this view in a number of his public and laboratory statements, the inhibition of subcortical activities by the cortex has become one of the most common principles in the physiology and pathology of higher nervous activity.

Characterizing the inhibitory function of the cortex with respect to the subcortex, Pavlov said:

Usually the cerebral hemispheres . . . always exert influence on the adjacent parts of the brain with their instinct and reflex activity. . . . the alert, active state of the cerebral hemispheres, manifested in the unceasing analysis and synthesis of external stimuli, of the influences of the surrounding medium, negatively induces the subcortex, i.e., inhibits its activity as a whole, liberating in a selective way only the activity needed by conditions of place and time [Pavlov, 1933b, see Pavlov, 1957, pp. 526-527].

Thus, in Pavlov's opinion this inhibitory or "moderating" influence of the cortex on the subcortical mechanisms is of an active nature, i.e., it is connected with an *increased positive* activity of the cortical neural elements, and ceases as soon as this active cortical activity becomes weaker for any reason. For example, in analyzing the case of a man becoming drunk, the falling asleep of children, etc., Pavlov explains the accompanying bursts of excitation by the fact that

... the neighbouring subcortex is ... freed from its usual control, *the constant inhibition from the hemispheres during the waking state* ... [italics—P.A.] [Pavlov, 1930b, see Pavlov, 1963, p. 41].

But emotionality is the predominance of a flood of very complicated unconditioned reflexes (aggressive; passive-defensive, and other functions of the subcortical centres) with weakening of the cortical control [Pavlov, 1928, see Pavlov, 1967, p. 378].

... the elimination or weakening of the activity of the cerebral hemispheres must necessarily lead to a more or less chaotic activity of the subcortex devoid of the right measure and of adequacy to the given surroundings [Pavlov, 1933b, see Pavlov, 1957, p. 526].

From all the cited statements of Pavlov, it clearly follows that in the waking state the cerebral cortex always *inhibits* the subcortical activities to some extent. But as soon as the activity of the cortex weakens, i.e., begins to be inhibited, the previously inhibited subcortical functions are released and become chaotic.

There can be no doubt about the validity of these postulates, which have defined the basic forms of interaction of the cortex and the adjacent subcortical structures. On the basis of these postulates of Pavlov, we must proceed with the study of the physiological nature of higher inhibition.

Upon summarizing all of Pavlov's statements concerning this problem, the control of the cerebral cortex over the subcortex can be expressed in three basic forms:

1. The *direct inhibitory effect of the cortex on the subcortex*.
2. The *inhibition of subcortical activity according to the law of negative induction from the cortex*.
3. The *excitation of subcortical structures by the cerebral cortex*.

As presented in this list, the forms of interaction of the cortex and the subcortex occur in one direction only—from the cortex to the subcortex. But these interactions also occur in the opposite direction of course, i.e., from the subcortex to the cerebral cortex. This second direction, however, has considerably different effects. As Pavlov expresses it, the subcortex provides the "blind force" for the cortical activity. He spoke more concretely about this "blind force" when he characterized the role of emotional states: "The main impetus for cortical activity comes from the subcortex. If these emotions are eliminated, the cortex is deprived of its main source of strength" (Pavlov, 1949b, p. 268).

If to this description of the subcortical effect on the cerebral cortex one adds as well Pavlov's repeated statements concerning the *inertness* of the subcortical processes, the general nature of these interactions becomes apparent: *the subcortical structures determine the energy level and the strength of manifestation of the cortical nervous processes*. They fulfill this role, according to Pavlov, by means of the "blind force," i.e., generalized volleys of impulses to the entire cerebral cortex as a whole. As we shall see below, these statements of Pavlov anticipated by many years the special investigations on the physiological role of the reticular formation of the brain stem which were performed by means of modern electroencephalographic techniques.

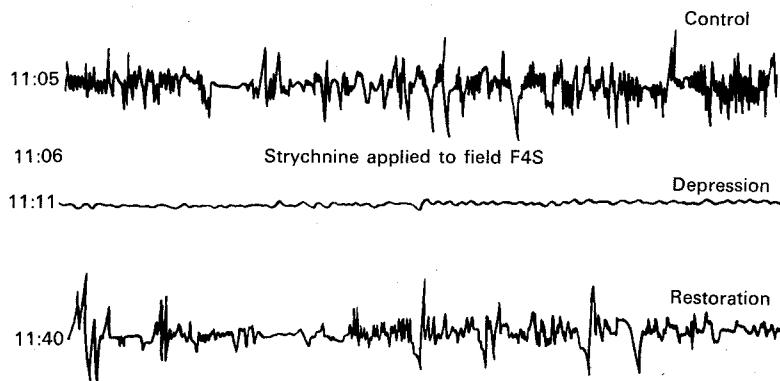


FIG. 17.1. Electroencephalographic demonstration of intracortical interrelations (neuronography). The inhibiting action of strychnine applied to the F4S zone is shown. All oscillograms were taken from field A4.

The entire characterization of the cortico-subcortical interactions elucidated above quite naturally presented us with the question: on which neural substrate do these interactions develop, by means of what specific pathways do these functional influences in either direction occur?

Modern morphological investigations of the nervous system and especially of the intracentral connections have benefited from a number of new, extraordinarily delicate methods making it possible to establish rather definite structural connections even between very remote regions of the central nervous system.

First of all I should point out the so-called *neuronographic* method. A small piece of filter paper moistened with a strychnine solution is applied to some point of the cerebral cortex. By exciting the neural elements under the paper, the strychnine produces rhythmic discharges in them, which sometimes are grouped into short volleys of high frequency (Fig. 17.1). The interest of this method, named "physiological neuronography" by Dusser de Barenne *et al.* (1941), is the observance of discharges of the spike type not only at the point stimulated with strychnine (Fig. 17.2), but also at very remote sites of the cerebral cortex (Dusser de Barenne, 1933; Dusser de Barenne *et al.*, 1941). Some neurophysiological problems pertaining to this method, called "epoch-making" by McCulloch, have not yet been solved. For example, it is still uncertain

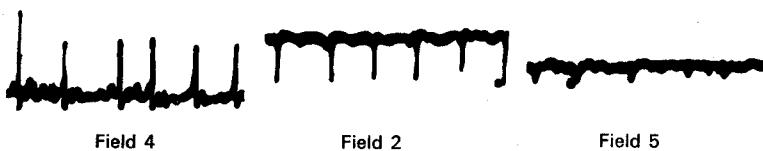


FIG. 17.2. Demonstration of selective intracortical connections by the neuronographic method. In spite of the fact that field 2 and field 5 are near each other, the application of strychnine to field 4 produces potential flashes only in field 2 and not in field 5.

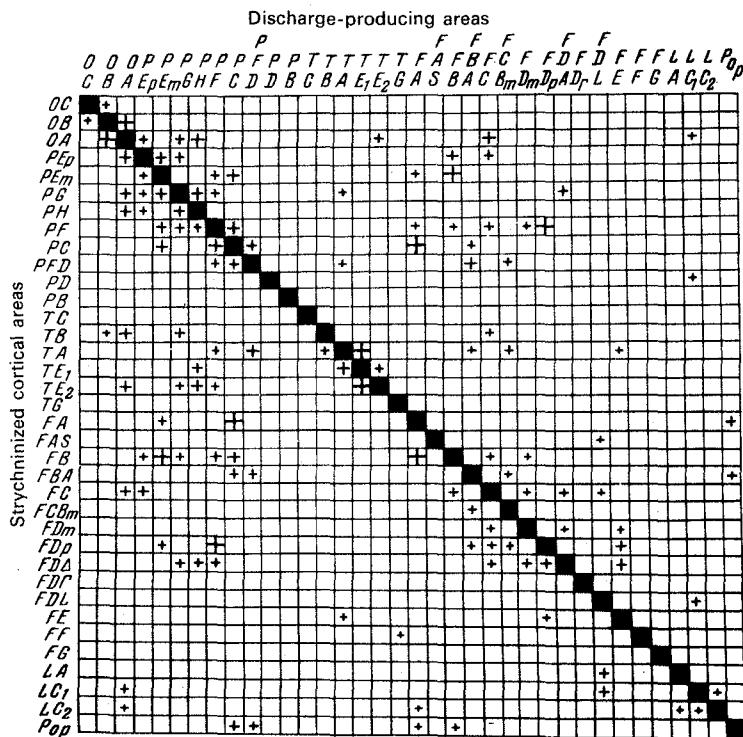


FIG. 17.3. Overall diagram of the interrelations between different zones of the cerebral cortex that were studied by the neuronographic method. The horizontal axis gives the regions in which flashes of excitation were detected. The vertical axis records the cortical zones to which pieces of paper moistened with strychnine had been applied. From Bailey *et al.* (1950).

whether the remote spike arises in the nerve cell receiving the primary strychnine discharge, or whether these remote discharges originate in the axons. It also remains undetermined whether the primary strychnine discharge passes through several synaptic relays before it can be detected, or whether it propagates over one axon.

Despite the lack of certainty concerning these problems, however, *the possibility of establishing a preferential functional connection between specific points of the central nervous system remains*.

This possibility served as the basis for the very extensive application of the method of physiological neuronography in the last few decades. Maps of the intracortical connections in a number of animals, especially in the chimpanzee (Bailey *et al.*, 1950), have been drawn in great detail, as indicated by the diagram in Fig. 17.3.

Dozens of investigations were also performed by this same method for determining the cortico-subcortical interrelations. In this case the authors proceeded in two ways. In some cases a piece of paper moistened with strychnine was applied to some point of the cerebral cortex, and the subcortical regions were "searched" oscillographically

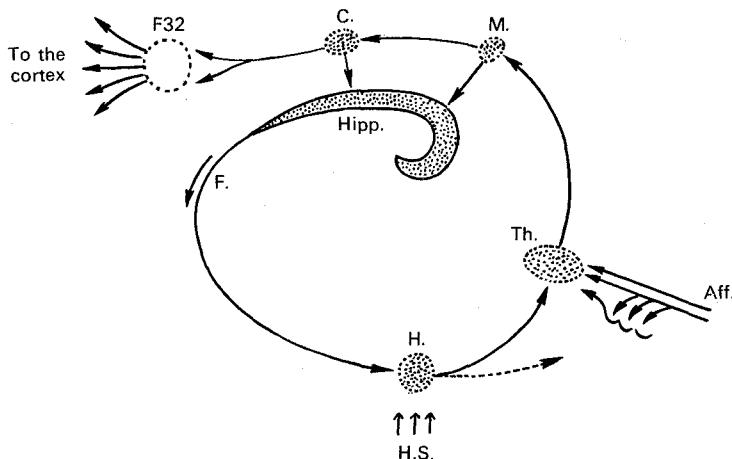


FIG. 17.4. Diagram of interrelations between cortex and subcortex, constructed by the author after Le Gros Clark and others. Th., thalamus; Aff., arrival of afferent impulses from the periphery over the lemniscal system; H., hypothalamus; H.S., humoral stimulations of its centers; F., fornix; Hipp., hippocampus; C., gyrus cinguli; M., marginal gyrus; F32, field 32. Since this circulation of impulses passes through the hippocampus, the entire cycle has been given this designation.

for spikes. At other times the reverse procedure was followed: a microinjection of strychnine was made into some point of the thalamus or hypothalamus, and a "search" was made over the entire surface of the cerebral cortex. When spikes were found in either case, the corresponding functional correlation was determined. As a result of a number of such investigations, maps of the cortico-subcortical interrelations were gradually created.

Especially significant investigations were carried out for determining the connections between the so-called visceral cortex (g. orbitalis, area limbica, etc.) and the hypothalamus. Exemplifying these correlations is the diagram in Fig. 17.4 of the interrelations of the cerebral cortex and the hypothalamus. In recent years, correlational diagrams of this kind have been appearing with such increasing frequency that we can now determine with sufficient reliability the substrate by means of which the predominant interrelations of the cortex and subcortex are established.

Let us try to characterize the structural basis of these interrelations. First it must be pointed out that both morphologists and physiologists were surprised by some unexpected data.

According to the generally held view, the hypothalamus is the organ of the primary regulation of the vegetative processes of the body and especially of the metabolic processes. In this respect the hypothalamus must rightfully be recognized, phylogenetically, as the most ancient formation. At the same time, our knowledge of the evolution of the cortical regions convinces us with equal certainty that the frontal lobes of the cerebral cortex are the most recent formations. What was amazing is that the frontal cortex, which developed last, is connected by an abundance of conducting pathways with the most ancient part of the brain, the hypothalamus. There is no doubt that

these morphological findings are of enormous physiological significance, which, however, has not yet been fully revealed.

The connections from the hypothalamus to the cerebral cortex are presently believed by most investigators to go through two thalamic nuclear formations—the nucleus ventralis and the nucleus dorsomedialis.

The ventral nucleus. It is known that the nucleus ventralis is connected primarily with the limbic cortex and, probably, is a kind of relay point (more correctly, junction) for the impulses coming from the mammillary bodies of the hypothalamus. Consequently, one of the main lines over which the hypothalamus can functionally influence the cerebral cortex is the corpora mammillaria—nucleus ventralis—area limbica line.

This chain, however, is not limited to these three links. From the area limbica the subcortical impulses can propagate further over two different pathways.

One possibility is the propagation of impulses over the cerebral cortex. Particular attention should here be given to the gyrus cinguli, which is connected by efferent fibres with the mysterious field 32. This field has the ability to suppress very energetically the activity of the other cortical fields and has therefore been named the "suppressing zone" (Le Gros Clark and Meyer, 1950). Meyer and McLardy (1949a, 1949b) indicate that field 32 is an especially important junction at which the cortico-subcortical interactions intersect.

Along with this cortical propagation of hypothalamic activity, there is possible in the region of the limbic cortex a reverse movement of impulses over the following pathway: area limbica—gyrus cinguli—hippocampus—fornix—corpora mammillaria.

Thus, the morphological and neuronographic data indicate that the *subcortical structures* (particularly the hypothalamus) are *in continuous cyclic interaction with the cerebral cortex*, probably constituting one of the substrates of cortico-subcortical integration.

It is of interest to note that this "hippocampal pathway," as it is called, is not closed (see Fig. 17.4). It may be continuously charged with energy from two different sources. On the one hand, in the hypothalamic region it is under the constant excitatory influence of humoral factors, which, by acting on this region whose sensitivity to chemical influences is very high, can thus promote an increase in cortical activity. Owing to the presence of certain connections with the peduncle of the mammillary body, along with the humoral energy basis, this circuit can also be charged by the continuously arriving ascending afferent impulses. It is very likely that the function of "charging" is also partly assumed by the reticular formation of the brain stem.

This cyclic neural formation has, however, one more connection needing a different explanation and probably having a different physiological significance. I am referring to the *direct efferent connection of the premotor field 6 with the mammillary bodies*. What is the function, in this case, of the cortical neuron whose cell body lies in the cortical region having mainly efferent functions by means of the long axons of the pyramidal tract?

One can hardly agree with Le Gros Clark, who contends that these cortical neurons, as well as the other external connections of the closed "Ammon's circle," maintain the excitatory power of this circle.

It seems that the function of this neuron must be exactly the opposite. Being a neuron

that is *highly integrated* with other cortical neurons and zones, it should, according to its anatomical position, fulfill that "moderating" role of the cortex with regard to the subcortex, spoken of so clearly by Pavlov. This assumption seems more reasonable. This is probably the evolutionary basis for the paradoxical connection between the most recent structure (frontal lobes) and the most ancient one (hypothalamus). The cortex had to gradually develop a "moderating" and "correcting" influence on the subcortical mechanisms, since the need for such an influence was arising in complete accordance with the increasing complexity of the conditions of life of higher animals.

In connection with this, it is of interest to note that the above-discussed circulation of impulses through the hippocampal pathway appears only in mammals and becomes more complex as they evolve. As it is not yet present in reptiles, one can hardly ascribe to this pathway any elementary or *only* vegetative functions, as is conceived by Ariëns Kappers (1942). Rather, the hippocampal pathway originates and develops as a coordinative mechanism between the highest functions of the cerebral cortex and those integrated emotional mechanisms which are localized mainly in the subcortical systems. At any rate, the further elucidation of the functional interrelations of the neural structures analyzed above should be an immediate task of the physiologists engaged in the study of higher nervous activity.

The dorsomedial nucleus. This thalamic nucleus is the second junction through which the hypothalamus functionally interacts with the cerebral cortex. The functional significance of this interaction of the hypothalamus with the frontal cortex was fully revealed in recent years in connection with the so-called leukotomy, i.e., the operation of disconnecting certain regions of the cerebral cortex in some mental patients. Morphological examinations of the brain after leukotomy have convincingly shown that the connections of the hypothalamus through the dorsomedial nucleus can be traced up to the orbital cortex and up to the frontal poles (Meyer *et al.*, 1947).

Observations on patients after destruction of part of the dorsomedial nucleus or its connections with the cerebral cortex show personality changes. This pertains especially to changes in the emotional realm, which after some operations is completely transformed (Meyer, 1944).

The actual presence of connections between the hypothalamus and the frontal lobes of the cerebral cortex via the dorsomedial thalamic nucleus had long been assumed on the basis of purely morphological descriptions of these pathways. For a long time, however, there were no direct physiological investigations to substantiate this. This deficiency was partially remedied by the investigations of Murphy and Gellhorn (1945a, 1945b). These authors have shown that upon application of strychnine to the frontal lobes of the cerebral cortex, quite distinct spikes can be obtained in the dorsomedial thalamic nucleus.

As in the case of the previously described interactions of the cortex and the subcortical mechanisms, the interaction via the dorsomedial thalamic nucleus occurs only in mammals and principally in higher mammals. This alone sufficiently emphasizes that the interaction of the cortex and the subcortex of the type described is an element of the higher integration related to the increasing complexity of behavior.

The data presented above convince us that present-day neuromorphology, as well as neurophysiology, can provide us with sufficient grounds to specify more exactly the above-mentioned three possible forms of interaction of the cortex and the subcortex.

We are especially interested at present in those effects of the cerebral cortex on the subcortical functions which could be called *inhibitory*. Unfortunately, all of the authors dealing with this problem, both morphologists and physiologists, had only one form of effect in mind: the *arousal to action* of some subcortical structures. Another, and, for the cortical level, most specific form of effect, the *inhibition of subcortical activity*, was left completely untouched. Such a one-sided approach to the cortico-subcortical interactions was taken because primarily those investigators not accepting the idea of cortical inhibition studied the morphological connections between the cortex and the subcortex. On the other hand, the investigators realizing the physiological significance of the inhibitory effect of the cortex on the subcortical system had never been interested in a study of the morphological substrate responsible for this effect. Thus, the whole problem of a profound physiological understanding of the cortical inhibitory effect on the subcortical systems is at present at the very beginning of its investigation. We must therefore limit ourselves to more or less likely assumptions.

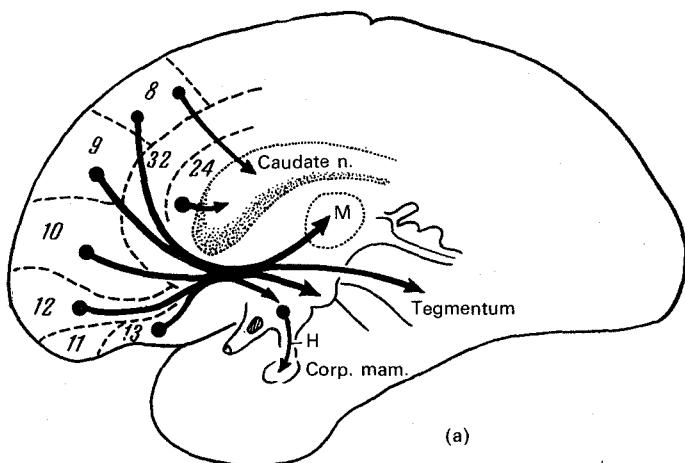
In regard to the efferent influences from the cortex on the hypothalamus, we have the most reliable data. But even here investigators considered their task complete if upon stimulation of certain regions of the cerebral cortex they detected a positive vegetative effect.

Upon strychninization of the orbital cortex, for example (field 13, according to Walker, 1940), or the premotor zone in the monkey (*Macaca mulata*), a quite definite change in the electric potentials in the ventromedial hypothalamic nucleus and in the medial bundle of the prosencephalon can be obtained (Sachs *et al.*, 1949). These physiological data are in complete agreement with the morphological investigations of Le Gros Clark's laboratory, which have demonstrated that after destruction of the posterior part of the orbital cortex or of the premotor zone, a marked degeneration of the fibers in the region of the ventromedial hypothalamic nucleus occurs (Le Gros Clark and Meyer, 1950).

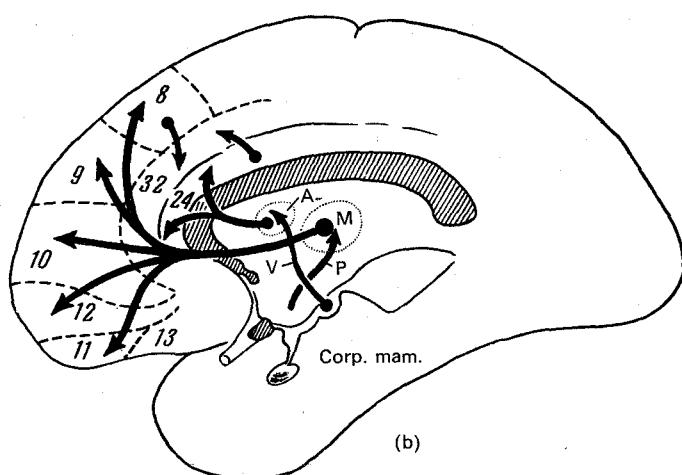
Similar results were also obtained by Hess (1949) and others. Of special interest in this respect are the investigations of Wheatley (1944), who obtained a typical "sham rage" upon destruction of the gray matter in the region of the ventromedial nucleus of the hypothalamus.

Related to these experimental data are the highly interesting morphological investigations of Le Gros Clark on the developing brain of the human fetus. He demonstrated that for a rather long time the nucleus ventromedialis is the only well-developed and differentiated nuclear formation of the hypothalamus and that only subsequently neighboring structures and connections begin to develop. If one adheres to the concept of the selective, heterochronous, and systemic nature of the development of neural structures during ontogenesis (systemogenesis), one can see in this fact the important and early organizing role of this hypothalamic nucleus in the life of the newborn (Le Gros Clark, 1938; Anokhin, 1948b, 1956a).

For a complete picture of the cortico-hypothalamic interrelations it is necessary to



(a)



(b)

FIG. 17.5. Two diagrams illustrating the cortico-subcortical connections that have a direct relation to the inhibiting action of the cerebral cortex on the subcortical formations, especially on the hypothalamus. (a) Frontal-hypothalamic interrelations; (b) hypothalamo-frontal connections. A, nucleus anterior of the optic thalamus; M, nucleus medialis of the optic thalamus; P, tractus periventricularis, connecting the hypothalamic region with the optic thalamus; V, Vicq d'Azyr's bundle, connecting the corpora mammillaria with the optic thalamus; H, conducting pathway, connecting the hypothalamic region with the hypophysis. From Le Gros Clark (1948, pp. 355, 354).

point also to the direct connection of the orbital and frontal cortex with the mammillary bodies.

These connections can be determined both by the method of degeneration and by the method of physiological neuronography. However, the physiological significance

of this rather extensive connection is still unclear because of the lack of special investigations.

All the interactions and connections between the cortex and the subcortical structures discussed above have not been well studied in many respects. It is beyond doubt that they all have a crucial function in uniting the higher associative functions of the brain with their vegetative equivalent through the area of hypothalamic integration. In other words, the structural interrelations analyzed are the material substrate for the formation of the integrated conditioned reaction in all the diversity of its somatic and vegetative components. However, we still cannot state with sufficient certainty the functional role of each of these structural components in the organization of the behavior of the animal.

Proceeding from neurophysiological data, we can, of course, say with some degree of probability that the "hippocampal pathway," over which impulses circulate continuously, determines mainly the tonic activation of the cerebral cortex and the strength and nature of the emotional states for a given moment. The frontal-hypothalamic and frontal-mammillary efferent connections, on the other hand, must be mainly a substrate for *occasional* interventions of cortical activity in the vegetative and emotional realm of animals and man (Fig. 17.5).

The permanent bilateral structural connection represented in Fig. 17.5 is of great importance for the patterning of higher nervous activity.

Let us try to understand the following example. A person in a large crowd is looking for another person who is very important to him. After looking over dozens of faces, he gradually reaches a state of grieved anguish and dissatisfaction, which constitutes a definite complex of emotional experiences with pronounced external (facial expression) and internal (cardiac and respiratory activity) components.

In order for the "search" as a basically cortical function to end in a definite emotional state, it is essential that the negative results of the searching (discordance) be able to signalize about themselves to the subcortical structures that pattern the emotional state. It is clear that this signalization can come about only via the specific neural structures of the cortico-hypothalamic direction. Let us now assume that the person has *found and recognized* the one he was looking for. We can hardly doubt that this occurred by means of cortical conditioned reflex connections. But we see that the person's heretofore sad face now expresses a happy mood and gaiety. Consequently, here again the cortical processes had to influence the hypothalamic region by means of the same or other efferent pathways.

The example given occurs most frequently in our everyday life and consequently confirms once more the important role of the efferent and afferent cortico-subcortical connections in human behavior.

Returning to the problem of the inhibitory effect of the cortex on the subcortical structures, we can assert that all forms of "higher inhibition" about which Pavlov spoke are brought about by the development of extremely strong complexes of inhibitory excitations at the cortical level. These excitations, which are mainly evoked by the conditions of life, are considerably intensified emotionally by means of cortico-hypothalamic reverberation. After this process of afferent synthesis is completed, they

spread over the efferent pathways to the subcortical complexes where they exert their inhibitory effect.

Thus, in this case of "higher inhibition," complexes of very strong cortical excitations are the source of inhibition, while the inhibitory process itself most probably arises in the subcortical structures, i.e., in those neural elements which pattern the behavioral acts inappropriate for the given moment.

Therefore, the answer to the question as to what specific process of the cerebral cortex maintains subcortical activities in a prolonged inhibited state is quite clear. On the basis of the above considerations, we can give only one answer to this question: *undoubtedly, by means of the process of excitation.*

It is, however, essential that this cortical excitation be an "inhibitory excitation" in the true sense, i.e., that it have a considerably greater strength and frequency than the subcortical excitation to be inhibited. Then, upon arriving from the cortex in the subcortical structures, it must collide with the already existing excitation of the subcortical cells and, owing to its strength, i.e., high frequency of impulses and electrotonic action, exert an inhibitory effect on them. *Such a form of cortical inhibitory effect on the subcortical structures is pessimal inhibition.* So that this conception of the inhibitory function of the cortex with respect to the subcortex may become even clearer, we can analyze a specific case of the cortex actively inhibiting any subcortical activity, e.g., the activity of imparting facial expressions.

Let us assume that a person is in a state of highest excitement, but that the *circumstances* do not allow him to show this excitation and that he, often with enormous effort, finally achieves this effect. It may be said about such a person that "not a single muscle moved on his face." An analysis of the structural and physiological basis of such a typical case of the "highest" inhibitory effect of the cortex on facial expression will be of great help in the solution of the problem that interests us.

The nucleus of the facial nerve is the final path for all the complex unconditioned reflex impulses of the subcortical apparatus (the emotions) going to the facial musculature. It is capable of selectively exciting the individual facial muscles and uniting them into complexes, creating a specific facial expression. The variety of human facial expressions makes it apparent how diverse these complexes of impulses of the nucleus of the facial nerve are. From this it follows that the emotional excitation evoked through the cerebral cortex by some external factors ultimately causes the systemic excitation of the neural elements of the subcortical apparatus and must inevitably emerge onto the facial musculature *through the nucleus of the facial nerve.* *The subcortical structures constitute the predominant, if not the only, path for the expression of emotional states in the newborn and in children during the first months of life.*

As was shown by direct investigations performed by our collaborators on human fetuses, the activity of the facial muscles is distinctly expressed even during the sixth month of intrauterine development (Golubeva and Shuleikina, 1957). This facial expression is so definite that it is difficult to be mistaken in the evaluation of its qualitative nature. A 5-month-old fetus is able to frown upon stimulation of the nose with a bristle and to express "unpleasantness" to a comic degree, to "sneeze," to "cry," and somewhat later even to show a transient "smile" (Fig. 17.6).

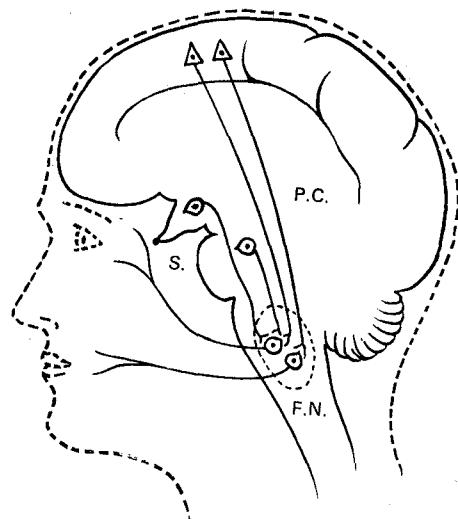


FIG. 17.6. Diagram of inhibiting influences of the cerebral cortex on the nucleus of the facial nerve. The interrelation between subcortical (S.) and cortical influences at the cells of the nucleus of the facial nerve (F.N.) can be seen. P.C., pyramidal control over the nucleus of the facial nerve.

A comparison of these phenomena with the degree of maturation of the neural structures of the brain shows that by this time even in the subcortical apparatus there is only an incipient differentiation of the individual interconnections. In the cortex one can see during this period of development a beginning differentiation of the neuroblastic elements in which the axons are only beginning to grow (Poliakov, 1957).

Consequently, the early movements of the facial musculature of the human fetus are the unquestionable result of systemic subcortical activity, since it can be brought about only by means of the well-known *subcortical* connections of the nucleus of the facial nerve, which structurally develop very early.

Throughout the first years of life, the structural bases for cortical control over the nucleus of the facial nerve gradually begin to mature in the child. This control is represented in the adult by special pyramidal fibers that branch off the capsulae internae in a separate bundle. As is known, the giant pyramidal Betz cells, from which these fibers originate, are located in the central part of the precentral gyrus of the human cerebral cortex. These pyramidal fibers and especially their synaptic connections with the motor cells of the facial nerve in the medulla oblongata, in view of the most delicate differentiation of the interactions between them, mature structurally over a rather lengthy period of time in accordance with the overall growth of the other cortico-subcortical connections of the child.

As soon as these pyramidal connections have sufficiently matured and have become capable of transmitting discrete impulses from the cerebral cortex, the previous subcortical impulses which had been freely emerging onto the periphery and forming the external expression of emotion, immediately begin to enter into interrelations of conflict with these new cortical impulses.

Since a giant pyramidal neuron of the cerebral cortex is subject to a large number of diverse cortical influences, they are all able to exert their effect on the cells of the nucleus of the facial nerve too. From this moment on in human life, the nucleus of the facial nerve and, consequently, the person's facial expression, become a reflection of the complex socially determined life. And the person's facial expression itself begins to appear only as a resultant of two forces: the person's emotional states and the cortical control over these emotional states, which is implemented in a continuous correcting activity from the cerebral cortex both on the cellular elements of the nucleus of the facial nerve and on other effector mechanisms of the emotions.

The very fact of the coincidence of the ontogenetic development of the pyramidal bundle to the nucleus of the facial nerve with the appearance in the child of the ability for "voluntary" control of facial expression is one proof of this proposition.

As is known from direct physiological investigations involving the stimulation of various points of the cortex with strychnine, the pyramidal cells have, as was shown by E. Jalovista (1942), an extremely high maximal frequency of nerve impulses: up to 800/sec! This is such a high frequency that even half of it is enough to inhibit instantaneously, i.e., bring into a pessimal state, any positive activity, if only the pyramidal tract has anatomical access to its neural mechanisms.

I would like to present a case of injury to the facial nerve in patient I., incurred during World War II. It illustrates our propositions concerning the dual subordination of the nucleus of the facial nerve.

A small shell fragment had pierced the left facial nerve proximal to the point of its division into the individual branches innervating the muscles of the forehead, cheeks, and mouth. At the location of the injury a nerve scar formed, and with time the fibers of the facial nerve regenerated up to the facial muscles themselves. The outward appearance of the patient at rest differed in no way from ordinary cases of unilateral paralysis of the facial nerve. Clinical examination revealed the following symptoms, which essentially are of the greatest interest: muscular atony, drooping of the corner of the mouth, etc. If one created some funny situation or exhilarated the patient with something, his smile, as is the case during paralysis of the facial nerve, was always "one-sided." In fact, all his emotional expressions were brought about by means of only one half of the face.

Thus, from the point of view of the above-described symptoms one could immediately give the diagnosis: either complete anatomical interruption of the facial nerve or complete cicatricial block of the conducting function of the facial nerve. As it later turned out, however, this diagnosis was not quite correct. If the patient was asked to voluntarily frown, make a face with the corner of the mouth on the afflicted side, etc., all these movements of the "paralyzed" side of the face were performed flawlessly.

As a result of a number of similar investigations we established that in patient I. there is a sharp distinction between the expression of natural emotions by the facial muscles and voluntary movements by the same muscles. In the former case the impulses arriving at the nucleus of the facial nerve and going out to the periphery are unable to pass through the region of the scar formations in the nerve and are blocked by them, and therefore the corresponding side of the face does not take part in the expression of

emotional states. In the latter case, i.e., during voluntary effort, the impulses of the cerebral cortex travel over the same pathways. However, these *voluntary* cortical impulses prove to be of sufficient strength to break through the region of the block and to emerge onto the effector mechanism—the facial muscles.

What physiological properties of these two kinds of impulses are the basis for this difference in their fate at the periphery? The first kind arises in the region of the subcortical structures and propagates symmetrically for both halves of the face. These impulses bear all the traits of the subcortical standard, the intensity of which is related only to the strength of the given emotional excitation and cannot be prolonged or increased in frequency for any individual facial muscle or for a group of muscles.

This characteristic of the impulses originating during the expression of emotions prevents their passage through the cicatricial zone, which usually creates difficulties for the propagation of efferent impulses.

Entirely different conditions result upon conduction through the cicatricial zone of cortical or voluntary impulses, which enter into the region of the scar formations with a frequency of impulses that can be increased at will. The duration of these series of impulses can be extended until reverse afferentation is received from the cutaneous receptors of the trigeminal nerve, i.e., until there is signalization about the success of the working effect.

This interpretation of the phenomenon of the dissociation of the two functions of the nucleus of the facial nerve eliminates all questions concerning the paradox of the phenomenon itself. At the same time it confirms once more the great importance of the high frequency of the nerve impulses for the cortical inhibition of those impulses originating in the subcortical system simultaneously with the patterning of the emotional discharge.

The physiological evaluation of the inhibitory influences from the cerebral cortex on the subcortical apparatuses would be incomplete if we omitted the role of the reticular formation of the brain stem in these processes. The physiological meaning of the reticular formation remained unknown for a long time. For many years after its initial description (Bekhterev, 1885) it existed in the anatomy of the nervous system as a kind of terra incognita. It was described both as a substrate for diffuse excitations and as a site of trophic functions. All its supposed functions, however, pertained mainly to lower structures—to the medulla oblongata and to the spinal cord. Until recently there existed no definite opinion or data for the evaluation of its effect in the ascending direction, i.e., on the cerebral cortex.

Recent investigations in this field have revealed the broad significance of cortico-subcortical interrelations. It has been proved to be even more difficult than before to separate these two structures, which constitute a truly *integrative whole*.

All the data from the study of the physiological properties of the reticular formation of the brain stem are of interest first of all to the physiologists of higher nervous activity. The problems of sleep and wakefulness, the problems of the irradiation of excitation, etc., all receive a different interpretation in the light of the new data than was the case in Pavlov's school. Therefore, there is needed the setting up of a series of synthetic experiments in which the different propositions existing in physiology could be

compared. This is just what we are undertaking at present. Right now, though, we will be analyzing only those investigations which help one to understand some forms of inhibitory effects of the cerebral cortex on the functions of the subcortex and the lower-lying structures.

It had been shown that in transmitting the influences of the cortex and the cerebellum, the reticular formation of the brain stem can considerably inhibit the motor activity of the spinal cord. Of special interest was the fact that in the region of the brain stem and the medulla oblongata two kinds of descending influences had been demonstrated. One part of the reticular formation always exerts an *inhibitory influence* on the motor elements of the spinal cord, while the other part exerts a *facilitating influence* on the same motor elements. Magoun (1950) indicates that no changes in the parameters of the stimulation being applied (frequency, strength) are capable of changing these effects qualitatively. Each one of the above-mentioned zones of the reticular formation always produced only the effect characteristic for it: either inhibitory or facilitatory. This seemingly does not agree with our concepts of the pessimal effect, which sooner or later should have arisen independently of the special features of the interneuronal formations. In this case, however, inhibition is of a "constitutional," i.e., hyperpolarizational, nature.

The inhibitory and facilitatory influence of the reticular formation on the motoneurons of the spinal cord is anatomically well localized: it occurs in the zone of the internuncial neurons of the spinal cord, which, according to some investigations, are a kind of homolog of the reticular formation of the brain stem.

Undoubtedly the indicated pathway of the elimination of the motor functions of the spinal cord can be one of the mechanisms by means of which the cerebral cortex exerts a regulatory action on the processes of peripheral coordination. Even more amazing data about the inhibitory effect of the reticular formation on the peripheral processes were recently presented by Hagbarth and Kerr (1954). By means of a stereotaxic technique these investigators demonstrated that stimulation of the reticular formation leads to a complete block of the afferent impulses evoked by the stimulation of one of the dorsal roots of the spinal cord.

Serbinenko had also demonstrated at our laboratory, in 1960, that intravenously administered chlorpromazine eliminates reciprocal relations at the level of the spinal cord. This inhibition is due to the release of inhibitory descending influences at the level of the medulla oblongata. It is most likely that Magoun's inhibitory centers, which have been released from the influence of the adrenergic mechanisms of the brain stem, are involved here. It is of interest that this inhibitory effect on the propagation of the afferent impulses over the conducting structures of the spinal cord is completely eliminated by the action of anesthetics.

Upon comparing all data on the propagation of impulses over the cortico-spinal and reticulo-spinal pathways, Lloyd (1944) came to the conclusion that the reticular component of these motor impulses propagating more rapidly than the cortico-spinal impulses, provides the appropriate setting for the latter at the spinal segments.

As is evident, this concept, which arose on the basis of entirely different data, fully confirms our views of the interrelation of the postural and the local impulses in the

conditioned defense reflex. At the same time, Lloyd's findings define more exactly the site of origin of the postural impulses. This can mean that the architecture of the conditioned defense reflex encompasses at the same time both a cortical and a subcortical, i.e., reticular, component.

Although the investigations of the *descending* influence of the reticular formation presented above are of unquestionable interest to us, the investigations of its *ascending* influence, mainly on the cerebral cortex, are more significant.

This influence is manifested primarily in a *generalized influence* on all regions of the cerebral cortex. The reticular formation of the thalamus and the so-called intralaminar nuclei (Jasper, 1949; and others) are probably the intermediate stage for this action. The generalized effect of the reticular formation of the brain stem on the cortex is *activating* by nature and always accompanies to some degree the propagation of an afferent impulse over the "classical" pathway, i.e., over the lemniscus medialis.

Thus, in view of a series of investigations the propagation of an afferent impulse into the cerebral cortex can be presented as follows: when passing over the brain stem, the afferent impulses *partially separate from the main stream and propagate via collaterals of the reticular formation of the brain stem*. Due to numerous synaptic relays they are delayed for some time. As a consequence of this, the impulses proceeding directly arrive in the cerebral cortex first and evoke a more or less localized excitation. After this, the collateral impulses that had been delayed, upon passing through several relays and being considerably potentiated, arrive as a broad, generalized wave involving the entire cerebral cortex. From these data, which were obtained by many investigators, it follows that every stimulus applied to the receptors of the organism is automatically transformed in the region of the reticular formation of the brain stem into two streams of qualitatively different impulses (Fig. 17.7).

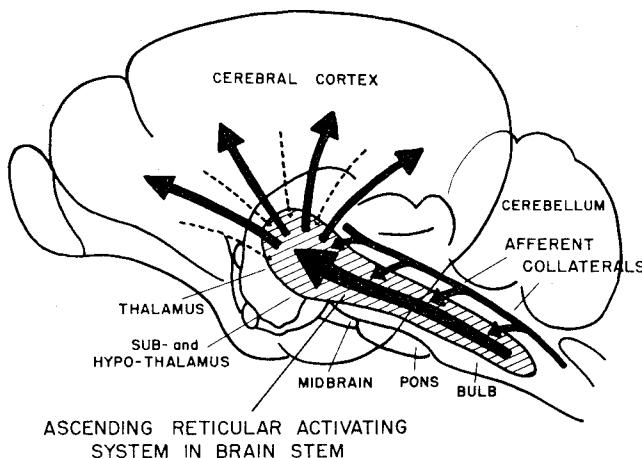


FIG. 17.7. Diagram of the connections of the reticular formation of the brain stem with the cerebral cortex. Ascending influence—heavy arrows; descending influence—broken arrows. From Starzl *et al.* (1951, p. 495).

However, not all afferent impulses excite the reticular formation with equal strength. Auditory stimuli evoke, as was shown by Starzl *et al.* (1951), an especially extensive collateral excitation of the reticular formation, while visual stimuli evoke a considerably lesser one.

Special attention was devoted to the study of the nature of the activating influence of the reticular formation on the cerebral cortex. As a criterion for this influence the electroencephalographic data were used, which, in chronic experiments involving the destruction of the reticular formation, were correlated with observations of the behavior of the animal. The authors proceeded from the well-established proposition that slow and high-amplitude electric oscillations (α -waves, δ -waves) correspond to the synchronized electric discharges of many nerve units of the cortex and indicate a quiet, i.e., nonworking, state of the cortical tissue. On the other hand, during any active state of the cortex arising as a result of the arrival of afferent impulses, the electric oscillations change to a state of desynchronization and assume a high frequency (β -rhythm). The amplitude of the oscillations decreases considerably; this is manifested in a "suppression" of the electric oscillations of the cortex.

A typical example of an active state of the electrical activity is the activity in the *waking* state of a person being subjected to various stimuli. However, by isolating the person in a soundproof chamber, turning off the light, and allowing him to relax, there appears instead a high-amplitude electrical activity of the α -rhythm type. An even more marked transition to a synchronized state of the cortical elements occurs upon the transition to sleep or in general anesthesia. In these cases even slower waves (1–3/sec) of high amplitude appear, indicating the synchronized activity of an enormous number of cortical elements.

Thus, in modern neurophysiology these two states—the synchronization and the desynchronization of the electrical activity of the cerebral cortex—have become the criterion both for the transition to sleep or to the *waking* state and for the evaluation of the activating influence of the reticular formation of the brain stem on the cerebral cortex.

If during general anesthesia the background of slow electric oscillations already described above has become established in the cerebral cortex, electrical stimulation of the reticular formation of the brain stem immediately evokes a general desynchronization of the electrical activity of the cortex with some ipsilateral predominance. The sensitivity of the reticular formation to stimulation is very high (low threshold). This physiological feature of the reticular formation during anesthesia conforms with its high lability in the *waking* state: its "spontaneous" activity is manifested by the firing of impulses with a frequency of up to 300/sec!

Almost all investigators give a similar interpretation to the desynchronization of the cortical electrical activity obtained upon stimulation of the reticular formation of the brain stem. They believe that stimulation of the reticular formation exerts an *activating influence* on the cerebral cortex, which, as a consequence, passes into a state of wakefulness.

The interpretation of the physiological role of the reticular formation was considerably influenced by Bremer's experiments with the isolated brain.

If a section is made *below the medulla oblongata*, the electrical activity of the cerebral cortex remains desynchronized and shows all signs of wakefulness. If, however, the section is made through the anterior part of the reticular formation of the brain stem, the electrical activity of the cortex changes drastically. It immediately becomes synchronized and characterized by the so-called spindle bursts, which constitute an occasional involvement of relatively frequent oscillations. The record fully suggests the electrical oscillations during sleep or during barbiturate anesthesia.

These phenomena are not observed if the lemniscal afferent pathways are destroyed; on the other hand, they invariably appear if the reticular formation is destroyed and the long afferent pathways remain intact.

Thus, an increasing number of data made it possible to come to the opinion that *the reticular formation of the brain stem stores the energy of the afferent impulses, which is then used in the activation of cortical activity*. The elimination of this activation leads to the loss of the cortical tonus and induces sleep.

This proposition was fully illustrated in animals with chronically implanted electrodes. If the anterior section of the reticular formation is destroyed, slow waves with features characteristic of sleep can be observed in the animal during the post-operative period. The animal remains asleep and awakes only if it is persistently stimulated. If, however, the reticular formation is intact, but in the same region the gray matter surrounding the aqueduct of Silvius is destroyed, the animal remains awake, and its cortical potentials indicate normal desynchronization.

Thus, behavioral tests compared with the nature of the disturbance of the electroencephalogram again emphasize the direct role of the reticular formation in the alternation of sleep and wakefulness. These observations have recently been supplemented with many additional data that have demonstrated the involvement of the reticular formation of the brain stem in the arousal reaction of an animal. All investigators emphasize one remarkable fact: arousal does not occur if the afferent impulses enter the cerebral cortex only via the "classical" pathway, i.e., through the lemniscus medialis and through the thalamus. Consequently, the reticular formation does indeed have an intense, generalized effect on the cerebral cortex. There is reason to believe that there are specific cortical areas for this arousal effect of the reticular formation, namely those fields upon the stimulation of which one can neuronographically determine the potential changes in the reticular formation of the brain stem, as was shown by Segundo *et al.* (1955).

However, these recent studies contain a number of contradictions which must be resolved by further investigations. In recent years more frequent attempts have been made to relate the activating influence of the reticular formation on the cerebral cortex to the development of emotional states and to the participation of the cortex in emotional discharges (Weinstein and Bender, 1947).

The problem of the reticular formation was given new direction after it was shown that it is itself under the control of cortical influences. We are faced with an interesting dynamic situation: the "diffusely" activating influence of the reticular formation on the cerebral cortex can be altered to some extent by the cerebral cortex itself, i.e., on the basis of the results of the highly delicate synthesis of the external and internal stimuli perceived

by the cortex via the "classical" sensory pathways.

How these two functions become interwoven, and from where they obtain the energy for suppressing each other, is one of the most intriguing problems of modern neurophysiology.

The experiments of Hernández-Péón and Hagbarth (1955) are most valuable in this respect. The investigations of these authors are of special interest to us, since they simulated the natural interrelations in the central nervous system by using tetanizing stimuli. In addition, they applied simultaneous or consecutive stimuli to different regions of the cortex and to the receptors. They observed the end effect at the reticular formation. In this way they *revealed the existence of and the conditions for the suppressing effect of the cerebral cortex on the reticular formation of the brain stem*, which is presently of special interest.

The experiments were carried out as follows. One of the stimuli (the "conditioning" stimulus) was applied, for example, to the cerebral cortex, and then at different time intervals afterwards the other stimulus (the "test stimulus") was applied either to the sciatic nerve or to the infraorbital nerve.

The authors have shown that stimulation of the cortex most strongly blocks all the afferent impulses that ordinarily change the potentials of the reticular formation. A block of the afferent impulses by a single "conditioning" stimulus can in individual cases be observed even 150 msec after the application of a "conditioning" stimulus to the sensorimotor region of the cortex; it could be observed even after 13 sec following a tetanizing "conditioning" stimulus (Fig. 17.8).

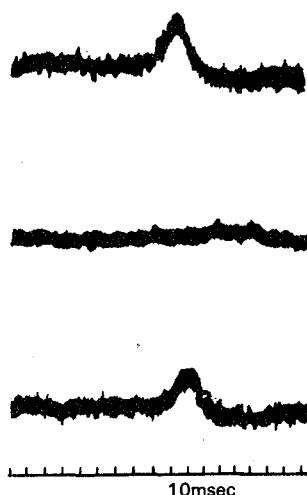


FIG. 17.8. Oscillogram from the reticular formation of the brain stem. Top line—control, normal effect from stimulation of the infraorbital sensory nerve; middle line—the same stimulation 13 sec after tetanic stimulation of the sensorimotor region of the cortex; bottom line—the same stimulation 20 sec after tetanization of the sensorimotor region of the cortex. The inhibiting action of the cortical neuron on the region of the reticular formation is clearly shown. Time in milliseconds, one scale division = 10 msec.

It is interesting that the block of any test stimulus is more distinct with an increasing strength of the "conditioning" stimulus. It is most likely that the strength of the excitations of any integrated activity of an animal is related to the strength of the generalized excitation in the reticular formation. On this basis the mutual exclusion of two competing activities, examples of which have been analyzed above, will become physiologically understandable.

The authors note one special circumstance. The activity of the reticular units can be either "blocked" or "facilitated," depending on their initial condition. This is in agreement with the principle of lability, a basic concept of the Vvedenskii—Ukhtomskii school (Makarov, 1957).

In these experiments there is much evidence for the *pessimal* nature of the blocking of the activity of the reticular formation (especially from the cerebral cortex). The authors, however, are evidently not familiar with Vvedenskii's theory of inhibition. This is all the more incomprehensible, since recently Forbes *et al.* (1949) have given a detailed explanation of Vvedenskii's theory in American scientific literature. Furthermore, they have explained, from this point of view, the cases of inhibition in the cerebral cortex which they observed.

Investigations of the corticifugal effect on the reticular formation have shown that between the cerebral cortex and the reticular formation there are continuous cyclic interactions in which the influences alternately dominate. The reticular formation itself becomes a junction at which both the ascending afferent influences and the corticifugal descending influences meet (see Fig. 17.7). The influences from the sensorimotor region of the cerebral cortex are able to block the afferent process not only in the reticular formation itself, but also at the first synapse. For example, according to the data of Hernández-Péón and Hagbarth (1955), the impulses from the stimulation of the infraorbital nerve are blocked already in the center of the trigeminal nerve.

The description of the interrelation of the cerebral cortex and the reticular formation would be incomplete if we failed to mention the relation of the latter to humoral stimuli. With regard to this, unexpected data have been obtained and have necessitated our reexamining the established tenets concerning the action of hormones and anesthetics on the central nervous system.

It is known that intravenous injection of adrenaline leads to a considerable activation of cortical electrical activity. However, in accordance with the traditional experimental thinking, this activation was usually ascribed to a *direct* action of adrenaline on the neural elements of the cerebral cortex.

The French school of physiologists has shown in a series of experiments that this increase in the cortical electrical activity is of a different physiological nature: *it is caused by the direct activating effect of the adrenaline on the anterior part of the reticular formation of the brain stem, which then secondarily causes the intensification of the cortical electrical activity* (Bonvallet *et al.*, 1953; Bonvallet *et al.*, 1954).

Analysis of this effect of adrenaline led to very interesting and broad generalizations concerning the role of the sympathetic tonus in cortical activity. Thus, it was established that the pressoreceptor impulses arising from stimulation of the carotid sinus region are capable of blocking the activity of the reticular formation and the electrical activity

of the cortex and, consequently, of assuming the role of absolute adrenaline antagonists. One cannot fail to see that these interrelations correspond fully to those existing under natural conditions as well.

As is known, any hypertension (including adrenaline hypertension) creates conditions for the immediate stimulation of the pressoreceptors of the aortic arch and the carotid sinus region, leading to the termination of the hypertension itself (Anokhin and Shumilina, 1947).

This antagonism goes so far that adrenaline, while promoting hypertension (by acting on blood vessels), *heightens the excitability of the pressoreceptors* at the same time, i.e., promotes the attenuation of the hypertension evoked by it (Anokhin, 1952b; Navakatikian, 1956).

It has recently been demonstrated that adrenaline and noradrenaline exert their effect on the hypothalamus and the rostral part of the reticular formation through local foci of increased permeability of the blood-brain barrier to these substances.

It was also shown that the reticular formation has an extraordinarily broad range of sensitivity to diverse chemical substances, especially to anesthetics and to tranquilizers. For example, the reticular formation is affected entirely differently by barbiturates than is the cerebral cortex. This means that, all other conditions being equal, the anesthetizing effect will be exerted through the reticular formation. If we assume that the activating effect of the reticular formation on the cortex is a necessary condition for wakefulness, our concepts of mechanisms of general anesthesia must be radically changed, which similarly happened to the concept of the mechanism of the effect of adrenaline on the cerebral cortex. Inhibiting the cellular elements of the reticular formation of the brain stem, the anesthetic can thereby *indirectly* bring the cerebral cortex into a state of generalized synchronization, which, as had already been stated, corresponds to the state of sleep.

Some authors (French *et al.*, 1955) emphasize that such a possibility is entirely plausible. Consequently, the question of the physiological mechanisms of general anesthesia must be subjected to discussion with regard to the new data.

Since the region of the reticular formation is most intimately connected with the hypothalamus, the thalamus, and the medulla oblongata, it is natural that the most general functions of the organism, such as the nociceptive reaction, thermoregulation, etc., must inevitably have some functional relation to it.

The hypothermal action of chlorpromazine and other drugs is not only the result, as was previously thought, of their ganglionic blocking action, but is primarily caused, as was shown by more accurate and direct investigations, by their effect on the reticular formation. This was clearly established by the investigations of our collaborator Agafonov (1956).

He showed that a strong nociceptive stimulus (water heated to 55°C) applied to the hind leg of a rabbit completely suppresses cortical electrical activity. The nature of this suppression suggests that it is brought about via the reticular formation. A preliminary injection of chlorpromazine completely prevents this suppressing action of the nociceptive stimulus on the cortical electrical activity. From these data we concluded that chlorpromazine affects primarily that part of the reticular formation which

imparts a generalized character to nociceptive stimulation, with desynchronization of cortical electrical activity (Anokhin, 1956b).

In summarizing the principal data obtained during the study of the reticular formation of the brain stem, we must say first of all that they can no longer be overlooked in the study of the general functional architecture of the brain. The problem of the cortico-subcortical interrelations is especially benefited by these data.

At the present time one can hardly present any model of higher nervous activity without considering all these recent data published by Mollica *et al.* (1953), Buser and Albe-Fessard (1953), and other authors.

Here it is important to state the following comprehensively proved propositions:

1. The reticular formation of the brain stem, receiving the collateral impulses from all afferent pathways, is an organ of generalizing activating effect on the cerebral cortex. In this sense it fully agrees with Pavlov's description of the influence of the subcortex on the cerebral cortex as a "blind force."
2. The cerebral cortex, having the ability to produce nerve impulses of high frequency, exerts an extensive inhibitory influence on the functions of the reticular formation and even on the functions of the spinal levels.

Since all those activities of the organism which require a general excitation, such as the emotions, prolonged orienting-investigative reactions, etc., are connected with the reticular formation, the inhibitory effect of the cortex on the functions of the reticular formation can be recognized as one of the forms of the higher inhibition about which I had spoken earlier.

Direct neuronographic investigations show that the inhibitory process arises in the region of the subcortical connections of the reticular formation, while the *inhibitory excitation* as the most essential stage of the inhibitory function originates in the cerebral cortex.

3. In the same way, direct investigations involving microelectrode techniques show that inherent in individual elements of the reticular formation are mutual exclusions, reciprocal relations, occlusions, etc. These physiological properties of the reticular formation cannot fail to become involved in those conflicts between two integrated activities which proceed at the high level of generalization of impulses. This question, however, must still be refined in many respects, with an indispensable correlation of the analytical data to behavioral reactions.

All the examples we have analyzed involving the inhibition of facial expressions and the unification of the cortex and the subcortex in emotional discharges, as well as the latest data regarding the cortico-subcortical interrelations (hippocampal pathway, reticular formation), are undoubtedly of a common nature and become organically united in the processes of the organization of the higher adaptation of animals and man. At the present time, however, we are still far from developing any complete concept concerning the cortico-subcortical interrelations in the implementation of inhibitory functions, since the data are still largely uncorrelated.

Beyond doubt, the *inhibitory excitations* always originate under the influence of the sum total of the external influences, while the controlling influence is exerted by the

cerebral cortex. However, the *place of origin* of the inhibitory process cannot be reliably determined in all cases.

All our ideas concerning cortical inhibition in regard to *its propagation over the cortex or from the cortex into the subcortex must be reexamined from the point of view of the indisputable fact that inhibition is always a local process and has no mechanism for propagation.*

The above examples of the patterning of inhibitory excitations contribute to the development of new points of view concerning the inhibitory function of the cerebral cortex in regard to forms of subcortical activity.

In all cases of the interpretation of this inhibitory function of the cerebral cortex we must constantly keep in mind the broad convergence of ascending impulses on the cortical neurons, which is the cause of the strength of the cortical inhibitory excitation. The cortical cells gain exceptional power to pattern corticifugal inhibitory impulses by receiving the strongest emotional ascending impulses converging from the hypothalamus and the reticular formation. These impulses then bring about the final stage of the inhibition of an activity which for some reason is not needed at the given moment.

How strong these inhibitory excitations may become can be seen from the outstanding examples of self-sacrifice or the overcoming of dangerous obstacles. In all these cases the cerebral cortex, mobilizing its entire previous experience and drawing on the emotional strength of this experience through the convergence of ascending impulses, is the organ which makes the preferable decision in all difficult situations in life.

The investigations of my collaborator V.G. Zilov justify the assumption that in the patterning of these inhibitory excitations, the activity of the hypothalamus rather than that of the reticular formation is of the greatest importance.

CHAPTER 18

The Theory of the Dominant and Its Relation to Higher Nervous Activity

THE theory of the dominant as developed by Ukhtomskii has been given a somewhat special position in the physiology of the nervous system. Incorporating all the most significant physiological features common to any activity of the organism, it nevertheless was not related to the other aspects of the physiology of the central nervous system. And, strange as it may seem, it had no influence on the hypotheses and ideas which are part of the physiology of higher nervous activity.

The lack of creative communication between the followers of Pavlov and those of Ukhtomskii is a great loss to the development of Russian physiology.

For this lack of communication both sides are to blame. Investigators of the physiology of higher nervous activity, it seems to me, are too sure that the physiology of higher nervous activity includes all possible mechanisms of the organization of the behavioral acts of animals and man. Proceeding from this incorrect position, the physiologist of higher nervous activity considers it unnecessary to utilize the laws of the general physiology of the nervous system, including the theory of the dominant. Various points of view are possible here.

Such a position cannot lead to progress in the understanding of the intimate physiological mechanisms which are the basis for the patterning of synthetic acts of higher nervous activity.

On the other hand, followers of Ukhtomskii have not seriously attempted to compare the ideas of both schools to show what is *common* and what is *different* in the interpretation of the fundamental mechanisms of higher nervous activity. The attempts of some authors (Magnitskii, 1949; Chukichev, 1953; Rusinov, 1955; and others) can hardly be considered sufficient, since they concentrated mainly on comparing the "parabiotic" and the "protective" inhibitions and left the theory of the dominant almost completely untouched. Besides this, in these studies there were many incidental and indirectly related data, so that they could not contribute to a closer communication between the two largest Russian schools of physiology.

In fact, the contradictions between the positions of the two schools were perpetuated (views concerning the nature of inhibition, the principle of the "conflict of excitation and inhibition," the theory of the dominant, etc.). Aside from the investigations of our school (see Pavlov, 1949b, p.185; Anokhin, 1949c, 1956d; Laptev, 1949b; Gavlichek, 1958; Shumilina, 1959; Polezhaev, 1960, 1966; and others), only a few attempts have

been made to constructively apply the theory of the dominant to the problems of higher nervous activity (Durmish'ian, 1952; Skipin, 1956).

Since the theory of the dominant is the link between the most precise data of analytical neurophysiology and the highest synthesis of these elementary mechanisms in the conditioned reflex, it should help the investigator of higher nervous activity to understand the intimate physiological mechanisms of conditioned reflex activity and especially the role of dominant motivation as a component of afferent synthesis.

The lack of any definite ideas on this problem prompted us to try to clarify the role of the processes of dominance in the patterning of integrated conditioned reflex acts.

The school of Vvedenskii had met the phenomena of dominance in the nervous system long ago, but these phenomena had not as yet been developed into a system or become unified in a completely defined physiological concept. It was noted that the presence of increased excitability in any region of the central nervous system led to a "complete distortion of normal relations." The "distortion" consisted of the appearance of a reflex reaction which is inappropriate for the stimulus applied.

This phenomenon was especially apparent in experiments with hysteriosis.* In evaluating all these observations of "distorted" reactions, Vvedenskii wrote:

In this sense for me the phenomenon is not quite unexpected. Long ago (1897) I had noticed that if a certain neural mechanism was brought to a state of increased excitability, then all the other impulses, which should have had an entirely different effect, proved at first to be capable of acting apparently as an aid to a preexisting tonic excitation. Similar observations are also described in the recently published investigation by A. A. Ukhtomskii.

These preliminary and somewhat unsystematic observations can, however, be called "chance" observations only in the sense of the famous Pasteur aphorism: "Chance favors only prepared minds."

In electric stimulation of the motor area of the cerebral cortex of a cat, Ukhtomskii noted that with some stimuli, instead of the expected movements of the limb, an act of defecation begins to be patterned. With further similar stimulation, it develops to the maximum and finally is resolved. As soon as the act of defecation is accomplished, the very same stimulation of cortical points begins to evoke a movement of the corresponding limb characteristic for this stimulation.

From these experiments it was found that quite definite neural mechanisms of specific activity (in this case the act of defecation) may be in a state of increased excitability and may continue to "accumulate" impulses.

From the physiological point of view, dominance consists first of all in the redirecting of impulses from the cortical motor area to the system of the central formations of an integrated act—defecation. In other words, *the stream of impulses, arising from the stimulation of the cortical point, somewhere on its pathway meets an obstacle to propagation in the former direction and has easier access to a system of impulses dominant at a given moment.*

From these data it can be seen that, together with the phenomenon of dominance, the inhibitory effect of the dominant activity on all other preexisting activities has

* Reference to Glossary.

become evident to the investigator. Therefore, even the first observations of the dominance of individual nerve centers confront the investigators with a number of questions directly related to the problems of higher nervous activity.

Where does the deviation of impulses from their own pathway onto the pathway of the dominant activity occur? What is the nature of dominance? By what mechanisms does the dominant activity inhibit all other activities of the organism?

Unfortunately, at present we cannot satisfactorily answer these and related questions. However, in this respect, as we shall see below, we can definitely indicate the direction for further experimentation.

Ukhtomskii believed that the prototype of any dominance is the phenomenon of "single tetanized muscle contraction." It is known that if one applies a subthreshold tetanizing stimulus to the nerve, from the electrodes closest to a muscle, then a single supraliminal stimulus, applied to the nerve in its proximal portion, will evoke a tetanic contraction of the muscle (Vvedenskii, 1886). According to Ukhtomskii, this phenomenon simply illustrates the relationship between the dominant and the "remote" impulses which leads the latent dominance to the peripheral effector.

Utilizing recent neurophysiological data, we can understand this phenomenon better. The subthreshold tetanization undoubtedly evokes a local excitation and a local nonpropagating potential. While not bringing the excitation of the nerve fibers to the critical point at which the explosive process begins, the subthreshold tetanization quite obviously causes some degree of depolarization of the nerve fibers being tetanized (Erlanger and Gasser, 1937).

How do the remote impulses act in the portion being tetanized? Depolarizing the nerve fibers and evoking spikes from their point of origin, they raise each subthreshold depolarization in the region of tetanization to the critical level. This, in our opinion, is the nature of a single tetanized muscle contraction.

What about the dominance of an integrated activity of the organism which is triggered by one insignificant provoking stimulus? It is quite possible that the neural structures related to the dominant integrated activity are somewhat depolarized. There is every reason for such an assumption.

In the specific case examined in Ukhtomskii's dissertation (1911), the act of defecation was undoubtedly patterned by a continuous and intensified stream of afferent impulses from the receptors of the rectum. But what is a continuous bombardment of nerve centers by impulses? It is first of all a selective depolarization of those synaptic formations which are among the central connections of a given functional system. Consequently, one can hardly deny that preexisting depolarization plays some role in the increased sensitivity of the dominant to the remote stimulation. In this sense, the analogy of the dominant to the single tetanized muscle contraction is undoubtedly justified. However, taking into account recent advances in the physiology of the nervous system, it is hardly possible to attribute the process of dominance of an integrated activity only to the preceding depolarization of neural elements. We will discuss this question in more detail below.

Ukhtomskii gives the following characteristic features of dominant "centers":

1. Increased excitability.

2. Stabilized excitation.
3. Capacity to summate excitation.
4. Inertia of the excitatory processes in the dominant.

Unfortunately, while giving a correct descriptive idea of the dominant, these characteristic features have not been given more definite morphological and physiological explanations. As yet we do not know what parts of the functional system may assume a state of dominance. The expressions "center," "organ," "apparatus," "integrated activity," etc., do not define the pathways of the patterning and operation of dominant states under natural conditions of life.

In the same way, the concept of the "accumulation" of impulses within a center is vague. What kind of impulses have the ability to accumulate and how are they changed when there is already a stable dominant state? What factors determine whether the dominant is subthreshold or will become supraliminal and will affect the function of the peripheral apparatuses? The mere observation of human behavior convinces us that a purely quantitative evaluation of the dominant excitation in the central nervous system is not enough to answer this.

Cases are known in which a rather high degree of the dominant state, i.e., excitability, does not appear to be externally effective. On the other hand, we know cases in which a negligible increase in excitability was sufficient for the dominant to become effective.

Therefore, the degree of excitability of the dominant depends not only on its capacity to "accumulate" impulses and on its level of excitability, but also on what kind of impulses of another activity oppose the dominant at a given moment, thus blocking its effectiveness.

The theory of the dominant is undoubtedly a very valuable contribution of Russian physiology. However, the absence of physiological precision in the individual concepts of this theory, as well as contradictions in Ukhtomskii's statements, have, up to the present, seriously hindered the application of the principle of the dominant to the physiological functions of the integrated organism. Such a condition is especially apparent if the principle of the dominant is used to explain the basic phenomena of higher nervous activity. Naturally, it is first necessary to understand these contradictory propositions to give them a physiological explanation acceptable at the present moment. Only after this can one use the theory of the dominant to decipher certain phenomena related to the nature of conditioned inhibition.

First of all we must consider what it is that dominates in the central nervous system. In other words, on what material substrate, under natural conditions, does a dominant appear? There is still no definite answer to this question. There is such a great variety of definitions of the dominant that the whole question concerning the dominant becomes confusing and sometimes misleading.

For example, the neural substrate which is the basis for the development of the dominant in the various statements of both Ukhtomskii and his students has received the most varied definitions. In one case, this substrate is called the "center," and the authors then base their considerations on this fully defined and limited point of the central nervous system. In another case, such a substrate is called a "focus," and then the entire interpretation of the experimental results proceeds on this level. The concept

of a "dominant focus" has been especially widely accepted in Soviet physiological literature. Constructed on the basis of this theory are, for example, all the experimental models of Rusinov, about which more will be said later.

At the same time, Ukhtomskii spoke of the dominant as a certain "organ" or even "apparatus," by means of which some group of nerve centers becomes dominant. Herein he defines the dominant as a "loosened area of the nervous system."

To these definitions there must also be added the definition of the dominant as an "integrated pattern" or as a "constellation of centers." In spite of all this variety of definitions of the same physiological phenomenon, Ukhtomskii nevertheless most often uses the expression "dominant center."

It is only necessary to closely examine all the above-mentioned definitions of the dominant state in order to ascertain a certain incompleteness in the physiological ideas concerning this important question. Indeed, all these definitions fall between the concept of the "dominant focus" (inspired by experiments involving local strychninization) and the concept of the all-inclusive "integrated pattern"; these two concepts are completely incompatible.

All this is an indication of the contradictory and as yet not physiologically sound ideas about the composition of the dominant as a universal physiological phenomenon. Meanwhile, there is no doubt that under natural conditions dominance is possible only for a complex system of connections and excitations which is unified in one particular functional task. In other words, only a functional system with a fully defined adaptive effect can be dominant.

Consequently, under natural conditions, not the "focus," not the "center," and not even the "constellation of centers" dominates, but a system of connections which invariably also includes central-peripheral relationships. It is known that in the orienting-investigative reaction, for example, the dominance of the excitations of this reaction spreads also to the peripheral area of the analyzer (Sniakin, 1953; Sokolov, 1957; Granit, 1955a, 1955b, 1966; Novikova and Farber, 1956).

Thus, dominance in natural adaptive activity is a far more complex process than is a simple "dominant focus." In fact, dominance encompasses selectively all processes and mechanisms constituting a given functional system and primarily all its central-peripheral relationships. Naturally, during inhibition of the dominant, all its component mechanisms, i.e., the functional system as a whole, must become inactive.

The erroneous opinion exists that the terms "dominant" and "constellation of centers" have the same meaning as our concept of the functional system. Of course, any synthetic concepts in the physiology of nervous activity will unavoidably overlap in some way. However, one can hardly doubt that the mutual understanding and progress of scientific investigation will always depend on how precisely and adequately we distinguish between our scientific concepts.

The concept of the functional system is first of all a dynamic concept in which the emphasis is on the principles of patterning of some kind of functional unit, inevitably ending in a beneficial adaptive effect and including mechanisms for the evaluation of this effect.

We are interested in the principles of the development of a functional system and in

the physiological properties which allow this system of excitations to result in an adaptive end effect beneficial to the integrated organism. The adaptive effect is the quintessence of the functional system. It determines the composition, the rearrangement of efferent excitations, and the inevitable reverse afferentation of the intermediate or final adaptive effect.

From the description of the concept of the functional system (see Chapter 6) it can be seen that it cannot exist without involving the central-peripheral relations and especially the constant afferent influence from the periphery. That is, the functional system is, for us, a kind of cyclic formation (Anokhin, 1935, 1948a, 1948b, 1949a, 1949c, 1949e, 1956a). Consequently, the functional system must be investigated so that we may *discover the mechanisms of its formation as an organized whole*. Furthermore, the study of the functional system encompasses both its functional properties and the laws of its historic development (ontogenesis, phylogenesis).

What is the purpose of the theory of the dominant? It demonstrates the universal principle according to which dominance, as a certain level of excitability, is a necessary condition for any activity. Consequently, the theory of the dominant is a theory concerning the conditions of functioning expressed in parameters of excitation and excitability, a theory about the necessary physiological basis for the occurrence of an activity.

The theory of the dominant, concentrating attention on the "focus" and "center," does not take into account the investigation of the principles governing dominance. Ukhtomskii was mainly interested in the phenomenon of dominance itself and in the physiological conditions of its origin at the level of the interaction of excitations (summation, "responsiveness," etc.). Meanwhile, we have always been interested in determining those principles which govern the development of the functional unit that dominates. As far as we know, Ukhtomskii dealt only slightly with this question and never returned to it in his later investigations.

Therefore, when saying that at a given moment there is a dominant in the central nervous system, we only refer to the intensity of particular excitations without characterizing the structure of the dominant excitations, i.e., the properties of their systemic organization. These properties, however, are an inseparable part of the concept of a functional system.

The following statement can briefly and most correctly establish the relationship between the dominant and the functional system: *dominance is a physiological means by which the functional systems are manifested in the adaptive effects of the organism by changing the levels of excitability*. The functional system, on the other hand, is dynamic, having specific characteristics of its architecture and principles of interaction of the processes within this architecture. Once again we may say that the functional system cannot exist without involving the central-peripheral relationships, because only the latter can coordinate the interaction of the central processes, establishing a successful adaptive effect.

Thus the concept of the functional system encompasses all aspects of adaptive activity of the entire organism and not only the interactions or combinations of nerve centers. Consequently, the concept of the dominant as a "constellation of centers" offers

little help in understanding the functional system as a physiological organization.

Therefore, in summing up the discussion on the physiological definition of dominance under natural conditions, we can state with sufficient confidence that only an integrated system of processes, united by a functional purpose, can dominate. *The laws and mechanisms of the development of this unification constitute our main interest.*

It follows that the further study and understanding of the dominant as the universal mechanism of the activity of the organism necessitates our comprehending the mechanisms of the patterning of the dominant system of excitations. There is reason to believe that dominance as an intensification of excitability of some nerve formations does not have any specificity and can be present in all activities of the organism. This gives us a basis for assuming that the central nervous system has special nonspecific mechanisms *imparting dominance to any integrated activity* which ensures the adaptive success of the organism at a given moment and under given conditions. If this were so, then both processes—the patterning of the adaptive activity itself (the functional system) and its transformation into a dominant—would constitute a single integrated act of the central nervous system, ensuring a successful adaptation to environmental conditions.

In connection with this, it is necessary to determine the reliability of the models of dominant states which investigators have increasingly used in their study of the dominant.

The necessity of studying experimental models of various normal and pathological states of the organism is obvious. Modeling is necessary and beneficial in studying the functions of the organism. By permitting the experimenter to direct physiological phenomena and arbitrarily to combine them, experimental models open broad horizons for disclosing the nature of functions. All this is indisputable.

Often, however, the beneficial effect of experimental models on the progress of our knowledge is considerably lessened because the experimenter has not established, at the very beginning of his investigation, what part of the natural integrated function of the organism the given experimental model includes; in what way it adequately reflects reality; and to what extent it artificially distorts some of its aspects. Without a clear idea about these peculiarities of the chosen experimental model, the experimenter will always risk making incorrect conclusions from his investigations.

It seems to me that something similar also occurs in investigations of the "dominant focus." Whatever causes it (strychnine, direct current, etc.) is always only an artificial creation which characterizes the property of the neural tissue to develop interaction between its separate points. However, this model, in attracting the attention of the experimenter to the "focus," distracts him from the true dominant in the natural activity of the organism where a very widespread and diffuse system of selectively interacting excitations always dominates, being unified by the adaptive end effect.

Therefore, we may welcome investigations of the physiological characteristics of the "dominant focus," but only on condition that we do not forget the complex and always systemic nervous process which dominates under natural conditions. Ukhтомский (1911) essentially discovered this principle in an example of natural activity.

Just as uncertain is the opinion as to what is the level of excitability of the "dominant center." It would seem that, in accordance with the basic properties of the dominant, the dominant center should have an increased excitability and therefore be more

capable of asserting its influence. Precisely in this sense one of the important collaborators of Ukhtomskii, Vasil'ev (1953), described the dominant as the "controlling focus of increased excitability and stationary excitation," or as the "focus of dominant excitation." However, at the same time, Ukhtomskii repeatedly emphasized another meaning of the level of excitability in the dominant. For example, touching on this question he wrote: "*It would, however, be very careless to say that the dominant is the 'center of strong excitation' in the sense of some kind of stationary condition.* In order to be exact, one can only say that the dominant is a center reacting very easily to the remote waves and easily summing the impulses caused by them! *In the course of the reaction itself, this center reaches high degrees of excitation.* Exaltation does not precede the reaction..." (Ukhtomskii, 1927, see Bykov, 1952c, p. 338).

From this statement by Ukhtomskii it obviously follows that the dominant state becomes a dominant only "in the course of the reaction," i.e., extempore and due only to the arrival at the "dominant focus" of a remote series of impulses. One can easily see that this concept contradicts those statements by Ukhtomskii in which he defines five characteristics of the dominant. The first of these is the "increase in excitability." What, then, is this increased excitability in the physiological sense if it does not have a parameter of intensity of excitation?

The vagueness of Ukhtomskii's views regarding this aspect of his theory of the dominant must naturally be further investigated by his followers so as to eliminate the lack of clarity.

The insufficiency of theoretical bases in regard to this aspect of the dominant is especially evident if one compares them with the phenomena of the natural behavior of both animals and man. For example, an animal with elaborated conditioned defense reflexes, coming into the experimental chamber, under the influence of environmental stimuli, at once develops a dominant state which is biologically negative. The animal in this environment usually reacts with an inhibitory response to conditioned alimentary stimuli (see the experiments by Shumilina above). Consequently, the defense dominant created in this experimental environment undoubtedly possesses definite qualities of intensity, for only by intensity of excitations can its inhibitory side effect on the alimentary activity be explained. At the same time, this anticipatory dominant state may fail to be accompanied by a defense activity appropriate for it (a leg lift, etc.).

Another quite obvious demonstration of the high intensity of the anticipatory dominant state is the experiment with a sudden single reinforcement with meat instead of the usual bread crumbs. As has been shown, the animal, after receiving the reinforcement of meat, in the subsequent trials goes to the feeder from which it had once received meat. Sitting near the feeder (instead of the usual place in the middle of the platform), it sits quietly without the usual apparent signs of alimentary excitation (secretion, respiration). However, with the next presentation of bread crumbs, it refuses to eat! Therefore, there is hardly any doubt that the anticipatory dominant state of a definite system of excitations ("meat excitation") was sufficiently strong enough to inhibit other alimentary reactions, even those related natural conditioned stimuli which, as is known, have great intensity of excitation (Anokhin and Strezh, 1933).

Do we not have examples from everyday life when a definite dominant state,

especially of a negative emotional character, not appearing in external activity, can completely inhibit and paralyze every other activity including mental operations? Is that not an expression of the intensity of excitation of the given dominant?

Comparing the above-mentioned observations, we can say that in the theory of the dominant, the idea concerning the physiological nature and the inhibitory strength of the anticipatory dominant states has not as yet been sufficiently clarified.

How strong and masked a dominant state can be may be seen from the following observations made by us under natural conditions. A kitten investigated for the first time a windowsill of an open window on the fourth floor. Moving carefully forward to the outer edge of the sill and looking down, it immediately jumped back as soon as the observer made a sudden noise. Let us try to interpret the physiological basis of this interesting phenomenon.

If we assume that any activity of an animal or man is the result of a corresponding dominant system of excitations, then the above-described effect would be difficult to explain. In this case one must reason somewhat differently. The latent dominant of biological caution is much stronger in the sense of the "accumulation of excitations." Therefore, the extraneous excitation disclosed the latent dominant, but did not intensify the actual forward movement of the animal.

But then we come to the very important conclusion regarding the evaluation of the strength of the dominant. Not only must the intensity of the system of impulses composing the dominant be included in the evaluation, but also the intensity of inhibitory side effects from some other activity which block the emergence of the impulses of the dominant to the periphery and bring it into the category of "latent dominants." Only by comparing the excitatory and inhibitory effects can one obtain a correct picture of the intensity of impulses of the latent dominant state.

The theory of the dominant is incomplete in that there have been no attempts to understand the physiological nature of dominance or the mechanisms which establish dominance as a result of an initiating or provoking stimulus. This can be partially explained by the immaturity of the field of neurophysiology when the basic concepts of the dominant, with respect to its mechanisms, were being formulated. Thus, the theory of the dominant was a daring synthesis of thought, greatly surpassing the information available at that time about the general physiology of the central nervous system.

However, the situation has changed considerably. While the physiology of the central nervous system has been enriched with new data and concepts about the architecture of central processes, the theory of the dominant remains on the level of earlier concepts and, as far as we know, only one attempt has been made to compare these latest advances with the basic features of the dominant state. This gap between the two fields of investigation has the result that a very valuable synthetic principle remains outside the main stream of neurophysiological investigation.

At present we have every reason to attempt to understand the physiological meaning of dominance itself as well as the mechanisms of "interception" of remote impulses by the dominant. It is best to make this attempt in those examples which served Ukhtomskii in discovering and confirming the very fact of dominance as a universal physiological phenomenon.

Especially interesting in the phenomenon described by Ukhtomskii of dominance in the act of defecation was the observation that before stimulation of the cortical site there was no defecation. Consequently, the appearance of defecation in this experiment is causally related to the effect of motor excitation on an established state of excitability in the system of neural pathways ensuring the act of defecation. This observation by Ukhtomskii was later supported by a number of data from other laboratories.

For example, in the laboratory of Razenkov the following interesting observation was made. When a copper sulfate solution was introduced into the stomach of a dog, the act of vomiting soon occurred so that the animal could relieve itself of the injurious substance. In response to the same solution being introduced into the rectum, defecation occurred. These reactions are appropriate, i.e., they correspond exactly to the afferent zone to which the stimulus is applied (experiments of E. B. Babskii).

One can, however, obtain a different result or, as expressed by Vvedenskii, a "distorted" result if one changes somewhat the experimental conditions. First the copper sulfate solution was introduced into the animal's stomach. However, for some reason the effect of the copper sulfate was subthreshold, and therefore no vomiting occurred. At this time it was necessary to introduce copper sulfate also into the rectum. The result was somewhat unexpected. With the second introduction of copper sulfate, instead of the expected act of defecation, vomiting occurred. In analyzing this observation, Ukhtomskii emphasizes that in this case interception of impulses is especially marked, since vomiting and defecation, as physiological acts of the intestinal tract, involve muscular contractions of opposite direction.

Ukhtomskii cites the above examples as illustrations of dominance at a purely phenomenological level. At that time they could not be subjected to deeper physiological analysis. This is now more feasible due to recent advances in the study of the physiology of the central nervous system.

First we must consider this question: what is the spatial relationship between these two different processes—the anticipatory dominance and the excitation arising from an extraneous or specific agent which intensifies the latent dominance so that the reaction occurs? In other words, at what stages of their development could these two excitations interact?

Acceptance of the concept that any behavioral act (as well as any function of the organism which ends in a beneficial adaptive effect) is accomplished according to the same physiological architecture considerably facilitates the understanding of the interrelation of these excitations.

We have in fact already seen that decision making is crucial in the patterning of any functional system, which is followed by the implementation of the activity via the efferent pathways of the central nervous system.

Instead of asking at what stages two competing excitations could interact, we must ask at what stage of development two functional systems can interact with each other, resulting in the elimination of one of them.

In the latent dominant state, excitation may *accelerate* the process of afferent synthesis, if it was heretofore delayed, and lead to decision making in favor of a given act. The same excitation, however, may also raise a latent decision to the *threshold level*, i.e.,

implement an already made, but for some reason delayed decision. One of the reasons may be the given specific interrelations of the excitations in the central nervous system.

Where and how is a latent dominant elicited? The primary reticular mechanism is most likely, which, lying on the pathway of the second excitation, rapidly raises the general excitability to the threshold level of the latent dominant. The essential point here is that *before the second stimulus has patterned the afferent synthesis and decision making appropriate for it, via the reticular formation* it intensifies the preexisting latent dominance of the first functional system. This process is possible only if a mechanism for the convergence of impulses on both subcortical and cortical neurons exists.

Figure 18.1a depicts the most probable relations of two series of impulses, one of which may lose its appropriate development already at the first stage.

These three effects have one physiological property: through the reticular formation they can spread to all mechanisms of the activity dominant at a given moment, although this dominance may be latent. Due to a summation of still nonspecific reticular impulses and already specific impulses of the latent dominant, the latter changes from a subthreshold to a threshold state, resulting in external activity. The most characteristic feature of this case is that the actual reaction, specific for the triggering agent, does not reach the moment of formation.

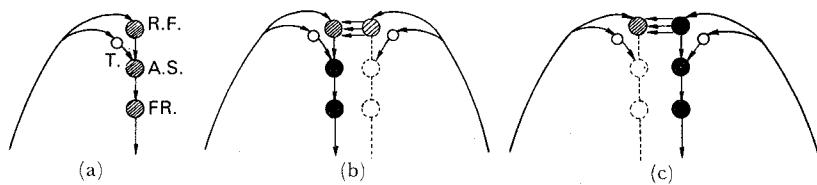


FIG. 18.1. Three possible relationships of two integrated activities of the central nervous system. R.F., reticular formation; A.S., zone of afferent synthesis; F.R., zone of formation of reaction; T., thalamus; (a) reflex activity is fully manifested; (b) one of the activities has, by its excitation, intensified another activity already at the level of the reticular formation, and therefore has not developed to the stage of formation; (c) an activity with intensified excitation (solid circles) inhibits another activity already at the level of the reticular formation, and therefore develops to the point of peripheral manifestation. The inhibited activity is not manifested.

If one applies the above concepts to an example in which the act of vomiting dominates, as discussed by Ukhtomskii, then they become especially convincing. As a matter of fact, for both defecation and vomiting the integrative formations are located at the level of the bulbar and diencephalic centers, i.e., precisely in the area where the activating influence of the reticular formation is especially strong. Consequently, at the very first site of interaction of triggering afferent impulses, belonging to two different activities of the organism, there is every possibility for the interception of impulses. However, processes later develop in direct relation to which functional system is, as a whole, patterned with greater speed. Thus, this system will comprise the final paths by which the act is effected.

From the concepts presented above, it follows that in the final analysis the determin-

ing factor is the speed of propagation of impulses from the receptor; the speed usually depends on the strength of the stimulus.

From the physiological point of view, it is not difficult to conceive of this most rapid propagation of impulses along the functional system dominant at a given moment. On the basis of contemporary data about the nature of excitation, it is reasonable to assume that a continuous stream of some afferent impulses "feeds" the dominant, i.e., creates conditions for facilitated or accelerated depolarization of all synaptic and cellular formations of a given functional system.

As an example of latent dominance created by an intentional facilitation of propagating impulses within a definite system of neural elements, one can cite the experiments of Shelikhov, a collaborator of mine. These involved a generalization of strychnine discharges in the cerebral cortex. Placing on the cortex, by the Baglioni and Amantea method (Baglioni and Amantea, 1912-14; Baglioni, 1916), pieces of filter paper moistened with a solution of strychnine sulfate, he observed after several minutes typical epileptiform discharges generalized throughout the cortex. After this, the cortical site to which the strychnine had been applied was cooled by pieces of ice placed on it in order to suppress its activity. In fact, a few minutes after the ice had been applied, the discharges at the site of strychnine application ceased, but at all the other sites of the cerebral cortex they continued.

This experiment, combined with severing the corpus callosum and isolating the "islet" of cortical tissue to which the strychnine was applied, convinced us that there is a definite dominance of rhythmical discharges in the subcortical areas.

Until now we have been concerned with the obvious dominant activity of definite subcortical structures discharging synchronous rhythmical impulses to the entire cerebral cortex. However, eventually these generalized discharges will cease. Sometimes, if a subthreshold concentration of strychnine is applied, the cerebral cortex shows normal electrical activity. Then on this background, if a thermal nociceptive stimulus is applied to the skin of a hind leg, the cerebral cortex immediately begins again to show rhythmical epileptiform discharges, synchronous for all regions of the cerebral cortex.

An analysis of this interesting phenomenon by means of chlorpromazine and adrenaline, described in detail by Shelikhov, leads us to the conclusion that the latent dominant excitation was here localized in the adrenergic part of the reticular formation and of the nonspecific thalamus (Anokhin, 1957b; Shelikhov, 1959). Precisely here occurs the summation of impulses evoked by the nociceptive stimulus on the background of intensified excitability which had been caused by strychninization.

We often observed an analogous phenomenon in the development of motor activity of an axolotl in the embryonic period. In this case the impulses from the tactile stimulus of the forelimbs have two possibilities for propagation: first, along the ascending pathways through the integrative mechanisms of the medulla oblongata to the musculature of the entire body (general reaction); second, through synapses of the corresponding cervical segments of the spinal cord and back to the muscles of the limb being stimulated (local reaction).

The maturation of cellular and synaptic structures of the central nervous system in

the axolotl proceeds, as is known, from head to tail. Consequently, at some stage of maturation, the propagation rate of impulses through the already matured synapses of the medulla oblongata will inevitably be higher than at the level of the cervical segments of the spinal cord.

This morphological principle suggests that the completely matured centers and synapses of the medulla oblongata, having a high excitability at a certain stage of development of the axolotl, will always intercept the afferent impulses coming from the forelimb. Afterwards, there begins a new stage of development in which both the spinal cells and the synapses have matured sufficiently well. The result is that now the same stimulation of the forelimb can cause local withdrawal of only the stimulated limb.

This example shows that the propagation rate of afferent impulses may become a factor determining the preferential formation of some adaptive activity. We do not as yet know more exactly what is the most excitable, and therefore dominant, functional system at a given moment. However, there is a basis for assuming that physiologically this latent dominance is a stationary excitation which needs only to be slightly intensified by a remote excitation in order for it to change immediately into a propagating explosive process reaching the terminal neurons and the effectors of the given functional system.

Once again we are faced with the question: if the preexisting latent dominance belongs to the complex system of interrelationships present at all levels of the central nervous system, then at what point or points of this system does the interaction of afferent excitation and preexisting stationary excitation occur? Moreover, what determines the threshold for the emergence of this latent excitation onto the peripheral effectors?

Although it is presently difficult to give a definite answer to all these questions, nevertheless one side of this problem has been lately sufficiently clarified: the question of where for the first time the extraneous afferent impulses come in contact with the afferent part of the dominant activity. The interaction occurs in the reticular formation of the brain stem.

From Fig. 18.1 it is evident that any given series of afferent impulses may intensify and trigger the preexisting dominant state even when propagating only along the reticular formation and not having patterned its own specific reaction. If the reaction has already begun to be patterned, i.e., decision making has occurred, then other activities of the organism will be inhibited.

Therefore, every afferent impulse, having acted at a given moment on the nervous system of the animal, may either intensify the latent dominant state and activate an effector, or pattern its own specific reaction. Which of these possibilities occurs depends on the relationship between the intensities of the competing impulses.

It is important to emphasize here that it is difficult to imagine the development of any dominant state without the intensifying, nonspecific action of the reticular formation of the brain stem.

In the study of conditioned reflexes, many cases are known of the dominance of some activity. In essence, the very fact of the elaboration of a conditioned reflex is a typical example of revealing a dominant state of the central nervous system.

Indeed, due to the fact that in a given experimental situation the animal always receives only bread crumbs or a meat and bread crumb mixture, the entire setup acts as an alimentary stimulus, bringing the alimentary excitation of the animal to the threshold, i.e., to the moment of actualization.

However, at the subthreshold level of initial alimentary excitability, the alimentary dominant state remains latent and is what we at one time called pretriggering integration, since the latent alimentary excitation is itself a complete functional system. The conditioned stimulus in this sense does not form *de novo* an alimentary excitation, as is for the most part tacitly assumed; it only brings the preexisting alimentary dominant state to the threshold (Anokhin, 1949c).

This anticipatory dominant state is quite apparent when the animal is in a state of intensified alimentary excitability. Then it is only necessary to place such an animal on the stand for salivation to begin immediately.

Special procedures can make this anticipatory dominance especially evident. This was well shown for the first time in the experiments of Konradi (1932), in which he compared conditioned alimentary and conditioned defense reflexes. Later, in a special form of experiment, the question concerning anticipatory dominance was examined by Laptev and by Asratian (1959, see English translation, Samuel A. Corson, ed., 1965, chapters 4 and 6), although Asratian interprets the mechanism of this dominance somewhat differently, naming it "switching." Since the question concerns the same dominant state, we will discuss it in more detail.

As was pointed out above, the whole setup connected with food reinforcement functions as a stimulus supporting a definite alimentary dominant state. But such a stimulus, evoking and maintaining a stationary dominant excitation, can be provided not only by the setup of the experimental chamber as a whole, but also by its separate components, and even by other factors of the environment.

For instance, the time of day at which the experiments with food reinforcement are always run inevitably becomes part of the experimental setup. Until the time when this component becomes a point of differentiation, its effect is masked.

However, if the experiments are conducted so that the time of day is the only distinguishing feature of two qualitatively different experiments (alimentary, defense), then this same time of day becomes a special signal stimulus evoking the appropriate stationary dominant state of a specific functional system. Then this same stimulus will provoke or, more accurately, intensify, the different dominant states.

If in the morning the bell is always reinforced with food and in the evening with an electric current, then the very act of bringing the dog into the chamber and placing it on the stand in the morning at once evokes an alimentary dominant state. On the other hand, bringing the dog into the same chamber in the evening will at once evoke the dominant state of the defense reaction.

Consequently, the time of day has become that aspect of the setup which determines the latent dominance of a particular functional system. According to the mechanism examined above, the latent dominance predetermines the reaction to the conditioned stimulus.

For a long time I have believed this to be the only physiologically acceptable expla-

nation of any kind of reaction in animals, including reactions based on a special dominant state.

We agree with Ukhtomskii that it is difficult to imagine a state of the central nervous system "without dominance." Dominance is invariably present, since the organism is always involved in some kind of activity. Such dominant states are usually evoked by a complex of afferent influences, whose composition determines the type of dominant state. The dominant state, in turn, predetermines the response to any external stimulus.

Various motor acts of a frog will illustrate this proposition. If a frog sitting on a bank is pinched on the leg, it jumps. If the frog is floating in water, the same pinch causes it to swim rapidly.

We usually consider as self-evident these types of reactions by a frog in two different situations in response to the same stimulus. It would be surprising if the frog were to "swim" on the ground and "jump" in the water. However, since this conclusion is only common sense, we do not attempt to understand the physiology of this self-evident phenomenon. In effect, it entirely agrees with those principles of dominant states which were discussed above.

In fact, the sum total of afferent impulses, coming from various receptors of the body of the frog on the shore, is the peculiar afferent integral which evokes in the central nervous system a dominant setup appropriate for it. Expressing it more precisely, we can say that in the frog sitting on the ground there develops a quite definite pretriggering integration of processes, which corresponds to the act of jumping. The sudden stimulus only adds new afferent impulses to this subthreshold dominant and thereby leads to the emergence of dominant impulses to the effectors.

The position of the frog in the water, with respect to a complex of afferent impulses coming from the skin and muscles to the central nervous system, is something distinctive and evokes a dominance of the system of impulses appropriate to the given situation. It is natural that the same stimulus under these new conditions will lead to the act of swimming.

Dominant states are especially apparent with motor acts, since the animal clearly manifests a motor reaction typical for its dominant state. An example of this kind is the above-described experiment with the unexpected reinforcement of the conditioned alimentary reflex with meat instead of bread crumbs. The animal received meat only once on the left side of the stand instead of the usual bread crumbs. But this was sufficient for all conditioned stimuli, both for the left and for the right side, to evoke on the next day a motor reaction only to the left side. It is clear that all the neural connections which usually brought about the reaction to the left side of the stand had now reached a dominant state. Moreover, upon entering the experimental chamber, the animal at once went to the left feeder and showed a marked orienting-investigative reaction by looking it over, sniffing it, etc.

In this example not only is the dominance of a definite system of nerve impulses evident, but also the inertia of the previously established dominant state. This feature of the dominant state, noted by Ukhtomskii as one of its general properties, has, as we shall see later, an important role. The inertia of dominant states of the central nervous system is particularly apparent in the changes of the vegetative components of the

conditioned reaction, all the more so if they are caused by one of the easily distinguishable unconditioned stimuli: the alimentary or the defense stimulus.

Makarov (see Makarov, 1960, 1961) conducted the following experiments in our laboratory. In several dogs in which at some time in the past conditioned defense reflexes had been elaborated in chamber A, he began to elaborate new conditioned alimentary reflexes, but this time in chamber B, while continuously recording the respiratory component of the conditioned reaction. From the very beginning of his work with conditioned alimentary reflexes there existed a dominant defense state. The animal had high respiratory activity and sometimes even lifted its right hind leg, to which electrocutaneous stimulation had been applied a year before.

These results indicate that the whole experimental situation, even with a new chamber and with biologically positive reinforcement, remained a strong stimulus, restoring the former dominant state. Of interest in these experiments was the high inertia of the biologically negative dominant, which was present for a long time in spite of food reinforcement.

However, after several months, a systematic reinforcement of new conditioned stimuli with food led to a gradual disappearance of the defense dominant and to its replacement by an alimentary dominant. This transition was clearly manifested in the change in the character of the respiratory component of the conditioned reactions: the panting disappeared and the respiration became more quiet and typical for an alimentary reaction.

At this stage of experimentation the animal was once more put on the stand in chamber A, that is, in the chamber where conditioned defense reflexes had been elaborated. Observation showed that the system of impulses related to electrocutaneous reinforcement became the dominant process in the central nervous system of the animal. The animal again began to lift its leg, the respiratory component became typical for defense reflexes, etc. (Fig. 18.2).

These observations quite clearly reveal the most important role of the experimental setup, or of any one of its components: it creates an initial dominant state of the animal

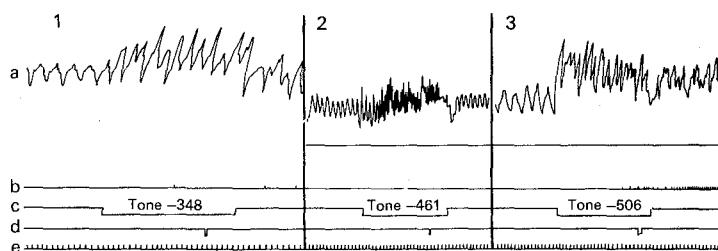


FIG. 18.2. Example of a stable dominant state in response to the total experimental environment. 1, changes in the respiratory component in response to an alimentary conditioned stimulus (tone) tested in a conditioning chamber where previously alimentary conditioned responses were elaborated; 2, the same tone presented in a conditioning chamber where a motor defense reflex was developed; 3, the same tone presented several days later, again in a conditioning room where conditioned alimentary responses were originally elaborated. a, pneumogram; b, salivation; c, unconditioned stimulus; d, conditioned stimulus; e, time.

and determines the level of excitability for a definite (integrated) activity of the organism. In some cases the intensity of the dominant state is such that the activity characteristic of it is externally apparent, while in other cases this dominant state remains latent.

It must be pointed out here that prolonged "trace" processes in the central nervous system occurring as a result of previous pathological states are also an example of latent dominant states (Speranskii, 1935; Durmish'ian, 1952).

In experiments with conditioned reflexes the latent dominant state can appear in the most diverse forms. For instance, the defense dominant may not appear in an activity specific for it, but nevertheless may be manifested either in an intensification of the respiratory component or in the suppression of the secretory component when a conditioned alimentary stimulus is applied.

Such a masked form of the dominant state was most clearly shown by my collaborator Shumilina. Wanting to obtain a differentiation of conditioned stimuli reinforced by alimentary and defense stimuli, she distributed the stimuli so that the first half of the experiment involved only conditioned alimentary stimuli, while the second half of the experiment had both conditioned defense and conditioned alimentary stimuli. The purpose of such a distribution of stimuli was to obtain a preferential alimentary dominant state in the animal. However, this did not result: the application of several electrocutaneous reinforcements in the first experiments led to the complete inhibition of conditioned alimentary reactions in both the first and second halves of the experiment; moreover, this inhibition lasted for a period of several months.

At this stage of the experiments the conditioned defense stimuli were discontinued and for a period of several months experiments were conducted with only alimentary reflexes. However, in spite of the fact that in the course of such a long period of time not once were either conditioned or unconditioned defense stimuli applied, the conditioned alimentary reactions remained inhibited as before, although the unconditioned alimentary stimulus evoked a normal reaction.

This is an excellent example of the degree to which the latent defense dominant may be inert. But it was necessary to conduct special experiments in order to be convinced that the cause of inhibition of conditioned alimentary reactions is the latent dominance of the defense reaction. For this purpose, it was decided to use a completely new indifferent stimulus, the sound of gurgling. The application of the new stimulus immediately evoked a clear defense reaction: the lifting of the leg which at one time had been stimulated by an electric current. The specific character of the respiratory component of the reaction also changed: respiration became quite typical of a defense (i.e., a biologically negative) reaction (Fig. 18.3).

Further experiments revealed an interesting property of latent dominant states. Shumilina switched those conditioned defense stimuli which had not been used for several months. From a certain moment a light, which some time ago had been reinforced with an electric current, was now reinforced with a meat and bread crumb mixture. After several days of experimentation the situation noticeably changed: all conditioned alimentary reflexes which for a period of five months had been inhibited began to give a positive secretory effect which gradually came close to the normal value.

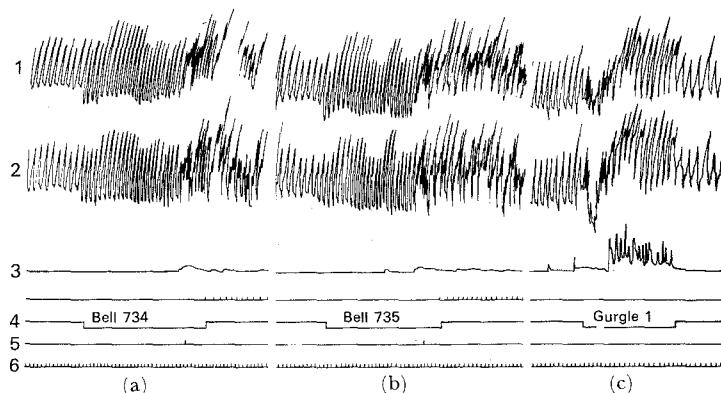


FIG. 18.3. Demonstration of a latent defense dominant. (a and b) Alimentary conditioned reflexes. For several months previous to this experiment defense stimuli had not been used. An activated but regular respiration is seen. (c) Gurgling, a stimulus never previously used, was given. A marked orienting reaction can be seen which then becomes a distinct defense reflex (line 3). Designations the same as in Fig. 14.8.

These experiments convinced us that the simple elimination of conditioned stimuli to which a dominant defense state had previously been developed is not sufficient to make the defense dominant disappear. It assumes a latent state and remains such for a long time.

On the other hand, if the conditioned defense stimuli (which had not been applied for some time) are given a new alimentary signal meaning (switching), the dominant defense state is completely eliminated, and the remaining conditioned alimentary reflexes are freed from the secondary inhibitory effect of this state.

Another interesting detail in the experiments of Shumilina gave evidence of the fact that latent dominant states occur as a result of elaboration. As previously stated, the conditioned secretory effect was completely inhibited when conditioned defense stimuli began to be used. However, because of the stereotyped arrangement of the conditioned stimuli, this inhibition appeared precisely in that period of the experiment when defense stimuli were applied.

As soon as the last defense stimulus was applied, the conditioned alimentary stimuli following it could already produce, to a certain extent, a positive conditioned alimentary effect. Consequently, inhibition of conditioned secretion by the latent dominant defense state occurred mainly in that part of the experiment in which electrocutaneous stimulation was yet to come. When this danger had passed, however, the inhibition disappeared from the cortical representation of the alimentary center, and the conditioned alimentary reflex was manifested.

These variations of inhibitory influences of the latent dominant state can be easily understood with the use of Fig. 18.1. The above experiments lead us to think that dominant states may result in three possible events:

1. The dominant state may be appropriately actualized in external activity under the influence of any external stimulus.

2. The dominant state may be completely inhibited by another dominant and already patterned activity.
3. The dominant state, without being actualized in external activity, may cause a nonspecific intensification of another activity dominant at the given moment.

It is quite possible that there are considerably more forms of actualization of the dominant excitation than have been enumerated. And yet, there is no doubt that these three forms occur most frequently and are the most significant ones in the experimental study of higher nervous activity.

The most typical form of dominance involves the interception of any new and extraneous stimulus. This can be easily accomplished under the experimental conditions of the secretory-motor method we have developed with bilateral and multilateral feeding.

The simplest phenomenon of dominance can be achieved by intensifying the system of excitations which determines the conditioned reaction of an animal to the right or to the left side of the platform. In our experiments with a bilateral platform, the number of unconditioned reinforcements from the right and the left feeders is approximately the same on each experimental day. As a consequence, the animal sits in the middle of the platform during the intervals between conditioned stimuli, and its chances for receiving the next reinforcement of bread crumbs are nearly the same for the right and the left sides.

On one day a conditioned stimulus, let us say for the *left* side of the stand, is used three times in succession; this does not occur in the usual experiments. This minor change in the experiment is quite sufficient to produce a characteristic dominant state.

If a conditioned stimulus for the *right* side is then presented, the animal gives a motor response to the *left* side. Because we conducted such experiments during that period of the work in which the animal had long since ceased to give incorrect motor responses, we may acknowledge that there is a dominance of the entire system of excitations which determines the conditioned motor response to the left. That the animal in these cases prefers to remain at the left feeder, rather than going to the middle of the stand as it usually does, further supports this conclusion.

We designated such a reaction of the animal by the term "switching" (which was vaguely used in physiology at that time), since the conditioned stimulus which usually produces a motor response to the right side of the platform was actually "switched" in this case to the system of cortical impulses which ensures a response to the left side (Anokhin, 1932b); we continue to adhere to the very clear concepts concerning the dominant which by that time had been developed in the school of Ukhtomskii.

In connection with this phenomenon observed in our laboratory, we wrote:

The training of one of the conditioned stimuli (A) leads to the development of dominance in the appropriate alimentary motor complex. Therefore, the presentation of an opposite stimulus leads to the switching of the impulses from the left alimentary motor complex to the more excitable one which has undergone Bahnung. . . . Experiments in which all stimuli of the left side are switched to the right complex provide evidence of the presence of dominance not in the cortex, but along an *entire vertical line* in the central nervous system (Anokhin, 1932b).

In subsequent years the phenomenon of "switching" in the processes of higher nervous activity was described in the previously mentioned experiments of Laptev and of Asratian, as well as in many others. The laboratory of Asratian has furnished many examples showing that "switching" is indeed widespread in the adaptive behavior of animals. In a number of experiments by collaborators of Asratian, it was shown that any factor of the external (and probably also of the internal) environment may be a "switch." Therefore, on the basis of the universal importance of these phenomena of higher nervous activity, these investigators are evidently inclined to single out the phenomenon of "switching" as a special principle in the function of the cerebral hemispheres (Asratian, 1953).

It is difficult, of course, to object to the use of the term "switching." This term undoubtedly gives us a descriptive idea about the interrelationship of the observed phenomena. Yet to believe that the use of the term "switching" brings us closer to an understanding of the physiological nature of this phenomenon would be a dangerous assumption. As a figure of speech it is of no more help to us than are other similar expressions, such as "interception," "conflict," or "distortion."

However, the physiological nature of this phenomenon is definite enough and apparent from what was said above: "*switching*," as a phenomenon, is the direct result of a preexisting dominant state (created in one way or another) of a specific functional system. For this reason, we accepted the above physiological interpretation of the phenomenon of "switching" in 1932. All of our subsequent experimental work has further convinced us of the correctness of this position.

It is clear that the transmission of any impulses to effector pathways other than the "legitimate" ones can occur only in the presence of some dominant system of excitation in the cortex and subcortex. The primary role of switches of any kind is that *they are stimuli which create or prepare a specific stationary dominant state* which is subsequently actualized by means of a triggering stimulus. If there is no pretriggering integration dominant at a given moment in the central nervous system, no stimulus will be able to induce an organized activity in the animal. This preparatory function is, in our opinion, the universal role of dominant states of the central nervous system in the adaptive behavior of animals and man.

Consequently, the next problem in the study of the physiological role of dominant states is first of all to gain an understanding of the structure and physiological nature of dominance itself and secondly to discover the *mechanisms and location* of the "switching" of any other stimulation to this dominant activity.

Concluding the brief description of the role of dominant states in the patterning of higher nervous activity, we cannot fail to point out that the advances in recent years in the field of the physiology of the central nervous system considerably enlarge our possibilities for a more detailed analysis of dominant states.

From the preceding account it can be seen that the rapidly increasing knowledge of the physiology of the reticular formation of the brain stem enables us to accomplish such an analysis. Here it is appropriate to recall the basic physiological properties of the reticular formation. It has the capacity to intensify any cortical activity in a general and nonspecific manner. This intensification appears so automatically and so

invariably for all afferent impulses arriving from the periphery at the cerebral cortex, that we must ask whether the reticular formation could be a special mechanism for the intensification of any cortical activity, regardless of its components and their interrelations during the patterning of this activity. This, at least, is the implication of the data of Yoshii *et al.* (1956).

There is reason to assume that an especially fruitful study of the neurophysiological aspect of the dominant would involve the further characterization of the intensifying action of the reticular formation of the brain stem on cortical activity. This is suggested by the following similarities between the physiological properties of the dominant state and those of the reticular formation of the brain stem:

1. Dominance is the maintenance of increased excitability and readiness to carry out any function of the organism. This readiness to act is primarily caused by the constant influx of afferent impulses from the periphery or by the automatic effect of humoral substances on specific substrates of the brain.

A basic property of the reticular formation of the brain stem is its ability to "store" afferent impulses (let us recall Shelikhov's experiments), and subsequently to activate all cortical zones.

2. According to Ukhtomskii, the dominant can intensify itself and can go into action upon the arrival of "remote" impulses.

The reticular formation can exert a *continuous* tonic influence on the cerebral cortex. Moreover, with each series of afferent impulses, it evokes *additional generalized activity* in the cerebral cortex.

3. The dominant state is closely related to the influx of impulses from the subcortical apparatuses, especially from the hypothalamus. This is clearly evident upon intensification of the emotional level of any activity. There are experimental data which convincingly show that any generalization has a definite biological modality, i.e., that on the whole any dominant functional system has features of biological specificity.

In constant interaction with the hypothalamus, by its activating effect the reticular formation ensures a high level of excitability in all emotional activity, especially when it becomes prolonged or "stagnant."

Comparing these three characteristics reveals the similarity in physiological content between the theory of the dominant and the most recent data on the reticular formation of the brain stem. In any case, we would err if we failed to seriously consider the interpretation of dominant states from the standpoint of cortico-subcortical interrelations. And, importantly enough, the dominant provides a link between the general laws of higher nervous activity and their detailed neurophysiological analysis. The following sequence depicts the study of nervous activity: conditioned reaction \Rightarrow dominant \Rightarrow general physiology of the reticular formation.

The above analysis would, however, be incomplete if we did not examine two fundamental questions in the systemic approach to the explanation of latent dominant

states of previously integrated acts. The *first question* may be formulated as follows: how complete in its *architecture* is a *latent* dominant functional system?

The absence in this case of external activities characteristic for this system clearly indicates that the efferent impulses have not reached the effectors yet. But how far has the patterning of the functional system progressed? Has decision making occurred, has the action acceptor been patterned, etc.? As for the action acceptor, it may be assumed that it exists even during latent dominance of a functional system. At any rate, the above-described experiments involving the substitution of meat for bread crumbs convincingly indicate this.

These considerations inevitably lead to the *second question*: where and how is the triggering mechanism organized which maintains the entire functional system in a latent state of readiness, but immediately allows it to proceed and develop as soon as the system receives additional impulses at the level of the brain stem?

As can be seen, the modern neurophysiological approach to so fundamental an aspect of the activity of the nervous system as *dominance* brings forth new, interesting problems concerning the activity of the brain. Motivation is one such problem. In its physiological essence, motivation naturally involves mechanisms of the dominance of one functional system and of the elimination of other competing functional systems by means of coordinative inhibition.

The significance of Ukhtomskii's concept concerning dominant states in the explanation of such universal cortical phenomena as "irradiation of inhibition" and "concentration of inhibition" will be shown in the next chapter. Here I have wanted only to bring the attention of investigators of higher nervous activity to the theory of the dominant, without which a *neurophysiological interpretation of the higher forms of adaptation of animals and man is impossible*.

CHAPTER 19

The Problem of the "Irradiation of Inhibition"

ANY new concept which reinterprets a given subject must sufficiently explain the new principal and significant data pertaining to the subject. This requirement had to be met several years ago when we were attempting to explain the origin of internal inhibition as described in the preceding chapters. We were well aware that an extension of our concepts of internal inhibition, as a consequence of the discordance and conflict between two nervous activities, must involve a convincing explanation of the principles of the spread of the fundamental nervous processes, excitation and inhibition, over the cerebral cortex as well.

There is no problem here regarding the spread of excitation, since all the available data from general neurophysiology are completely unequivocal about this.

We are familiar with the general physicochemical bases of the origin of excitation, with the nature of its propagation along the nerve fiber, and, finally, with the transmission of excitation from one excitable system to another by way of interneuronal and organ synapses (Vvedenskii, 1886; Nachmansohn, 1959, 1961; Koshtoiants, 1956; Golikov, 1950; Latmanizova, 1949; Rusinov, 1955; Eccles, 1966, pp. 24-58; and others). However, we encounter enormous difficulties as soon as we attempt to similarly explain the spread of inhibition over the neural structures in general and over the cerebral cortex in particular. This is one of the most difficult points impeding the development of a unitary *physiological basis* for general neurophysiology and for the physiology of higher nervous activity. It is therefore not surprising that this point came to be discussed in non-Russian literature (Fulton, 1949; Liddell, 1949; Gantt, 1948; Hilgard and Marquis, 1940, 1961; Hebb, 1949; Hull, 1943; and others).

We must, therefore, first of all discern the neural mechanisms of the processes of the generalization and irradiation of conditioned inhibition which are supported by abundant data in the theory of higher nervous activity.

For the analysis of any problem, it is necessary to establish from the very beginning what is *entirely certain* and what is only *probable*.

If one proceeds from the generally accepted propositions of Pavlov's laboratories, then we can recognize as a certainty that in the process of the generalization of excitations, any new or indifferent stimulus presented alongside already elaborated conditioned alimentary reflexes immediately evokes a conditioned secretory effect. Since this new stimulus had itself never been specifically paired with feeding, the question must naturally arise: why did the excitation from this new stimulus proceed precisely to the

cortical representation of the alimentary center and to the unconditioned alimentary center?

In the general concept of temporary connections there is no basis for this conditioned secretory effect, and therefore Pavlov naturally turned to a search for general physiological principles. The explanation was based on a well-known neurophysiological fact: the ability of excitation to irradiate over neural substrate to a considerable distance from its point of origin. Therefore, from the very beginning this *certain* fact, i.e., the presence of a secretory effect in response to a new stimulus, was given the *most probable explanation*: at a certain stage in the elaboration of a conditioned reflex, a conditioned stimulus evokes in the corresponding cortical area of the analyzer a process of excitation which encompasses a substantially greater number of cortical neural elements than would be appropriate for the cortical projection of the given stimulus.

As a result of this initial irradiation of conditioned excitation over the cortical area of the analyzer, the impulses evoked by a new stimulus applied to the same analyzer will arrive at the area with an elevated level of excitation and therefore evoke a conditioned secretory effect even though it was not previously reinforced.

At the first stage in the development of the science of conditioned reflexes, this working hypothesis satisfactorily explained a series of phenomena and therefore often served as the basis for further investigations.

However, Pavlov repeatedly pointed to a certain contradiction in this working hypothesis: a conditioned secretory effect can be evoked according to the principle of generalization not only by a new stimulus *applied to the given analyzer*, where the conditioned excitation was initially irradiated, but also by any other stimulus pertaining to other analyzers. Pavlov was faced with the dilemma of either extending the previous hypothesis concerning the initial irradiation of excitation within the limits of one analyzer *to the entire cerebral cortex* or searching for a new explanation. How did Pavlov resolve this dilemma?

Fortunately, we possess a remarkable document of how Pavlov persistently strove to develop a satisfactory working hypothesis, namely, his statements concerning the possible mechanisms of generalization of excitation over the cerebral cortex.

His arguments in regard to this question are of such significance for the solution of the whole problem of the *irradiation of cortical inhibition* that we shall take the liberty of quoting them in more detailed excerpts. This is all the more essential since most of the investigators working in the field of higher nervous activity retain the original point of view which is based entirely on the assumption of the irradiation of excitation and inhibition *within the limits of one analyzer*.

Pavlov, in the face of this dilemma, decided upon the development of a *new* working hypothesis which considerably extends the previous possible explanations. He said:

Here one can imagine that when one has formed some kind of conditioned defense reflexes, either motor or secretory, and continues to present the same stimuli throughout the entire experiment in the same setting, one must reasonably assume that the center which corresponds to the unconditioned stimulus becomes strongly charged. Its representations in the cortex are in a more or less continuous working condition

and in a particular state of tonus. If an alimentary stimulus is presented during the experiment, it must be assumed that throughout the entire experiment the *alimentary center and its cortical representations* are *continuously* in a certain degree of tonus, . . . if a secretory defense stimulus—the secretory defense centers, if a motor defense stimulus—the motor defense centers, etc.

In the intervals between stimuli, this center is *in a state of latent excitation*. . . . However, if you involve some other center of stimulation, then quite often the irradiation from it reveals the excitation of the periodically stimulated center, and the effect of this center appears. This is what Ukhtomskii has called the "dominant" [italics—P.A.] [Pavlov, 1949c, p. 21].

Thus, these considerations led Pavlov to recognize a continuous latent and intensified excitation of the system of neural connections in the subcortex and cerebral cortex.

From the preceding chapter, it is clear that this "latent excitation" is that most characteristic condition of the experimental animal which inevitably develops after the presentation of a given unconditioned stimulus in a certain experimental setting. One must not forget the important factor that this complex system of latent excitations, which is dominant at the given moment, is created either by the setting as a whole or by any one of its individual components which acts as a signaling stimulus for this dominant state. These signaling stimuli, which create the latent dominant state, can be highly diverse. Such a stimulus may be the magnitude of the first unconditioned reinforcement which subsequently creates a definite alimentary tonus of the animal for the entire experiment (Lomonos, 1953). It may also be any preceding stimulus which creates an attitude or definite tendency in the reactions of the animal for the subsequent experimental period ["attitudinal stimuli" according to Vatsuro (1947, 1948)]. They also include the various "switching" types of experiments conducted by Asratian (1953).

It is only important to remember that in all the enumerated cases, in spite of the extreme diversity of these signaling stimuli, *they invariably lead to a latent dominant excitation of some system of neural connections which then becomes expressed as a behavioral act under the influence of a triggering stimulus*. This is the mechanism also indicated by our experiments involving the secretory-motor technique [see Fig. 15.1—S.A.C.], in which we were deliberately creating a dominant state related to one of the sides of the reinforcement (Anokhin, 1932b).

Concluding these considerations about the nature of the process of the generalization of excitations, Pavlov said: "One must choose one of two explanations: *either this is generalization, or it is a Bahnungsreflex*" [italics—P.A.] (Pavlov, 1949c, p. 21).

In order to resolve this question, Pavlov assigned to K. S. Abuladze (see Pavlov, 1949c, p. 20) a very ingenious experiment, which is the prototype for all experiments involving dominant states. Abuladze performed the experiments as follows: the *first* half of an experiment was conducted with reinforcement by an unconditioned alimentary stimulus, but the *second* half with reinforcement by acid, i.e., by an unconditioned defense stimulus.

Since the recording of only salivary secretion provided no criteria for deciding to

which unconditioned stimulus it belonged, the character of the motor reaction was selected as the criterion. As is known, in response to an acid signaling stimulus, the animal begins to perform characteristic spitting movements. Experiments in such a setting have clearly demonstrated that any *new* stimulus presented *during the first half* of the experiment evokes a clearly alimentary reaction, while *during the second half* it evokes a distinct secretory defense reflex.

It was certain, then, that *during each half of the experiment there was a qualitatively distinct latent dominant* for which the "new" stimulus was only a triggering factor. On the basis of this experiment, Pavlov arrived at a quite definite conclusion: "This experiment has made it certain that *in all our experiments* there always exists a *Bahnungsreflex*, or summational reflex" [italics—P.A.] (Pavlov, 1949c, p. 22). This conclusion Pavlov considered to be "final."

If we take into consideration that the "Bahnungsreflex" and "summational reflex" are but synonyms of the dominant, it becomes clear to us that Pavlov regarded the dominant state to be an indispensable factor of higher nervous activity occurring in all our experiments.

In Abuladze's experiments, the movement characteristic for the substance being rejected served as the criterion for determining the nature of the reaction (defense or alimentary). These experiments did not permit an accurate analysis of all the transitional stages from one type of reaction to the other. Moreover, they did not permit detection of the presence of a *latent* dominant state of one of the two reactions (due to the lack of behavioral signs).

In view of the importance of this mechanism, Shumilina conducted the experiments described in Chapter 18, using a nociceptive defense stimulus in the second half of the experiment.

Recording the respiratory component of the conditioned reaction enabled us to determine how the substitution of one antipodal condition for another proceeds and what happens to the vegetative reactions of the animal when visible signs of motor reactions are no longer present.

Shumilina's experiments have demonstrated the presence of a persistent latent dominant state of the defense reaction and the influence of this dominant on the intensity of the respiratory component in the first half of the experiment. An unusual combination of two biologically opposite states of the central nervous system developed. On the one hand, it clearly reacts to the conditioned alimentary stimulus with the *specific* alimentary components; on the other hand, the vegetative components of the alimentary reaction *intensify* the alimentary reaction resulting from the defense dominant which is latent at the given moment.

In summary, we must point out that in the experiments of Abuladze and Shumilina one important property of the central nervous system is apparent: *the wavelike alternation of biologically opposite dominant states during one experiment*.

How should the nature of these wavelike changes in the general states of the central nervous system be interpreted? What processes *in the neural tissue* correspond to this wavelike alternation?

The answers to these questions are of great importance to the physiologist studying

higher nervous activity. They would enable us to understand the cerebral substrate directly involved and at the same time the mechanism of some very widespread dominant states and phenomena of higher nervous activity, such as the reflex to time, the dynamic stereotype, etc. In other words, I am referring to those processes in which wavelike fluctuations of the excitability of the brain occur according to an established stereotype, and in which the reactions of the animal anticipate the appearance of the appropriate stimulus.

The elucidation of the cause of these phenomena was accomplished by our collaborator A. D. Simonenko (see Anokhin, 1957a) by the same procedures used in Pavlov's laboratory for the study of the dynamic stereotype. In one of the sequential presentations of the complex of three stimuli, we suddenly substituted a bell for the light. In spite of the fact that the physical stimulus (the light) was absent in this experiment, and there was a bell in its place, which does not suppress the α -rhythm, *the suppression of the α -rhythm was as great as if the light itself had been presented* (see Fig. 1.2a). This experiment has convincingly shown that the brain has acquired its own wavelike alternation of excitability corresponding to the stereotypic order of the previously presented stimuli.

In addition to emphasizing the extraordinarily important ability of the central nervous system to fix and retain acquired dominant states in a definite sequence and in a definite localization, this observation also explains the results obtained in the study of the classical form of the dynamic stereotype.

Indeed, when presented in the dynamic stereotype in place of the light, why does the bell not produce its own conditioned effect, but the one characteristic for the light?

Now we can give a definite answer to this question : *at the moment of presentation of the light in the dynamic stereotype, the cerebral cortex and the subcortical structures acquire, in a wavelike manner, a definite dominant state, especially in that afferent area of the cortex which corresponds to the action of the light.* The bell itself is only a triggering factor which, probably at the level of the subcortical structures, brings the latent dominance to an external expression. We have already discussed in detail this fundamentally important problem, and we refer the reader to Chapter 18.

It is important to emphasize that the latent dominant has a definite physiological architecture which constitutes an established integration that we have termed "pretriggering integration" ("integrated pattern" according to Ukhтомский). But it does not reach the threshold at which its impulses could emerge onto the final pathways. Our investigations have previously established two important mechanisms on the basis of which this integration is patterned and remains in a latent state. There is reason to believe that the frontal lobes of the cerebral cortex play a significant part in this latter mechanism (Anokhin, 1949c; Shumilina, 1949, pp. 561-688).

Yoshii *et al.* (1956) have presented interesting data pertaining to this problem. Their experiments have revealed several new electroencephalographic characteristics of the conditioned reaction. They should, therefore, be described in detail.

The investigators employed the usual procedure of elaborating a temporary connection between an auditory stimulus and a flash of light. As has been known for a long time (Jasper and Cruikshank, 1937), this combination of stimuli soon resulted in the

following: after some pairings with light, the sound, which previously did not suppress the α -rhythm in the occipital region, began to suppress it. In order to make the unconditioned "reinforcement" more apparent, the investigators presented it in the form of rhythmic flashes. They recorded the electric potentials simultaneously from the reticular formation, the thalamus, and the cerebral cortex. They established the fact that "conditioned" excitation in response to an uninterrupted bell, occurring as rhythmic fluctuations of the potential and corresponding to the flashes of light, appears first in the reticular formation and only afterwards in the cerebral cortex. This is, of course, very interesting, and it is also fully understandable since it has already been thoroughly discussed in Chapter 14.

However, these authors describe another very interesting phenomenon which, in our opinion, leads them to erroneously interpret the architecture of the conditioned reflex. They have established that in a number of cases rhythmic conditioned discharges of a *spontaneous* nature, i.e., appearing without any stimulation, occur *only* in the reticular formation and are absent in the cerebral cortex. The authors regard this as one of the phenomena of "memory," whose location they consider to be the reticular formation. In addition, they emphasize that the cause of the appearance of such rhythmic discharges in the reticular formation, which reflect the rhythm of the "unconditioned" flashes, is not this stimulation, *but the action of the experimental setting as a whole*. While it is difficult to agree that the reticular formation alone is the "seat" of memory, their second conclusion is of unquestionable interest.

During the discussion of the physiological nature of dominant states, we have repeatedly pointed out that the experimental setting establishes a dominant *alimentary* or *defense* state at the very beginning of the experiment, even before the presentation of the conditioned stimuli. This was precisely the view maintained by Pavlov. Only by this anticipatory excitation can one explain the presence of the conditioned secretory effect.

From the above-described experiments of Simonenko, we learn that the electroencephalographic equivalent of such elaborated and stereotypic relations in the cerebral cortex is an anticipatory, i.e., to some degree *preparatory*, dominant state of the afferent areas of the cortex which precedes the actual presentation of the elaborated conditioned stimuli aimed at these cortical areas (see Fig. 1.2b).

Consequently, the results of the experiments of Yoshii *et al.* should not surprise us. At the present time, one can hardly assume that only the cerebral cortex is involved in the establishment of the conditioned reflex. On the basis of the study of conditioned secretory-motor reflexes, our laboratory has long since concluded that the conditioned reflex as a functional whole is represented both in the cortex and in the subcortex.

I have previously written :

The question of where the interference of the impulses from the conditioned stimuli for the different feeders occurs can be discussed with respect to both the cortex and the subcortical complexes. . . . Experiments in which all the stimuli of the left side are switched to the right complex indicate the presence of dominance not only at the cortical point, but *along the entire vertical* in the central nervous system (Anokhin, 1932b).

Thus, experimental data have long since suggested that the dominant state, which determines the preferential conditioned motor reaction, occurs in the subcortical structures as well as in the cortex, and that interference, i.e., the interaction and intensification of the conditioned stimuli, may take place in the subcortical structures.

Of course, at that time we could not accurately localize these "subcortical complexes." However, the progress made during recent years in the study of the physiological characteristics of the reticular formation of the brain stem and the intralaminar formation of the thalamus convinces us that the source of dominance, i.e., of the generalized intensification of all components of the conditioned reaction, must be sought here.

Returning to the conclusions of Yoshii *et al.*, we must say that the dominance demonstrated by them in the reticular formation leaves no doubt that it reflects the characteristics of the "unconditioned" stimulus, i.e., of the rhythmic flashes. It would, however, be premature to claim that this is "conditioned excitation" or that conditioned reflexes can be formed in the reticular formation. Such an assertion was made by Yoshii *et al.* (1957), but it can hardly be accepted without reservation, if we take into consideration everything we know about the true conditioned reflex in the broad biological sense of the term.

After a considerable number of investigators revealed that any afferent stimulation of a specific afferent system enters over the collaterals into the region of the "nonspecific system," i.e., the reticular formation, it became clear that all afferent impulses can enter into *intimate contact with each other* at this subcortical level (Moruzzi and Magoun, 1949; and others). Probably, the second location of such contact is the region of the intralaminar nuclei of the thalamus and, finally, the cerebral cortex (Jasper, 1954, 1966).

The latest investigations in this field, performed by means of the microelectrode technique, have shown that in the region of the reticular formation of the brain stem there is considerable overlapping of afferent regions with a pronounced occlusion phenomenon. This has further convinced us that the possibilities of interaction between the different afferent impulses are practically unlimited, even at the level of the reticular formation of the brain stem.

In view of these morphophysiological characteristics of the reticular formation, it is difficult to deny that it has a primitive form of *temporary connections* which is widespread, for example, in animals with primitive ganglionic nervous systems.

What, indeed, is the significance of sound in the reticular formation? It is a series of afferent impulses, having a definite level of intensity, which enters here via the collateral and increases the activation capacity of this system to a certain extent.

Stimulation of the gustatory receptors consists of the same kind of afferent impulses; however, they excite the reticular formation perhaps more extensively, and they inevitably interact with the preceding indifferent stimulation already in the axoplasm of the same neuron, as is the case in the elaboration of the conditioned reflex (see Chapter 5).

Taking all these accurately established data into consideration, it would be difficult for us to deny the possibility of *primitive associations* in the reticular formation. However,

it would be incorrect to assume, as Yoshii *et al.* did, that this is the conditioned reflex which is usually encountered during its elaboration in the animal in a relatively natural setting.

Undoubtedly, the cortex plays the decisive role in the conditioned reflex. It is the cortex which transforms the simple coupling of two excitations coinciding in time into a reflex act which is appropriate for a definite setting and is connected in the most intimate way with the individual history of the animal. The error of those authors who overestimate the potentialities of the reticular formation is that they take the bare fact of the coupling of the contact between excitations coinciding in time and discard everything which gives the conditioned reflex its structuring as a behavioral act.

This high function of *signalization*, i.e., the elaboration of mechanisms of reverse afferentation (feedback) and the elaboration of acceptors of the numerous actions of animals and man, is, in our opinion, fulfilled by the cerebral cortex.

At any rate, one can say with certainty that the newly discovered principles in the interrelation of the cortex, the thalamus, the hypothalamus, and the reticular formation provide us with abundant possibilities for understanding the data accumulated by the laboratories of Pavlov and his students. And the assumption we have expressed is but *one of the possible assumptions*; it more fully encompasses the data of these two related fields of physiology.

Returning to the problem of the nature of dominance, we can say that it can be understood if one visualizes all those levels of the circulation of conditioned excitations which have now been accurately determined.

As can be seen from Fig. 19.1, conditioned excitation of a triggering stimulus has several possibilities for interacting with the already existing dominant state, which

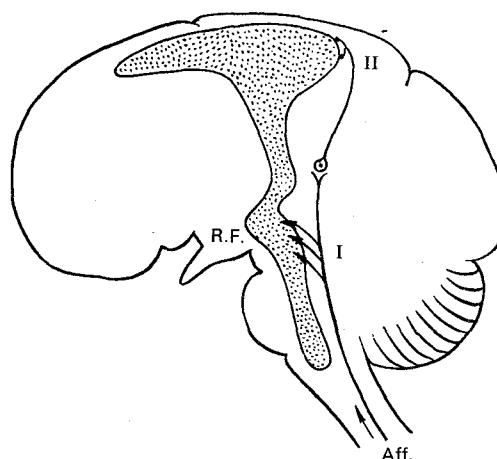


FIG. 19.1. Two possible contacts of any afferent stimulus with a system of preexisting dominant excitations. I, contact at the level of the reticular formation of the brain stem; II, contact at the level of the cerebral cortex. The third possibility of contact with the thalamic diffuse system is not presented in view of the uncertainty of its anatomic connections. R.F., reticular formation; Aff., entry of afferent impulses from the surface of the skin.

had arisen under the influence of the integrated action of the factors of the entire setting. First, it interacts with this preceding dominant state at the level of the reticular formation of the brain stem (see Fig. 19.1, I). Secondly, there are reasons, although not entirely convincing, for assuming that via the collateral it also excites the reticular formations of the thalamus and then finally establishes contact with the extensive cortical system of alimentary excitation, which undoubtedly dominates under the influence of the continuous tonic action of the reticular formation.

Let us return to the problem of the *irradiation of inhibition*, since it should now receive a reasonably satisfactory explanation. A comparison of the findings of general neurophysiology with all the data on higher nervous activity available at this time leads us to the conclusion that we can visualize the process of the irradiation of inhibition in a somewhat different plane.

As could be seen, our concept of the mechanisms of the origin of conditioned inhibition is based on the fact that any nonreinforcement with food of an elaborated conditioned reflex inevitably leads to the development of a biologically negative reaction. When the strength of its excitations is sufficient, this negative reaction eliminates the existing alimentary reaction together with its secretory component by means of secondary inhibition. This is the elaboration of inhibition, as determined by the experimenter.

Thus, during repeated nonreinforcements, e.g., during extinction, we invariably intensify the biologically negative reaction. Consequently, its inhibitory effect on the alimentary reaction is intensified.

Using the previously discussed principles of the development of dominant states, we can say that the "*stressful state*," *formed on the basis of the absence of food and the discordance in the action acceptor, becomes at this moment a dominant*. As could be seen from its vegetative components, the biologically negative reaction assumes a dominant position in the central nervous system. The reticular formation probably has the main role in the activation and intensification of all its components. This intensification of precisely the biologically *negative* reactions occurs not only on the basis of purely nervous influences, i.e., by means of collateral excitations of specific afferent pathways. We now know that a fraction of a second after these excitations, the reticular formation receives through the blood *a powerful and prolonged excitation of a humoral nature, mainly by means of adrenaline* (Dell and Bonvallet, 1956).

All these factors taken together ensure the successful adaptation of the organism to unfavorable conditions by making it strong and resistant in the struggle against obstacles and dangerous life situations. This is the profound biological meaning of that complex of physiological processes which takes shape in the central nervous system as soon as an animal or man encounters difficult life conditions. In our opinion, this represents the rational nucleus of the "*stress*" theory of Selye (1952, 1954).

Sufficient data are available to understand the sources of *strength and stability* of the biologically negative reaction. Its *strength* is determined by the extensive neurohumoral influences on the reticular formation, which in its turn transforms this energy into activation of cortical activity. Its *stability* is determined by the prolonged influences

of circulating adrenaline which, as was shown by direct investigations, significantly extends the initial action of the collateral afferent impulses (Dell and Bonvallet, 1956).

All these findings, correlated with the many years of investigations in our laboratory, allow one to draw the following conclusion : *the biologically negative reaction, having arisen on the basis of the nonreinforcement of the conditioned reflex with food, acquires for a certain period all the physiological features of a strong and inert dominant state of the central nervous system.* This process decides the fate of the reaction to any conditioned stimulus presented on the background of the given dominant state.

The excitation from this stimulus, just as the excitation from a new stimulus under conditions of generalization, strengthens the existing biologically negative dominant state. This dominant state must then exert a secondary inhibitory effect on the alimentary reaction of the organism, eliminating it either completely or partially. *Consecutive inhibition originates on this basis.*

In all its forms, consecutive inhibition, from our point of view, results from the fact that the stimulus is presented after nonreinforcement and is then taken over by that dominant negative state which was previously created by extinction or the use of differentiation, i.e., *by the nonreinforcement of the conditioned stimulus with food.* A direct evaluation of the vegetative components of the conditioned reaction, appearing under these conditions, confirms this assumption.

A stimulus presented immediately after extinction or after differentiation usually causes the respiratory component of the conditioned reaction to show signs of a biologically negative reaction. And, even when presented under ordinary conditions, this stimulus produces a respiratory curve characteristic for an alimentary reaction. The degree of consecutive inhibition of the secretory effect depends on the degree to which the respiratory component acquires a biologically negative character.

Proceeding from these considerations, which are supported by data, we can easily understand the phenomena of the *irradiation of inhibition* as well. In fact, the spread of a dominant state, connected with a specific physical stimulation, to other stimuli will naturally depend on the degree of their similarity with this stimulation. For example, the qualitative similarity of the tone "do" and the tone "re" will undoubtedly also determine their proximity both in the subcortex and in the cortical area of the analyzer. All other conditions being equal, if a biologically negative dominant has already been created by the tone "do," the tone "re" nearest it will always intensify this negative dominant and, consequently, decrease the secretory effect.

On the other hand, any conditioned alimentary stimulus which is spatially remote from the tone "do," e.g., "light" or a "tactile stimulus," will give a more pronounced alimentary reaction, since it will summate less successfully with the existing negative dominant. This *spatial dependence* of the manifestation of the latent dominant state on the point of cortical application of the given triggering stimulus must naturally occur both within one analyzer and between different analyzers, the *absolute* determining factor in all cases being the strength of the dominant system of excitations. Pavlov's school provides excellent examples of how, depending on the relationship of strength between two dominant states, the triggering stimulus can be intercepted at times by one and at times by the other.

In fact, by merely increasing the strength of the alimentary excitation, i.e., by making the whole system of alimentary relations more dominant, the manifestations of the consecutive inhibition will be considerably decreased. These spatial interrelations can be seen in Fig. 19.2.

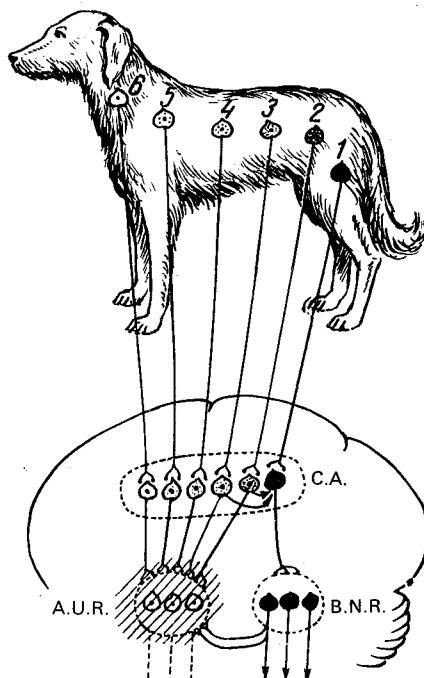


FIG. 19.2. Diagram of the interrelations between the positive alimentary reaction and the biologically negative reaction resulting from the elaboration of cutaneous differentiation. The diagram shows how the phenomena of the irradiation of inhibition are brought about. 1, 2, 3, 4, 5, 6, tactile stimuli; the differentiating tactile stimulus is 1; C.A., cutaneous analyzer in the cerebral cortex; A.U.R., cortical representation of the alimentary unconditioned reflex; B.N.R., cortical representation of biologically negative reaction. For explanation see text.

We have already shown that every stimulation has two neural pathways by which it can manifest a latent dominant state: first, through the reticular formation, and secondly, through action on the dominant excitation in the appropriate analyzer.

Let us assume that point 1 (see Fig. 19.2) of the cortex is that point of the cutaneous analyzer with which differentiation is connected (e.g., a conditioned, biologically negative reaction resulting from nonreinforcement with food has been elaborated). Its threshold of sensitivity to any other conditioned stimulus will be directly related to the strength of this dominant state.

Because of these interrelations, any conditioned stimulus connected with a point of the skin *in the vicinity* of the inhibitory point will very successfully intensify specifically the biologically negative dominant with all the resulting physiological consequences:

outward manifestation of behavior appropriate for the biologically negative reaction (whining, growling); the inhibition of the alimentary reaction and of secretion, its specific component; etc.

On the other hand, the presentation of a conditioned stimulus remote from the initial inhibitory cutaneous point will naturally lead to a lesser intensification of the negative dominant and to a greater manifestation of the conditioned secretory effect.

Finally, a conditioned stimulus presented after differentiation can be aimed at such a point of the cutaneous analyzer or of the cerebral cortex which is altogether outside of the negative dominant. It will then evoke its appropriate conditioned secretory effect to the full extent.

We thus see that the above-described principles of the interrelation of two dominant integrated activities of the organism can satisfactorily explain all the phenomena that correspond to the *irradiation of inhibition*.

This explanation is in complete accord with the mechanism of the origin of conditioned inhibition which I have explained in the preceding chapters. Moreover, what is especially important, it eliminates those physiological contradictions which are connected with the assumption of *an irradiation of specifically the process of inhibition* over the cerebral cortex, since there is no neurophysiological basis for such an irradiation.

Modern neurophysiology gives no evidence of a process of inhibition which would spread over the conducting neural elements just as excitation does; Vvedenskii established this fact long ago. Meanwhile, in all our assumptions concerning the spread of nervous processes over the cerebral cortex, we speak as freely of the irradiation of inhibition as we do of the irradiation of excitation. At some stage in the development of the general concepts of the inhibitory processes of the cerebral cortex, this working hypothesis was satisfactory.

Now, however, the previous concept of the irradiation of inhibition becomes clearly contradictory to the expanding knowledge of the nature of the processes of nervous activity. This contradiction also hinders the utilization of modern neurophysiological data in the elucidation of the problems of higher nervous activity.

The concept of the irradiation of the inhibitory process over the cerebral cortex began to be used so extensively in the explanation of the most diverse forms of nervous activity and of the relations between specific nervous phenomena that it has become an integral part of the thinking not only of physiologists, but also of clinicians.

We frequently see that in the explanation of a number of pathological processes, one proceeds from the premise that inhibition not only flows out over the cortex, but often even "descends" into the medulla oblongata. Such an interpretation of the spread of the inhibitory process is due to the initial assumption that *an inhibitory stimulus directly inhibits the positive conditioned reaction*. One can give numerous examples from the field of physiological investigations in which this erroneous assumption is clearly evident.

A typical example of this way of thinking is shown in experiments involving the inflation of various sections of the intestines with air. As is known, such an inflation leads to a distinct inhibition of the gastric secretion evoked by preliminary feeding. The investigators hold that the excitation which has arisen in the interoceptors of the

rectum comes into the central nervous system and *directly* inhibits the activity of those centers which were previously determining the current activity of the gastric glands. This kind of conclusion is typical for such experiments.

But is this what actually happens?

We can positively assert that in experiments of this kind, the interrelation of the processes of excitation and inhibition is different. The stimulation of the interreceptors will only be able to inhibit the current secretory activity, if, upon passing through the initial generalization in the reticular formation, it patterns its own reaction, specific for expanding the rectum and having stronger excitations. Only this new reaction or activity can exert a *secondary* inhibitory effect on the current activity in the form of gastric secretion. In other words, the inhibition must necessarily arise as a result of the secondary inhibitory effect of a stronger activity.

Such interrelations of two activities can be easily understood on the basis of the prevailing dominance of one of them. Consequently, any extension of the inhibitory (or in this case, negative) effect of stimuli can be ascribed to its influence on the activity dominant at the given moment, rather than to the irradiation of the inhibitory process over the cerebral cortex.

The existence of dominance interrelations is especially clear when the latent dominant appears as a result of the presentation of a stimulus connected with another specific activity of the organism. I have in mind situations in which a conditioned nociceptive stimulus reveals an alimentary dominant. In connection with this, I wish to emphasize the interesting observations of Struchkov (1955, 1956a, 1956b, 1956c), which were carried out at the laboratory of Asratian. Upon combining conditioned defense stimuli with alimentary ones, Struchkov noted one seemingly strange circumstance: the *negative alimentary* stimulus not only fails to evoke a secretory reaction, but, on the contrary, it activates a *positive defense* reaction—the leg lift.

These experiments indirectly confirm the point of view presented in this book concerning the qualitative characteristics of the biologically negative reaction. They show that the condition of the animal which results from nonreinforcement with food, as well as the excitation from the inhibitory stimulation, summates with the *defense dominant* in regard to biological quality. As we already know, the electrocutaneous stimulation, although theoretically "positive," is actually biologically negative *for the dog*.

Another important factor which has considerable influence on the effect of the "irradiation of inhibition" is that the biologically negative dominant is especially *inert*. Having once arisen, it remains the dominant activity for a long time, intercepting the most diverse conditioned positive excitations and thus creating an external impression of an "irradiation of inhibition," especially when the biologically negative dominant is "latent." Every experimenter working with electrocutaneous defense reinforcement is familiar with the great stability and strength of both the biologically negative dominant and the "reflex of biological caution" related to it.

This is why the negative emotions of man have such an extensive pathogenic influence on the functions of his body.

Here it is of great interest to note that Pavlov's reference to the resemblance between

the mechanisms of the influence of the experimental setting and "Ukhtomskii's dominant" is not accidental, just as his references to the inertness of certain excitations are not accidental.

As far back as 1913, Pavlov said in discussing the well-known experiments of Erofeeva: "The nervous process is thus despatched in the direction of the most powerful stimulation" (Pavlov, 1913, see Pavlov, 1967, pp. 216-217).

Pavlov spoke even more clearly about the inertness of once established conditions of an animal:

The latent after-effects of foregoing stimulations at any given moment have enormous significance for the activity of the hemispheres . . . [italics—P.A.] The introduction of acid into the mouth of the dog alters the conditioned food reflex for 10 to 15 minutes after its application. The eating of sugar can change for several days the conditioned reflex on meat and bread powder. [Pavlov, 1913, see Pavlov, 1967, p. 217].

It is appropriate to mention again our experiment involving the sudden presentation of meat instead of the usually presented bread as an unconditioned reinforcement. Just as in the cases cited by Pavlov, a definite dominant state was created for the duration of several weeks. The latent dominance of the preceding activities or reactions of the animal is the most widespread phenomenon in experiments involving conditioned reflexes, and therefore Pavlov's remarks must be regarded as quite correct: "... it is necessary to make a careful study of the duration of such effects" [italics—P.A.] (Pavlov, 1913, see Pavlov, 1967, p. 217).

These remarks are especially applicable to the stressful state, i.e., to the biologically negative reaction which develops as a result of nonreinforcement with food.

In order to prove that this principle, i.e., the formation of a biologically negative dominant, is the basis for the external expression of the "irradiation" of inhibition over the cerebral cortex, one may also discuss the example of the conditioned inhibitor.

This form of conditioned inhibition is especially suitable for demonstrating the role of a previously established dominant state. In fact, here the new and initially indifferent stimulus and the well-stabilized conditioned stimulus become a nonreinforced pair. The new stimulus gradually becomes a *signal* of nonreinforcement and therefore during the 5 sec of its isolated action is able to establish a negative dominant state.

In connection with this, one should also keep in mind the evolution of the *quality* of the action acceptor, since it determines the degree of discordance and, consequently, the strength and intensity of the biologically negative functional system. The most negative stages are the mixed stages, i.e., stages of conflict, in which there is rhythmic alternation between a positive and a negative action acceptor. Figuratively speaking, there is alternation between "hope" and "disappointment."

It follows that the presentation of a positive conditioned stimulus on this negative background may have two consequences: either the positive conditioned excitation will inhibit the negative dominant, or the conditioned excitation will, according to the principle of reinforcement of the dominant, intensify the existing negativity which in

turn will inevitably exert a secondary inhibitory effect on the alimentary reaction and its secretory effect. It is only necessary to present the "indifferent" stimulus to cause the animal to turn immediately away from the feeder, begin to whine, etc. The same phenomenon can also be seen in the direct recording of the respiratory component of the reaction of an animal: from the beginning of presentation of the "indifferent" stimulus, the respiration in most experimental animals immediately becomes the same as during biologically negative reactions.

Thus, our explanation of the physiological nature of the phenomenon of the irradiation of inhibition can be rather broadly extended to all forms of inhibition, the appearance of which is related to nonreinforcement with food.

* * * * *

To give a complete picture, we shall analyze two more very extensively studied phenomena in higher nervous activity: *the concentration of inhibition, and disinhibition*.

From all that has been said about the irradiation of inhibition, it follows that "irradiation" is the external expression of the degree of dominance of a biologically negative reaction and of its inhibitory effect on the alimentary reaction, which are related to discordance in the action acceptor. However, with the formation of a new negative action acceptor and the elimination of discordance, there is a progressive resolution of the conflict and a lessening of the dominance of the biologically negative reaction. Afterwards, any positive conditioned stimulus newly presented on this background will be decreasingly intercepted by this negative dominant, and in accordance with this, its positive secretory effect will be more and more pronounced.

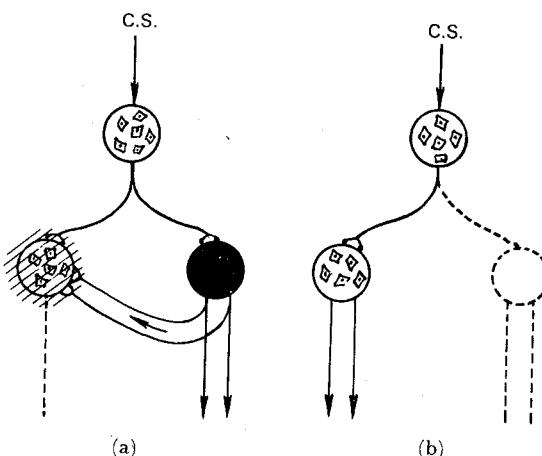


FIG. 19.3. Two stages in the development of a biologically negative reaction during the extinction of a conditioned reflex. (a) The stage of active conflict with the alimentary reaction, with maximum successive inhibition; (b) the stage of decrease in the strength of the negative reaction (depicted by broken lines); the conditioned stimulus, tested after the inhibitory one, gives the full secretory effect; C.S., conditioned stimulus.

In other words, the "concentration of inhibition" can in this sense be regarded as an increasing limitation of the initially widespread negative dominance and a restoration of the ability of the positive conditioned excitation to propagate toward its *alimentary dominant* (Fig. 19.3).

The mechanisms of disinhibition are much more difficult to visualize. The difficulty here lies not in understanding the actual fact of disinhibition, but rather in understanding those physiological conditions during which either disinhibition or an even deeper inhibition results.

Pavlov regarded the explanation of the phenomenon of disinhibition as one of the most difficult tasks in the physiology of higher nervous activity. He pointed out, for example, that, before understanding the mechanisms of disinhibition, we must elucidate the mechanism of conditioned inhibition itself.

The explanation of disinhibition depends directly on how well the mechanism of the origin of conditioned inhibition is understood. But this is precisely the "accursed question." From our point of view on the origin of conditioned inhibition, this difficulty has considerably decreased, even though much still remains to be clarified.

In the explanation of disinhibition, we must proceed from already known and firmly established facts. If the conditioned stimulus presented (either an extinguished one, or differentiation) produces a negative effect, the excitation from this stimulus propagates toward the negative dominant created by the nonreinforcement. The former, dominant alimentary activity is under secondary inhibition from the biologically negative state. Thus, at this moment, two competing specific activities exist.

What new events occur in their interrelation when *suddenly* some extraneous (disinhibiting) stimulus acts?

Here a very interesting situation develops: on the background of the already established interrelation of two integrated activities, the biologically negative and the

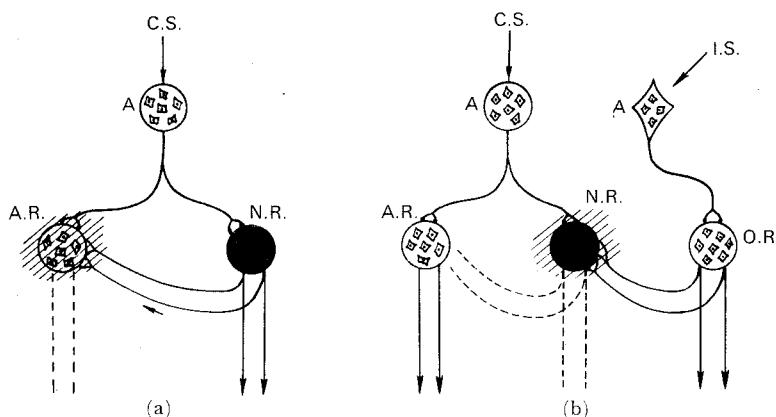


FIG. 19.4. (a) The usual interrelations during the elaboration of inhibition; (b) the mechanism of disinhibition as a result of the action of a new indifferent stimulus (I.S.); O.R., orienting-investigative reaction; N.R., the negative reaction is inhibited and the previously inhibited alimentary reaction (A.R.) is set free; C.S., conditioned stimulus; A., analyzer.

alimentary ones, there arises a third and equally *integrated* activity--an *orienting-investigative reaction* (Fig. 19.4).

Since the excitation from the orienting-investigative reaction is very intense, the main question is which of the two previous activities the orienting-investigative reaction will intensify and which one it will inhibit. The excitation of the orienting-investigative reaction can be directed toward the latent alimentary dominant, intensify it, and make its excitation supraliminal. This, then, will be the phenomenon of *disinhibition*. If, however, the excitation of the orienting-investigative reaction is intercepted by the negative dominant, and its *inhibitory* effect on the positive alimentary reaction is correspondingly intensified, a deepening of inhibition will occur.

One further possibility is conceivable, however: the orienting-investigative reaction may inhibit the biologically negative reaction and thus release the alimentary reaction from its inhibitory effect.

Therefore, the mechanism of disinhibition has become basically clear. However, the variations in the spread of the excitations from the orienting-investigative reaction are not fully understood.

In order to understand the two above-described possibilities of the spread of these excitations, it is important to keep in mind the two possibilities of contact between any new stimulation and the dominant state existing in the central nervous system (see Fig. 18.1). The disinhibitory effect of the excitation from the orienting reaction will probably depend on where this excitation exerts its predominant influence. One must also consider the characteristics of the orienting-investigative reaction itself. It must be related to the dominant state preceding it. In one way or another, it will "feed" one of the existing dominant activities.

In the cases of "disinhibition," why does the orienting-investigative reaction "feed" the latent and even inhibited *alimentary* dominant?

At the present time it is difficult to provide a sufficiently conclusive answer to this question, although some data are available which make it possible to explain this phenomenon to a certain extent.

The alimentary dominant, under experimental conditions involving only alimentary reinforcement, is a permanent and consolidated dominant. Moreover, even in cases of its suppression during the action of one stimulus (differentiation, extinction, etc.), all the other conditioned stimuli perpetuate this dominant. On the other hand, the suppression of the alimentary system of excitations by excitations of a sudden biologically negative reaction is inevitably specialized by the experimental conditions with regard to one particular stimulus, i.e., it is less generalized than the alimentary reaction.

Thus, the two dominant states, the suppressed alimentary state and the present negative state, clearly do not have the same relation to the newly appearing excitations from the orienting-investigative reaction.

It seems to us that in this way one may approach an understanding of why in the case of disinhibition the new system of excitations, upon inhibiting the biologically negative reaction, intensifies and makes apparent the alimentary activity *inhibited* for the given moment (third possibility). Here conditions arise which are somewhat similar to the example we gave in Chapter 18, in which the kitten *advancing* toward the

dangerous edge of the windowsill jumps back as soon as a sudden auditory stimulus acts upon it.

And do not examples of this kind occur frequently in everyday life? A person expecting an important telephone call may be having a very animated conversation with the people around him, and yet at the first sound of the bell he rushes toward the telephone. Is it not on this basis that a person depressed by some unpleasant event is able to perform his normal activity, even though the dominant determining his state is a latent *but considerably stronger system of negative excitations?*

Now we are confronted by the one universal principle of higher nervous activity which we have repeatedly encountered in connection with the analysis of the function of the frontal lobes of the cerebral cortex (Anokhin, 1949c). This principle involves the transition of any integrated activity or reaction of the organism to a *latent* state when there occurs a blocking of the emergence of this reaction onto the terminal neurons, which does not affect its central integration and excitability which is often of a high level.

There is no doubt that this example is a special case of the intracentral relations between several alternatives of behavior which, by mutual equilibration, result in the most beneficial adaptive effect in the given setting.

The discovery of direct and reverse connections between the reticular formation and the cerebral cortex has considerably enhanced our possibilities for explaining this principle. At any rate, the source of energy for latent dominant states of this kind has become rather clear.

Thus, in summarizing the above-presented material and considerations concerning the physiological mechanisms of the irradiation of inhibition, we can express them in the following four propositions:

1. All experiments involving inhibitory stimuli, i.e., stimuli which are not reinforced with food, always cause discordance in the action acceptor and dominance of a system of excitations which pattern a biologically negative reaction.
2. Any positive conditioned stimulus, presented on the background of a biologically negative dominant which has previously developed, will intensify it to a certain extent, thus causing a secondary inhibitory effect on the developing alimentary reaction.
3. The extent of the inhibitory effect (the "irradiation of the inhibition") will in this situation, all other conditions being equal, depend on the spatial proximity in the cerebral cortex of the given conditioned stimulus to the initial biologically negative dominant.
4. The manifestation of a latent dominant state can, in our opinion, in accordance with the latest neurophysiological data, result from an interaction of the triggering stimulus and the dominant at two levels of the central nervous system: at the level of the reticular formation of the brain stem and at the level of the cerebral cortex. The intimate mechanisms of this contact between the arriving excitation and the preceding dominant are presently the object of comprehensive research at our laboratory.

The above explanation of the mechanism of the irradiation of inhibition over the cerebral cortex is most satisfactory for those interrelations in the nervous activity which are observed under natural conditions. In addition, it corresponds entirely with those mechanisms of the origin of conditioned inhibition presented in the preceding chapters.

CHAPTER 20

The Conflict Between Excitation and Inhibition and the Origin of Neurotic Conditions

ACCORDING to the views of Pavlov and his school, neurotic breakdowns of nervous activity occur as one of the possible results of collisions between inhibitory and excitatory processes in the cerebral cortex. Adherents of this concept believe that, depending on the strength of the competing processes, and depending also on the duration of the conflict between excitation and inhibition, there occurs such an overstraining of both these processes as can cause the cortical cell to exceed its functional capacity. A "break-down" of nervous activity and a neurotic state of longer or shorter duration always appears in such cases as a result of the disturbance of the normal balance between excitation and inhibition, which is a necessary condition for normal relationships of animals and man with their surroundings.

There can hardly be any doubt that these concepts, developed in the laboratories of Pavlov and his students, are correct and can serve as a starting point for their further development.

Therefore one must naturally first raise the question as to precisely what in the theory of neurosis originated by Pavlov must become the object of further investigation, and which of its aspects demand a physiological interpretation and perfection.

In view of the importance of neuroses as a widespread disease, the urgency of this question is beyond doubt. Therefore, we cannot neglect to analyze that possible development of the Pavlovian concept to which the previously described ideas concerning the origin and localization of conditioned inhibition lead.

From the above formulations it follows that the neurotic state is the result of a disturbance of the *normal relationship between the processes of excitation and inhibition in the cerebral cortex*.

Our success, then, in understanding the origin of neurotic states depends directly on how we understand the relationship between excitation and inhibition and how we picture the specific mechanisms of the *origin* of conditioned cortical inhibition. The latter must determine our concepts concerning the origin of neurotic states. Moreover, an analysis of the origin of neuroses will permit us to further check the correctness of our point of view regarding this problem. These generally held views state that a neurotic breakdown is the result of overstraining of the cortical processes of excitation and inhibition upon their collision in a short span of time. However, only the appearance of excitation in this conflict is well understood. Usually it is some positive integrated

activity developing in response to a positive conditioned stimulus. Excitation as one of the opposing sides in the conflict is a tangible nervous process, all the pathways of which can be followed exactly.

But how does inhibition originate? Its role is no less and perhaps even more important in the development of the neurotic state.

Until recently there was no answer to this question. It is therefore quite natural that the study of the *origin of the neurotic state* could not progress with regard to understanding its basic physiological mechanisms better. Meanwhile, the question concerning the clinical application of the theory of experimental neuroses has become especially untenable in recent years. Like physiologists, both neuropathologists and psychiatrists who have accepted the theory of higher nervous activity are in need of understanding the origin of inhibition. Possibly the clinician may have a more acute need.

Indeed, as the experience of the Pavlovian school has shown, physiologists could quite successfully investigate the problem of neurotic breakdowns as well as the relationship between excitation and inhibition without knowing the mechanisms of the origin of inhibition. This is understandable: the clinic did not confront the clinician with these questions every day. Meanwhile the position of the clinician in this respect is quite special. In every case he must ask himself: where did inhibition as one of the conflicting processes come from in a *specific* patient and in *specific* disease? Therefore, feeling that this aspect of the physiological concept of neuroses is not sufficiently developed, the clinician has taken the course of an empirical evaluation of the conflicts in man, in which he has always seen an *agonizing clash between two positive motives*, i.e., a clash between two positive activities of the integrated organism.

The concept of the origin of inhibition described in preceding chapters could of course not fail to confront us with the question of the examination of the entire problem of neurotic breakdowns from this point of view.

Naturally the question arises: how can one apply our concept of the relationship between excitation and inhibition and of the origin of conditioned inhibition to the understanding of the neurotic breakdown which, in the classical Pavlovian experiment, is interpreted as being a result of the collision of the *two basic processes* of excitation and inhibition?

The greatest difficulty at first glance was that, according to our point of view, conditioned inhibition arises as a result of the collision of two systems of excitation and is the means by which a stronger activity of the organism inhibits all the weaker activities present, whereas according to the classical concept, experimental neurosis appears as a result of the collision of two *independent* nervous processes: excitation and inhibition.

In order to size up more graphically the relationship between these two concepts and to show just how the new concept is an expansion of the previous one, I present the following diagram (Fig. 20.1).

In the diagram there are two systems of excitation corresponding to two integrated activities of the organism: the alimentary activity (A.R.), and the biologically negative activity (B.N.R.) which arises in response to nonreinforcement of the conditioned stimulus. The diagram depicts the stage corresponding to several nonreinforcements of the conditioned alimentary stimulus. As a result of these nonreinforcements, the

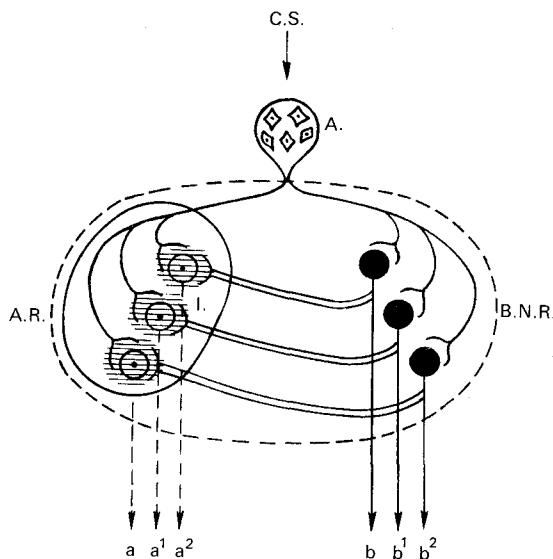


FIG. 20.1. Comparison of two concepts of the origin of neurotic states. C.S., conditioned inhibitory stimulus; A.R., alimentary reaction; B.N.R., biologically negative reaction; I., inhibitions at the points of contact of the two systems of excitation; A., analyzer; a, a¹, a², missing components of alimentary reaction; b, b¹, b², manifested components of biologically negative reaction.

conditioned stimulus (C.S.) which is to be extinguished evokes in the cerebral cortex a system of excitations pertaining chiefly to the biologically negative reaction (solid lines, B.N.R.). The latter, developing into an integrated reaction with all its characteristic peripheral components (b, b¹, b²), shows in its cortical part an additional inhibitory effect (I.) on the alimentary reaction (A.R.), as a result of which components specific for this reaction, such as secretion, prove not to be manifested (dotted lines, a, a¹, a²).

This is how we visualize that relationship between integrated activities of the organism as a result of which one of them is inhibited and, consequently, its specific peripheral components are eliminated from the external expression.

If we now look at this universal principle using those processes which are included in our diagram within the ellipse bounded by a solid line, we shall see that the relationship of the processes in this area fully corresponds to our usual concept of the "conflict between excitation and inhibition." Here is an excitation evoked in this case by the conditioned stimulus (C.S.) to be extinguished. Moreover, there is also inhibition which develops, let us suppose, in the zone of the patterning of the conditioned alimentary reaction (shaded areas). The special feature of this diagram is that, although there is inhibition within the area bounded by the solid line, its origin is unknown. We are in the situation which had been repeatedly formulated by Pavlov.

However, if we expand our study of the interactions, as we had done on the basis of the experiments mentioned in earlier chapters, then immediately all facets of the

relationship under study (the processes included in the dotted-line ellipse) become understandable (see Fig. 20.1). Then the origin of the inhibition limiting the spread of the alimentary excitation becomes clear: *it is the result of a stronger system of excitations from a biologically negative reaction acting on the alimentary reaction.*

With the acceptance of this scheme there also appears a new concept of the intimate mechanism of the "conflict between excitation and inhibition." The central mechanism becomes, not the conflict between "excitation and inhibition," but rather *the conflict between two integrated activities, two systems of excitation with inhibition being the universal tool.*

From all that has been said regarding the origin of inhibition, there inevitably follows a change in our concept concerning the origin of neurotic states. These, of course, are in the final analysis (the solid-line ellipse) the result of interaction of excitations, one of which is inhibited. However, in order to discover the origin of neurosis itself, it is essential to know *what integrated activities of the organism resulted in this interaction and the origin of the process of inhibition* (dotted-line ellipse).

The elucidation of these mechanisms is especially important for clinical practice, where inhibition is never an independent process, but is always only a means for the elimination of an activity which is unnecessary or harmful at a given moment.

The interaction of two activities of the organism and the elimination of one of them by means of inhibition is a universal principle of life. Due to this principle, which in the final analysis is based on the relationships of intensity of different systems of excitation, the behavior of animals and man is systematized, and a chaotic activity of their peripheral effectors is prevented.

First of all it is necessary to answer the question: what changes can occur in the interaction of two activities of the organism depending on the intensity of their constituent excitations?

Experience shows that with an increase in the intensity of the biologically negative reaction, which develops after the first nonreinforcements of the conditioned stimulus being extinguished, the excitations from the alimentary reaction being inhibited also increase. This is clearly evident when both activities begin to alternate at a high level of intensity. Conspicuous conflict between the two activities of a different nature arises and proceeds at a considerably elevated level of excitation.

Therefore we see that in the presence of a conflict between two activities, a distinct mutual induction of these activities occurs. This conflict may end in the complete inhibition of the alimentary activity, as a result of which the conflict itself between the two activities is eliminated and the animal acquires an inhibitory conditioned reflex. From this point of view, any adaptive activity of an animal which ends in the elimination, without conflict, of an unnecessary activity evidently proceeds with the formation of a new action acceptor.

However, from the experience in Pavlov's laboratories and those of his students, as well as from clinical practice, it is known that the conflict of excitation and inhibition can also end in an overstraining of nervous processes and a neurotic breakdown. This overstraining comes at the moment when two competing activities, increasing the intensity of their excitations, mutually stabilize each other; therefore, the conflict

is maintained for a somewhat prolonged period and at a high level of excitability. This is the form of neurotic breakdown which is the object of investigation of clinical neurology. In the practice of the clinician there is always occasion to encounter this particular origin of neurosis, since in life situations one motive always enters into conflict with another system of excitations which for some reason does not allow the realization of the first motive and suppresses it by means of the process of inhibition. Pavlov repeatedly expressed this principle in a very graphic form. He used to say, "I am involved by an intensive excitatory process, but circumstances imperatively demand its inhibition. Then I am in a stressful state."

In this statement Pavlov clearly shows that in human life two positive activities enter into conflict, one of which is finally inhibited.

A great majority, if not all, of the conflicts in human behavior develop in the same way as expressed by Pavlov. They are almost always the result of the suppression of some unnecessary activity or inadmissible motive by means of a process of inhibition appearing under the influence of "circumstances," i.e., under the influence of a stronger and more extensive system of excitations that usually is developed throughout life by social conditions. On this basis the neuropathologist is able to explain a great many cases of neurotic ailments.

However, the cause of neuroses we propose not only *explains* the mechanisms of the origin of neuroses in man, but it also permits physiological *intervention* in the neurotic process for the purpose of controlling it.

Indeed, if the specific systems of excitations or the specific nervous functions which entered into conflict with each other are discovered, then by judiciously intensifying one of the conflicting sides and weakening the other, it is possible to remove the neurotic tension which always accompanies a state of conflict.

All these cases of neurotic breakdowns cannot be understood if they are examined only from the point of view of a "conflict between inhibition and excitation." When the question is stated in this manner, one of the competing activities is inevitably masked or latent. Therefore the origin of any specific neurotic state in man cannot be interpreted physiologically.

On the other hand, in the above presentation of the development of this concept, it is assumed that if there is inhibition of any activity of the organism or even of one of its individual components, the investigator must look for that other integrated activity which, due to the strength of its excitations, proved to be the "inhibitory activity" and therefore precipitated the observed inhibition.

Without the discovery of the mechanisms of the *origin* of inhibition itself, the concept of a conflict between excitation and inhibition leaves not only the psychiatrist and the neuropathologist in a difficult position, but also the educator. The latter, having set for himself the goal of "training the inhibition" of unnecessary actions in a child, proves to be helpless when he is faced with the question: how does one "train inhibition" without which it is of course impossible to eliminate inadmissible or unnecessary activity of a child?

An analysis of observed cases and of existing theories of education shows that in this case also the teacher is rescued by the method he has found empirically and which is an

illustration of the universal importance of the principle of the "encounter of excitations." Indeed, there are several conceivable forms of suppression of unnecessary or undesirable behavioral acts. One can *threaten punishment, promise a reward, or use motives of a moral or social nature.*

We shall attempt to understand the physiological basis of all these three factors of educational tactics. It is not difficult to see that in all three cases there inevitably occurs an encounter of two independent systems of excitation which are characterized by specific activities of the integrated organism. In the case of a threat of physical punishment or even the implementation of this threat, it is a matter of a biologically negative activity which, according to the nature of its component excitations and the composition of the peripheral effectors, is a completely defined and independent activity of the organism. At a sufficient intensity of the central excitations of this activity, it can become "inhibitory" with respect to the forms of behavior of the child which are undesirable to the educator.

As the role of the second signaling system increases in the life of the child, the threat of punishment acquires a considerably more extensive system of signals, and therefore the inhibitory influence of the threat usually increases considerably.

From this example it can be seen that with the appearance of speech in the child, that is, of the second signaling system, the former connections at the level of the first signals are supplemented by new extensive connections with other activities of the organism. If the effect of rewarding or encouraging the child in the most primitive form (candy, sweets, etc.) is analyzed from this point of view, then there are in essence *two* systems of excitation. One system, the reward, is the stronger and proves to be inhibitory to the undesirable activity. For the child, though, the latter is in some respect just as desirable as the reward. Consequently, the inhibition of the unnecessary or undesirable activity is inevitably the result of the competition between two systems of excitation.

To "train inhibition" means to create such a complex system of excitations or impelling motives that their intensity would markedly exceed the intensity of the excitations of the undesirable activity. The neurological basis of the more lofty motives of man which guide his behavior is that the extensive systems of excitations of the cerebral cortex, created by the entire social life, are the strongest. Therefore, these excitations inhibit all other behavior which is undesirable or incompatible with human morality. When a Soviet flier is ramming an enemy plane, he does this not because he is without fear, which is present in everyone in dangerous life situations. His heroic act is dictated by something else: he accomplishes it because a motive of tremendous intensity, created by a sense of duty to the fatherland formed in the course of his conscious life, is an absolutely inhibitory system of excitations with respect to the primitive protective biological reaction which gives rise to the feeling of fear. Thus, in this case too, there is a conflict between two integrated activities. In some cases, though, the intensity of both activities is approximately the same, and the conflict is delayed for a long period, while in other cases a stronger system of excitations resolves the conflict quickly.

It follows, then, that the educator must not direct his attention towards the "*training*

of inhibition," but rather towards the training of strongly impelling guidelines for behavior which must inevitably inhibit unnecessary activity.

Since, however, every inhibition of undesirable actions inevitably passes through the stage of a *collision of two independent systems* of excitation, we face the possibility of their mutual intensification to a certain limit. The basic nature of any integrated activity of the organism is such that it has the tendency to be unique. Only with this condition is it possible to avoid chaos in the functions of the organism. Therefore, the inhibition of any integrated activity, *especially an habitual one*, is usually accompanied by an increased intensity of excitations and of the emotional basis of the activity being inhibited. This is especially marked in those cases in which the harmful activity that should be inhibited has become habitual and stereotypic and is accompanied by a high intensity of positive emotions (craving for alcohol, smoking, sexual excesses).

However, the peculiarity of man's versatile behavior is that circumstances often compel him to inhibit certain individual components of behavior while retaining others, i.e., to carry out a *fractional and selective inhibition*. Let us assume, for example, that due to some external circumstances there has arisen a strong reaction of anger with all its characteristic violent emotions. And yet "circumstances imperatively demand" the concealment of this reaction. That is, all those motor manifestations which usually accompany the reaction of anger must be inhibited: general movement, appropriate facial expressions, excited speech, etc.

The unusual characteristic of this inhibitory effect of "circumstances" as a complex and very strong system of excitations that has been developed in life is that it pertains only to the voluntarily controlled muscular components of the integrated reaction of anger. All the other components (the *vegetative ones*) of the same reaction escape this cortical inhibition and occur to their full extent. Here relationships of exceptional physiological and pathological significance are created. With respect to its specific

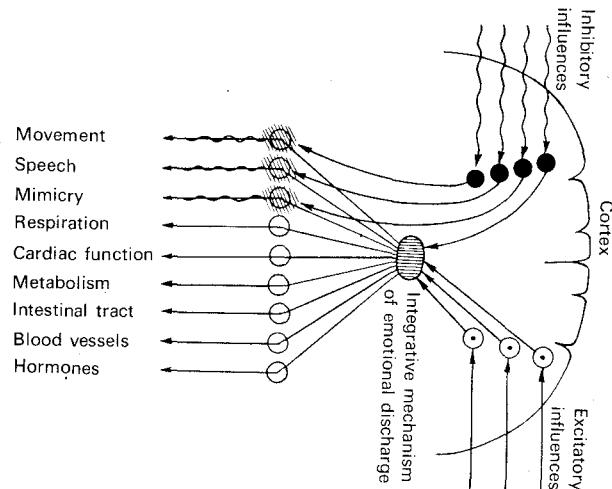


FIG. 20.2. Inhibition of cortically controlled components of an integrated emotional discharge under the influence of external circumstances. For explanation see text.

emotional content, the anger reaction does not cease to be an integrated reaction of the organism. Consequently, the whole force of its central excitations is directed along definite vegetative efferent pathways (Fig. 20.2).

The human nervous system may reach its functional limits, the limit of efficiency of the cortical nerve cells. As a result of the prolonged conflict between two such mutually intensifying activities of the organism, alternately each may become preponderant. These preponderances appear suddenly and at an increased intensification of the nervous processes, which is the physiological basis for the "explosiveness" repeatedly described by Pavlov and his students (M.K. Petrova, P.S. Kupalov, and others). This explosiveness is especially apparent in such vegetative components of the conditioned reactions as respiration and cardiac activity.

We have already shown (experiments by Shidlovskii, 1963, 1964, and Sanginov, 1957) that these components can instantaneously change their character from a violently negative reaction to a quiet, positive alimentary reaction (Anokhin, 1956c). It is important to emphasize that this "explosiveness" is an obvious result of the encounter of two systems of excitations, and signals a temporary victory of one of these systems and the complete or partial inhibition of the other.

Pascal expressed this critical relationship between two competing activities of the human organism in his famous aphorism: "Man is neither animal nor angel, but he becomes an animal as soon as he wants to be an angel . . ."

In the most diverse life situations as well as during upbringing, the relationships of two competing activities can become the source of overstraining of the nervous processes, and create inertness of one of the contending systems of excitation, possibly resulting in neurotic states of various kinds. One characteristic is common to all the above examples: in them the "encounter of excitations" and the conflict occur between two integrated activities, and the accompanying inhibition spreads to the entire activity being inhibited.

The inhibitory effect of the vast system of excitations, created by various circumstances, on individual components of another system of excitations may also have important consequences for the organism as a whole. As already indicated, upon the conflict of two activities there occurs an inevitable increase in their energy levels, which eventually leads to an alternate preponderance of each of them, and then to the phenomenon of "explosiveness."

These characteristics of the conflict of activities are also valid for a conflict with partial inhibition of the components of a reaction. In this case, too, there occurs an induction and increase in the intensity of excitations in both integrated activities. While not manifested in the motor components, the intensified impulses of the reaction being inhibited *emerge with accentuated intensity onto the efferent pathways to the vegetative and visceral organs*. Figuratively speaking, man, having placed all facial manifestations of his emotional state under cortical control, invariably "pales" or "blushes" by means of the activity of his visceral organs and their smooth musculature.

It is quite evident that under some unfavorable conditions, and especially in cases of prolonged and repeated discharges of emotional excitations onto the vegetative organs, all the conditions are created for the onset of so-called vegetative neuroses.

Exactly what effector pathway proves to be prevalent for the emergence of emotional excitations onto the periphery depends on the characteristics of the given emotion, the nervous constitution of the individual, and his entire life history. As a result of these determining factors, there will be neurotic disorders of a different kind in each individual. These disorders can involve the smooth muscles (pylorospasm, cardiospasm, spastic constipation), appear chiefly in the blood vessels (hypertension), find an outlet to the heart (stenocardia), etc. Of most importance is that in all these cases of over-excitation of the vegetative organs, on the basis of conflicting emotional states and the fractional inhibition of one of these reactions, the initiative always belongs to the acquired cortical connections. Under the influence of conflicting environmental conditions, the emotional mechanisms of the subcortex are charged, resulting in the involvement of some reaction of the somatic and vegetative organs.

In recent years the problem of the different behavior of somatic and vegetative components of the conditioned reaction has become especially important in relation to the typological differences in the visceral components of reactions of different animals exposed to the same stressful situation. Here I wish to refer particularly to the highly interesting and systematic investigations by S.A. Corson at the Ohio State University in Columbus, Ohio. Corson's investigations have acquired special significance in connection with the unexpected discovery of remarkable differences in the visceral components of the overall reactions of an animal, differences which investigators had almost never taken into account. Overlooking these differences had led to incorrect interpretation of data and to misunderstanding.

Corson discovered that, in the same situation of stress, different dogs exhibit systematic and persistent differences in their visceral reactions, specifically with respect to renal function (Corson, 1966a, 1966b, 1967, 1969, 1971a, 1971b; Corson and Corson, 1967, 1968, 1969, 1971; Corson *et al.*, 1969, 1970). While some animals consistently exhibited *antidiuretic* responses to the experimental setting alone, others, on the contrary, did not exhibit this antidiuretic component of the general-adaptation syndrome, although both types of dogs exhibited good differentiation of the conditioned motor defense reflex (leg lift). Corson has termed this phenomenon "somatovisceral dichotomy."

The psychologic stress in Corson's experiments was produced by Pavlovian conditioning experiments in several breeds of dogs by using electrocutaneous reinforcement to a leg. In the antidiuretic dogs the aversive Pavlovian conditioning room actually evoked a tetrad of reactions: hyperpnea, copious salivation, tachycardia, and antidiuresis. These reactions were comparable to those associated with intensive muscular effort such as described by Walter B. Cannon for the "fight or flight" reaction. Corson postulated that the primary response of the antidiuretic dogs to an unavoidable aversive situation (Pavlovian conditioning room) is increased heat production. The antidiuresis thus represents a compensatory reaction for conserving body water by the kidneys, so that the water will be available for thermoregulatory salivation associated with the hyperpnea.

Direct measurements of oxygen consumption and carbon dioxide production (Corson *et al.*, 1969, 1970; Corson, 1971a) demonstrated that the antidiuretic dogs

do indeed show consistent and significant increases in energy metabolism in the aversive room. In contrast, the diuretic dogs exhibit no such increase in oxygen consumption in the aversive Pavlovian room, nor do they exhibit hyperpnea, salivation, or tachycardia. These animals do not exhibit antidiuresis, since they do not require diversion of body water toward thermoregulatory functions.

In these experiments two factors should be emphasized which must play an important part in our approach to the evaluation of the typological differences in the responses of animals to stressful situations. In fact, it is well known in clinical practice that stressful situations identical in nature and intensity may produce different effects in different individuals.

For example, the prolonged bombardment of a city under siege has very diverse results. Whereas some people may respond to this situation with cardiovascular disorders and hypertension, others may respond with spastic conditions of the intestinal tract, and still others may respond with endocrine disturbances.

Corson's experiments suggest that the above-mentioned nature of the reactions in different subjects may depend considerably on some of their genotypic properties.

As I have already indicated, Corson's experiments have shown that taking the animal into the chamber where it had been exposed to a stressful situation sufficed to bring it immediately to an antidiuretic state. This clearly demonstrates the principle of the anticipatory patterning of the parameters of a *future* result before the nociceptive stimulus has acted (formation and persistent activation of action acceptor—see Chapter 6).

Such cases of the formation of a *latent* integrated system of processes activated only by a triggering stimulus are rather frequent in the activity of the organism. We have termed these latent integrations, which are activated in response to a triggering stimulus, "pretriggering integrations" (Anokhin, 1949c, p. 45).

It seems to us that this idea concerning the origin of neurotic states, which is based on our concept of the origin of inhibition, is a further development of Pavlov's theory on experimental neuroses and on cortico-subcortical relationships. Also, it is hardly inappropriate to state here that corticovisceral pathology, extensively investigated by K.M. Bykov and his collaborators, originates for the most part according to the same fundamental mechanisms which we discussed above.

In fact, the cortical level of neural integration does not have a direct and governing control over the processes occurring in the visceral organs. The latter are included only if the cerebral cortex, under the influence of external factors, mobilizes some powerful subcortical complex with definite functional qualities. Only due to this subcortical complex, and *in direct relation to its strength and quality*, are various internal organs also included in the reaction.

* * * *

The fact that normal higher nervous activity is always the result of a normal balance between excitation and inhibition, and that these relationships may be reflected differently in the function of the peripheral mechanisms creates extreme difficulty in

finding the *true* central interactions. Since the final effect on the periphery is to a certain degree the resultant of two forces, it is natural that the *same* peripheral effect can be the result of at least two combinations of intensities of excitation and inhibition.

Let the experimenter observe, for example, the external manifestation of a *weakening* of the inhibitory process. This weakening may, however, be the result of either an intensification of excitation or a weakening of the inhibitory process with a constant intensity of excitation.

Pavlov repeatedly noted this difficulty of judging the *true interrelationship of the nervous processes* in the cerebral cortex from the *external activity* of an animal. When examining the case of a primary weakening of the inhibitory process, Pavlov said: "Once more we speak of the difficulty of our analysis. We are constantly dealing with two opposite processes, and always when we have a certain kind of phenomena, we must answer the question: is this an intensification of one and a weakening of the other, or vice versa?

Therefore, the facts can not be taken exactly *as they seem to be*, but a difficult analysis must be made" [italics—P.A.] (Pavlov, 1949d, p. 306).

In essence, this important statement pertains to any complex system of nervous processes, if we are to study it and evaluate its mechanisms on the basis of external behavior. It is known that the cerebral cortex exerts a double influence on the subcortical formations: some of them it excites to activity; others it inhibits and suppresses. Consequently, any elimination of cortical influences will always have a double result at the subcortical formations: the neural elements previously excited will decrease their excitability and then will cease the activity of their effectors; those activities, on the other hand, which were formerly inhibited, will be freed from cortical suppression, and will manifest increased activity ("release"). Further evaluation will depend directly upon what indicators, and how many, are used for the analysis of the actual state of the central nervous system. If this analysis of the associated changes of excitation and inhibition, which Pavlov recommended, is not performed, one may reach erroneous conclusions.

Let us consider specifically that component of subcortical activity which was excited by the cerebral cortex. If an inhibition of the cortical cells occurs, then there will follow a cessation of the particular subcortical activity. In this kind of relationship, it is often assumed that cortical inhibition has "spread to the subcortex" and has suppressed the corresponding activity there. With the complex system of interlocking central processes, there is always the danger of an erroneous conclusion if the experimenter interprets the results "as they seem to be."

As we have seen, in the analysis of the intimate physiological mechanisms of the irradiation of inhibition over the cerebral cortex, there is something similar to the example mentioned.

All that has been said above concerning erroneous conclusions is also applicable to understanding the "weakening of the inhibitory process" in the cerebral cortex. The possibility of an error becomes especially evident when, in the evaluation of this problem, one proceeds from our concept of the origin of conditioned inhibition.

According to our concept, the success of inhibiting any activity depends on the relationship of three participating factors: the inhibitory excitation, the excitation

being inhibited, and the process of inhibition itself which arises at the point where the two systems of excitation encounter. These relationships are present whenever two activities conflict.

It is clear that when the external evidence of inhibition, i.e., the suppression of the activity being inhibited, disappears, and the previously inhibited activity reappears, we do not yet have a basis for attributing this to a weakening of the inhibitory process.

Let us try to understand the varieties of relationships which allow the external expression of a "weakening of the inhibitory process":

1. The first relationship most often occurs during a *weakening of the inhibitory excitation itself*. In a number of special circumstances, the intensity of the inhibitory excitations may be considerably reduced. Under experimental conditions, this resulted from decreasing the tone of the biologically negative dominant, which accomplishes the inhibitory effect on the alimentary reaction of the animal.

Upon castration, hormonal disturbances may decrease the tone of the subcortical structures and of the cortex, thus leading to a reduced efficiency of the cortical cell. Under these conditions, the inhibitory excitation will be affected *first*, since it is patterned on the basis of high-frequency and strong electrotonic signals.

As a result of these physiological characteristics of the inhibitory excitation which cause it to be especially demanding on the level of energy processes, it will weaken first. Consequently, the activity being inhibited will to some degree "slip away" from its inhibitory influence. There will be an external expression of a "weakness of the inhibitory process," although the inhibitory excitation may be affected selectively without a change in the excitation being inhibited and without any transformation of the process of synaptic inhibition.

It seems to us that this decrease in the intensity of the inhibitory excitations is the relationship which occurs most frequently in man. Due to this decrease, various kinds of "breakdowns" and disinhibitions occur which lead to antisocial behavior. This may be the result of intoxication or a decrease in the inhibitory effect of social factors (a lessening of the danger of punishment), etc. In each case, with an unchanged intensity of the initially inhibited motive, its "break-through" and actualization in external activity is possible. Of course, all this pertains only to those persons in whom the inhibitory excitation has already been developed. For those people never having any inhibitory excitations, i.e., never being able to respond to the inhibitory effect of "circumstances," the same kind of antisocial behavior is the sad result of improper training.

2. The second type of relationship in this mechanism of conditioned inhibition which may give an external expression of a "weakening of inhibition" involves the intensification of the excitation being inhibited. This may occur under the most diverse circumstances. With an alimentary reaction as the activity being inhibited, for example, such intensification may occur after a period of fasting when the excitability of the unconditioned alimentary reflex increases markedly. It is natural, then, that this alimentary activity ceases to be subject to the action of the inhibitory excitation which in this case is assumed to be of constant intensity.

If this phenomenon is not analyzed, it may be thought that it, too, is a

"weakening of the inhibitory process." True, an indirect indication that we are dealing here with disinhibition due to the increased excitability of the reaction being inhibited is the fact that all positive conditioned reflexes prove to be intensified. Nevertheless, if one only considers the appearance of a positive response to an inhibitory stimulus, then one may interpret this fact to be a weakening of the inhibitory process.

Special tests of the intensity of inhibition decrease the possibility of such an error. In principle, though, the *same external phenomenon* may appear as a result of the most diverse intracentral relationships.

3. The third case of a positive effect in response to the presentation of an inhibitory stimulus may be the result of an actual weakening of the inhibitory process which develops in the region of the synaptic formations (zone of patterning) of the central integrative mechanism of the reaction being inhibited.

As we have seen, Pavlov refuted the possibility of identifying the process of excitation with that of inhibition, although he did consider them to be identical in origin. Physiologically, this concept is most acceptable, since *inhibition as a chemical arrangement with its own distinct electrical concomitant cannot be identified with excitation*.

Let us assume that during inhibition it is not possible to implement some phase of the complex chemical reaction of excitation. By way of illustration, this may be the suppression of the processes of resynthesis of adenosine triphosphate, of acetylcholine, or of still something else. In all such cases there is an elimination or retardation of an original external working effect. At the same time, however, in each of these cases there will be an arrangement of chemical processes of different quality. From this point of view it must be admitted that Pavlov's denial of the *identity* of the processes of excitation and inhibition, on the basis of their *external* opposite effects, is absolutely correct. They cannot be identical, regardless of their similarities.

Thus, we may well agree that the delicate chemical mechanism of the blocking of excitation may be selectively affected by any nonspecific causes. These may either be its "overstraining" or its "weakening." It is difficult to imagine that the *unique and undoubtedly energetically costly chemical structure of inhibition* would not change under the influence of general conditions, especially those of a hormonal or metabolic nature. Yet, in each case of "weakening of the inhibitory process," there must be sufficient evidence that the weakening is related specifically to this third cause and not to the two preceding ones.

Our analysis of these possible relationships, on which the same phenomenon may be based, convinces us that the central processes are far more complex than they first seem to be. Our approach considerably facilitates the analysis of the origin of internal inhibition by bringing us closer to comprehending the natural relationships in nervous activity. At the same time, such an approach decreases the possibility for errors and the accumulation of contradictions in understanding the individual principles of higher nervous activity.

CHAPTER 21

Sleep and Sleeplike States

As is known, the necessity of classifying the inhibitory states of the cerebral cortex arose during the initial stage of the study of higher nervous activity. The *conditions of origin* were essentially the initial criterion for such a classification. Three basic forms of inhibition were specified in accordance with the conditions of origin: external, internal, and sleep inhibition. Later, however, the boundaries separating these forms of inhibition became less distinct with the introduction of new data which supplied different criteria for each form of inhibition, one example being the criterion of phasic changes.

It was shown that under certain conditions, for example, during gradual intensification and spreading of *internal* inhibition over the cerebral cortex during extinction, or in sequential presentation of a number of differentiating stimuli, there gradually develops a somnolent state which subsequently changes into deep sleep. Hence Pavlov made the generalization: "... sleep and what we call internal inhibition are one and the same process" (Pavlov, 1927, see Pavlov, 1960, p. 251).

This synthesizing in the problem of cortical inhibition found further credence several years later. Phasic changes were used as the criterion for similarity between various forms of inhibition (Razenkov, 1926). Special experiments revealed that under conditions typical for obtaining external inhibition, exactly as during the development of internal inhibition, phasic changes are observed in the excitability of the cerebral cortex (Anokhin, 1926b; Prorokov, 1940).

Thus, in such an essential feature as phasic states, external and internal inhibition proved to be identical. Therefore, another generalization emerged concerning the *identity of internal and external inhibition*. The data at our disposal indicate that the difference in the two above forms of inhibition lies mainly in their *conditions of origin*, while their physiological mechanisms and physicochemical natures are identical.

At the same time, certain difficulties have prevented, for a number of years, the complete identification of internal inhibition with sleep inhibition. It was clear that sleep, as a phenomenon encompassing the entire brain, owes its function to specific mechanisms imparted by evolution to the cerebral cortex and the subcortex. In other words, sleep began to be regarded as a phenomenon organized on the level of cortical-subcortical relationships. This concept was affirmed by numerous data obtained in Pavlov's laboratories and other laboratories and clinics. For example, it was demonstrated that decorticated dogs, in spite of their invalid condition and a considerably

reduced or even completely eliminated function of internal inhibition, continue to fall asleep at regular intervals (Zelenyi, 1912; Asratian, 1953).

A large number of similar occurrences were also observed in clinical patients with morphologically verified anencephaly. Comparable to this is the alternation of sleep and wakefulness in a neonate, in whom, as morphological investigations show, the mature cortical elements for bringing about an active inhibitory function are still lacking (Poliakov, 1957). Thus, many observations *unequivocally* indicate that even at the subcortical level there is some organized system of neural connections which determines the elementary forms of alternation of sleep and wakefulness.

In recent years, experimental investigations involving stimulation of some hypothalamic nuclei have furnished evidence for the existence of such neural formations in the hypothalamus (Hess, 1956). Clinical neurology and especially trauma to the walls of the third ventricle have yielded the most abundant material towards a solution of this problem. In a number of cases, quite isolated injuries of this region led to a marked disturbance of the sleep mechanism, resulting in insomnia, drowsiness, and "sleeping sickness." Most of these observations have been verified by postmortem morphological examination.

It is therefore natural that the cortical theory of sleep, expounded by Pavlov on the basis of the irradiation of internal inhibition, had to reflect to some degree all the previously described contradictions. These were resolved by the experiments of Galkin (1933). After the destruction of a dog's three main analyzers (sight, smell, and hearing), the dog remained mostly in a state of sleep. Results obtained were similar to the well-known clinical case described by Strümpell (1877), who had a patient in whom all paths of sensory perception were afflicted by a pathological process. Only one eye functioned normally; this served as the patient's "window to the world." As Strümpell described it, this patient, when awake, needed only to close this one eye and he would immediately fall asleep. It was clear that the waking state was sustained only by that part of the visual analyzer which remained unaffected by the pathological process.

Thus, on the basis of experiments involving the *elimination* of the afferent function of the cortex, Pavlov developed an hypothesis concerning "active" and "passive" sleep. In this hypothesis he said that "passive" sleep, which develops after the removal of most of the receptor areas of the animal, occurs as a *natural result of the elimination of the afferent impulses and of the tonicizing of the cerebral cortex by these impulses*. On the other hand, "active" sleep, according to this hypothesis, results from an *active internal inhibition* of the cortical cells.

In relation to this classification of the states of sleep, the question arises: does the *final state* of the cortical cells differ in any fundamental way in cases of active and passive sleep? Irrespective of what had caused sleep, it is manifested by similar symptoms: primarily the main symptom of sleep—loss of consciousness—and also in changes in muscular tone, in the cardiovascular system, and in the respiration.

Recent electroencephalographic investigations have shown that falling asleep and awakening (arousal reaction) are connected with phenomena of synchronization and desynchronization of cortical electrical potentials. These processes, evoked by differing causes at various stages of sleep (including complete sleep), can be visualized with some

clarity. However, a transition from a synchronized rhythm (α -rhythm, δ -rhythm) to a desynchronized rhythm (predominant β -rhythm) usually accompanies the moment of awakening, i.e., the transition from a resting to an active state. "Paradoxical" sleep is an exception.

It seems that for sleep only the *conditions of origin differ*, while after the integrative mechanisms become involved, the phenomena of sleep, in the sense of the presence of its characteristic symptoms, develop in a more or less standard manner.

Here it is appropriate to refer to our previous investigations which have demonstrated that the desynchronization of cortical activity may be due to the most diverse functional causes, involving an active state of various subcortical apparatuses. A paradoxical case of such a dissociation of different activations occurs with urethane general anesthesia (Agafonov, 1956). The simultaneous existence of an activated state on the electroencephalogram and of deep sleep during nociceptive stimulation shows that there are at least two separate subcortical structures whose activity can be dissociated. Experiments involving evoked potentials have also demonstrated that during the deepening of nembutal general anesthesia there comes a moment at which the amplitude of the evoked potentials of the hypothalamus considerably increases (Shevchenko, 1965).

An interesting case of the dissociation between individual ascending activating influences is the action of those new general anesthetics which to some degree are antipodes of urethane, e.g., Gamma OH (Laborit *et al.*, 1962) and phentanyl. Some of these drugs fully maintain wakefulness, but eliminate pain sensations (Laborit, 1961). From our point of view, the phenomenon of paradoxical sleep, discovered and studied by Jouvet (1965), is a special case of the dissociation of various ascending activations. The activation of wakefulness is suppressed and the animal is asleep, but any other activation (either nociceptive activation or the activation of isolated subcortical complexes) freely reaches the cortex.

At present, one can hardly deny that sleep, being the result of an integrated activity, has complex subcortical apparatuses which are strictly coordinated into one functional system, the adaptive effect of which is an intensification of the vegetative processes in the entire organism and an acceleration of the regenerative processes in the cerebral cortex itself.

In accordance with this, *cortical inhibition* can be only one of the causes initiating the mechanism of sleep, for it would be difficult to assume that the cerebral cortex contains all those mechanisms of coordination which govern sleep.

With the above considerations in mind, as early as 1945 we advanced the hypothesis of the development of sleep as a cortico-subcortical phenomenon (Anokhin, 1945a). Later events in neurophysiology, especially in the study of the role of the reticular formation in sleep and arousal, proved that our hypothesis was quite accurate.

Our hypothesis clarified the relationships between active and passive sleep, and at the same time it explained the numerous examples of sleep disturbances of hypothalamic origin. We have diagrammed the relation between the cortex and the subcortex in the development of sleep in the following way (Fig. 21.1). As shown by this diagram, active sleep, caused by the inhibition of cortical activity, develops as a

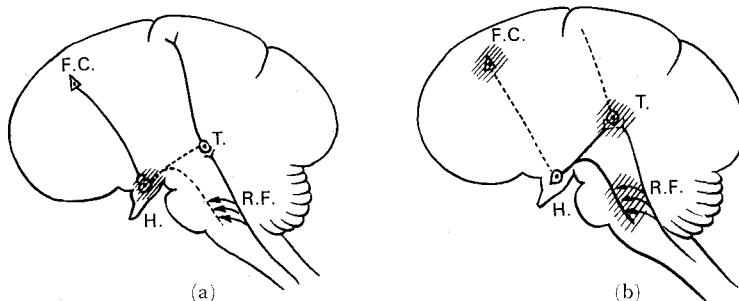


FIG. 21.1. The relationship of cortical and subcortical components in the sleep apparatus as an integrated manifestation of the organism. T., thalamus; F.C., frontal cortex; H., hypothalamus; R.F., reticular formation.

result of the release of the hypothalamic structures which remain active throughout the entire period of sleep.

Such relationships may quite possibly arise if one assumes that some cortical regions, especially the frontal lobes *which have abundant conducting connections with the hypothalamus*, exert a continuous inhibitory influence on some hypothalamic centers. This is confirmed by the existence of high-frequency impulses which propagate from the frontal lobes to the hypothalamus. Inhibition of the cerebral cortex must inevitably lead to the release, i.e., to the excitation, of hypothalamic centers, probably those centers which, when stimulated with electric current, put the animal to sleep (Hess, 1956; Orbeli, 1949).

The hypothesis makes possible a second assumption. Excitation from the "released" hypothalamic centers, upon propagating into the region of the thalamus, blocks the passage to the cerebral cortex of those afferent impulses which ensure the state of wakefulness. The advantage of this hypothesis is that it agrees exactly with the physiological and morphological data concerning the relation between the cortex and the hypothalamus; furthermore, it eliminates all those contradictions which had arisen in the cortical theory of sleep in connection with the acquisition of *entirely reliable* physiological and clinical data concerning the participation of the hypothalamus in the alternation of sleep and wakefulness.

By way of illustration, let us examine the sleep of a newborn infant. The cortical elements in the brain of the newborn do not yet have the potentiality of acting on the hypothalamic region which has already *considerably matured*. According to our hypothesis, the basic state of the newborn infant must be a *state of constant sleep*. The infant awakens only when the "starved blood" of some hypothalamic centers elicits a *strong excitation* and reciprocally inhibits other centers which, due to their activity, had caused a continuous sleep. This scheme is equally applicable to the explanation of sleep in decorticated animals and to the explanation of traumatic disturbances of sleep and wakefulness. We had advanced this hypothesis long before the activating effect of the reticular formation on the cerebral cortex became known. It is therefore natural that we could not take it into account in our scheme.

As previously indicated, according to the existing ideas regarding the function of the reticular formation, the waking state in animals and man is maintained because the reticular formation of the brain stem exerts a constant generalized excitatory influence on the cerebral cortex as a whole. This activating effect needs only to cease for any given reason and the cerebral cortex immediately loses its necessary level of activity. The animal falls asleep (Moruzzi and Magoun, 1949; Moruzzi, 1966).

This hypothesis, which strongly supports the activating effect of the reticular formation, has two weak points:

1. It does not establish the direct reasons why, upon the onset of sleep, the "activating substance" ceases its generalized effect on the cerebral cortex. The difficulty in explaining these reasons is that the elimination of the afferent influences which "feed" the reticular formation is not the cause of sleep, but is the result of an already initiated interaction in the mechanism of sleep.
2. According to this concept, the state of sleep is *identified* with the transition of the cerebral cortex from *desynchronization* to *synchronization*, i.e., to slow activity of the α - and δ -wave types which are regarded as the primary cause of sleep. A comparison of these phenomena with the natural picture of sleep in animals has been made only in isolated experiments, and therefore these data cannot as yet be considered to be entirely convincing.

It should, of course, be noted that the data on the role of the reticular formation in maintaining the active states of the cerebral cortex considerably expand our possibilities of explaining sleep as the result of coordinated cortical-subcortical interactions.

In our proposed hypothesis of the origin of sleep, in which the cortical level is of primary and decisive importance, the inhibitory effect of the hypothalamus can easily spread to the region of the reticular formation of the brain stem or to the *thalamic* reticular formation.

Consequently, rather than excluding our hypothesis, the reticular theory of sleep supports it by affirming the cortical-subcortical relationships in the onset of sleep. Even more does it strengthen our hypothesis by the far more complete involvement of all those cases in which sleep sets in as a result of the direct intervention of cortical levels (e.g., sleep induced by verbal suggestion).

With the analysis of the material presented above, we have partially answered the question of how it is possible to understand the origin of sleep inhibition or of sleep from the point of view of our suggested concept on the origin of conditioned inhibition.

First, it must be considered to be firmly established that the central interactions of the processes are substantially more polymorphous than the behavior of the indicator selected for evaluation of these central processes. We have indices of plus and minus in a given reaction. The minus may be the result of a central arrangement of processes rather than the result of intervention, let us say, by an inhibitory process. Moreover, the inhibitory process itself is not homogeneous, and an externally identical *elimination* of some activity of the organism may result from completely different central causes.

For example, the well-known inhibitory effect of the orienting-investigative reaction on weeping in a child is rapid and energetically economical. Just as rapidly and *without any effort on our part*, any ongoing activity is inhibited if there appears in us an

orienting-investigative reaction to a *sudden* stimulus. On the other hand, the inhibition of some emotional state, and especially of its external expression, involves intense participation by the cerebral cortex.

There can hardly be any doubt that in these two examples we have *entirely different mechanisms* for inhibiting specific activities of the organism. The difference may be related to the localization of the inhibitory process itself or to its dissimilar nature (hyperpolarization or high-frequency pessimum). Briefly, we can see that *the same external manifestation* of the elimination of some integrated activity or of its individual components might be due to *fundamentally different* inhibitory mechanisms. At times, there arises a situation in which an activity can be eliminated without any direct inhibition of the excitations comprising it. For instance, the activity may be secondarily eliminated because the action of those neural substrates which maintained the "inhibited" activity has ceased. This characteristic of intracentral relationships must be remembered in order to avoid error in evaluating the *external manifestation* of the elimination of some activity or one of its components. Clarification of this is necessary because of the widespread tendency to identify any *disappearance* of an observed phenomenon with the presence of "inhibition in the cortex." This pertains especially to the condition of cortical neural elements during sleep. We believe that this problem can be examined by using the most recent data. First, it is essential to resolve the following two contradictions:

1. The idea that "internal inhibition and sleep are the same process" inevitably leads to several logical conclusions which contradict this very idea. From the works of the Pavlovian school we know that internal inhibition is an active process which is energetically very costly. As we have seen, Ukhtomskii reached the same conclusion. This established, physiological characteristic of internal inhibition naturally leads to the contradiction that cortical cells, in an *active inhibitory state* during sleep, restore their energy at the same time. One of the primary tasks of experimental investigation should be to bring about a resolution between our concept of internal inhibition as an "active" and "difficult to accomplish" process and those data emphasizing the passive, resting state of the cortical cells during sleep.
2. The development of electroencephalographic investigations has led to a significant generalization describing the state of cortical cells. It is already axiomatic that the slow electrical oscillations in the cerebral cortex are indicative of *synchronized* electrical states of individual cellular elements. Any synchronization of the electrical activity of enormous numbers of neural elements represents a resting state of the neural cellular elements, as demonstrated by Adrian and Matthews (1934), Moruzzi (1956), Adrian and Moruzzi (1939), and Clare and Bishop (1956).

Schematically, these two phenomena of the cortical states can be shown as in Fig. 21.2. The first part of the diagram shows that the resting state of the cellular elements allows for a large number of them to enter simultaneously into a common, synchronized electrical pulsation which gives slow oscillations in its electroencephalographic manifestation: the α - and δ -rhythm. This tendency of the resting cortical

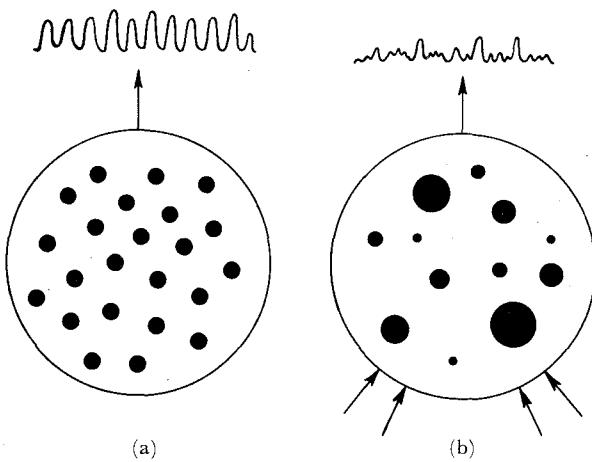


FIG. 21.2. Relationship of individual cell elements of the cerebral cortex under conditions of synchronization (a) and desynchronization (b). At the top are the corresponding electroencephalograms.

elements to unite in a synchronized electrical discharge with many other cortical elements of the same kind was clearly demonstrated in experiments involving the isolation of an islet of cortical tissue.

The experiments have shown that a completely isolated islet of cortical tissue, connected with the organism by only a vascular peduncle, produces rhythmic, slow, i.e., synchronized, discharges. These synchronized electrical discharges at times may appear in spindle bursts and usually constitute, in the intact brain, a sign of the transition of the cerebral cortex to a resting state or sleep.

In the study of the function of the reticular formation, it was also shown that as soon as the cerebral cortex separates in one way or another from the activating system of the brain stem, spindle bursts immediately arise. It is of interest that the same spindle bursts, having slow oscillations, also arise when an animal is given chlorpromazine, which selectively inhibits the reticular formation of the brain stem. The cerebral cortex, deprived of activation by the reticular formation, synchronizes the electrical discharges of great masses of cells.

These data are of particular interest since they emphasize the relation between the *state of sleep* and the presence of slow, synchronized electrical oscillations in the cerebral cortex. This series of phenomena gives no support to the view that the inhibited state of the cerebral cortex during sleep is *identical* with the active effect of internal inhibition. Therefore, during sleep a kind of third state of the cellular elements exists, coinciding with neither external nor internal inhibition. Such a number of contradictions shows that it is absolutely essential to study further the relationship of sleep and internal inhibition.

This becomes even more necessary because, although the contradictions in the problems of inhibition and sleep are quite obvious, they continue to accumulate in the

scientific publications of recent years, and there is no attempt at a more profound analysis. Due to the coordinated relationships between the cortex and the subcortical structures, sleep itself constitutes an entirely different condition for the cerebral cortex: the release from the activating effect of afferent stimulation and the transition of the cellular masses of the cortex to a passive synchronized activity.

The above conclusion is in complete agreement with all the data, and easily eliminates the contradictions between our concept of the *active nature* of internal inhibition and the quite obvious signs of *passive synchronization* of the cortical cellular masses during sleep. Moreover, this conclusion corresponds well to all the clinical data which indicate a difference between the nature of the mechanisms of the onset of sleep and the nature of sleep itself, as a state dependent on a specialized nervous apparatus.

From what has been said, it follows that it is not at all difficult to explain the development of sleep in accordance with our concept of the origin of conditioned inhibition. Conditioned inhibition is not constant and uniform at all stages of its elaboration and stabilization. Knowing that during the transition from the stage of conflict to the stage of "concentrated" inhibition the biologically negative reaction is largely reduced, and the orienting-investigative reaction with all its characteristic vegetative manifestations is eliminated, we can easily decide upon the next area of investigation of this problem.

Why does any external stimulus which has lost the ability to activate any unconditioned activity of the organism, especially the orienting-investigative reaction, automatically initiate the complex mechanism of sleep? The mechanism of sleep will always be automatically turned on in the manner of a "release" as soon as the functioning tonus of the cortical cells is reduced to a certain level, regardless of the causes of this reduction.

This explanation satisfies us for the present because it agrees with all the current advances in the study of cortical-subcortical relationships and especially with the causes of the onset of sleep.

Indeed, in the opinion of most authors, the desynchronization of the cortical electrical activity corresponds to "attention," the working condition of the cortical cells, which is undoubtedly accompanied by an intensification of their impulse and electrotonic activity (Magoun, 1950; Jasper, 1958). It is natural that in this condition of the cerebral cortex, and especially of its frontal lobes, the subcortical apparatuses of sleep will be in a depressed, i.e., inhibited, state.

A number of authors have come to the conclusion that "attention," "interest in the surroundings," "emotional tone," and other psychic phenomena are intimately connected with the activating effect of the hypothalamus and the reticular formation on the cerebral cortex (Moruzzi, 1956; Dell and Bonvallet, 1956; and others). Consequently, the physiological result of a loss of "interest" in and "attention" to a given situation will be a considerable decrease in the tonus of the cortical cells with the release of the subcortical apparatuses of sleep. The explanation which we propose (still hypothetical, of course) for the relation of conditioned inhibition to the onset of sleep may be regarded as sufficiently substantiated. Thus, the search for a more profound and more perfect understanding of the mechanisms of the relation between sleep and internal inhibition must begin from here.

CHAPTER 22

Certain Correlations in the Study of Conditioned Inhibition

As shown by the analysis of specific key questions in the study of higher nervous activity, the further development of the theory of conditioned inhibition is of enormous importance for many borderline questions of the physiology of the nervous system. We have already discussed in detail the irradiation of nervous processes, neuroses, sleep, and other general phenomena of higher nervous activity, and have shown what new aspect of their study results from the concept of the origin of conditioned inhibition which we are proposing. All this emphasizes once more what an important position the problem of conditioned inhibition occupies in the study of higher nervous activity.

However, it must be noted that this new aspect of the study of higher nervous activity problems is by far not the only one. The generally accepted hypothesis of the mechanisms of conditioned inhibition has decisively influenced a number of neighboring disciplines and has determined both the approach to it and the specific methods for its investigation.

It is therefore natural that a new approach to the explanation of the intimate neurophysiological mechanisms of the conditioned reflex and conditioned inhibition must result in an improvement of the methods of investigation in neighboring disciplines as well. This is especially important where formal transfers of interpretations from one field of study into another have become entrenched, or where errors resulting from incorrect approaches to the investigated problems have been accumulating. In the latter cases, it can frequently be seen how each subsequent investigation promotes the growth of the initially erroneous position in a geometrical progression.

By way of example, one may note even such a popular research trend as the *electroencephalographic characterization* of inhibition and excitation in the cerebral cortex. These extensive fields of investigation call for a special analysis at this time, since the vague and often even erroneous premises concerning this question lead, in our opinion, to a considerable distraction from the true problem of conditioned inhibition.

In fact, as could be seen from the entire presented material, conditioned inhibition is not a process of *territorially united cellular masses*. Rather, it is a selective process, a process of central interrelations which occur at the *synaptic formations* and individual cellular elements that are very widely scattered over the central nervous system.

Conditioned inhibition is a complex process. The degree of its dispersion over the cerebral cortex is directly related to the degree of complexity and composition of the *activity being inhibited*. From this purely physiological point of view it is difficult to

assume a homogeneity of the process of inhibition even in a score of neighboring cortical cells. It is therefore natural that any attempt to detect the process of conditioned inhibition in some fragment of cerebral tissue can hardly lead to a positive result, since the chemical processes that have determined the conditioned inhibition at a few *selective synapses* constitute a negligible portion of all the metabolic processes of this fragment.

Many positive results have been achieved in the biochemistry of inhibition (Palladin, 1956; Vladimirov, 1955; and others). However, these results can be related only to those inhibitory states which involve entire regions of cortical cellular masses. Among these inhibitory states may be included extensive protective inhibition, the state of sleep as described in the preceding chapter, the state of drug-induced sleep, etc. As for internal, and by nature *coordinative*, inhibition, it appears to me impossible to obtain any of its chemical equivalents through the study of the chemical composition of specimens of large cellular masses.

To illustrate the difficulty in making correlations of this kind, one may cite an experiment of Vladimirov (1955). Conditioned positive and conditioned inhibitory motor reflexes toward the feeder were elaborated in rats. By means of special devices he intended to capture, for biochemical study, that state of the cerebral cortex in which conditioned inhibition is present. This was achieved by letting the rat suddenly fall through a trap into liquid air. On the basis of the subsequent biochemical investigation, a conclusion about the "biochemistry of conditioned inhibition" and the "biochemistry of excitation" was drawn.

It is quite clear that this experiment does not meet the requirements for the precise study of the inhibitory process. Quite aside from the fundamental condition for the origin of conditioned inhibition, namely, its *selective synaptic origin*, the conditions for the above-described experiment were created without accounting for the dynamic properties of nervous processes. The investigators seem to have assumed that at a certain moment the entire cortex is occupied by conditioned inhibition; therefore, they subjected the entire brain to biochemical analysis. This is undoubtedly an incorrect premise. In addition, upon taking into account the dynamic nature of nervous processes and the rapidity of the alternation between the different states in animals, it is impossible to assume that at the moment the rat took a wrong step and fell into the liquid air, it retained the "inhibitory" state required by the investigators.

A fraction of a second is enough for such a powerful stimulus as the *vestibular stimulus* to immediately alter the entire state of the central nervous system and, of course, of the cerebral cortex. This becomes particularly significant because the rate of propagation of all impulses connected with the postural reactions of animals and man is especially high. One can therefore assert that long before the rat has fallen into the liquid air, its cerebral cortex has changed its dominant state to such an extent that not a trace of those "inhibitions," which had been of interest to the investigators, has remained.

Figuratively speaking, it cannot be assumed that while falling suddenly into a pit, the rat would still retain its alimentary interests, to say nothing of the fact that the

action of the liquid air as a contact stimulus cannot fail to exert its specific influence on the central nervous system *before the fixation of the brain occurs*.

These fundamental and procedural characteristics of the experiments on the "biochemistry of conditioned inhibition" do not yet give us any right to a scientific conclusion. On the basis of these initial failures, it would be wrong to deny the possibility of chemical characterization of conditioned inhibition by, for example, *histochemical methods on condition that the cellular or synaptic localization of the given kind of inhibition is exactly determined*.

The development of biochemical investigations of conditioned inhibition has proved to be somewhat premature in this sense, since they naturally cannot lead to a tangible answer to the question without a preliminary solution of three fundamental problems: the mechanisms of the origin, the localization, and the spread of conditioned inhibition. As we have seen, however, this triad of conditioned inhibition is only now beginning to receive an appropriate solution.

To an equal degree, all this pertains to the numerous attempts to find an electroencephalographic equivalent to the processes of conditioned inhibition (Livanov, 1947; Rusinov, 1955; Maiorchik, 1957; Gastaut *et al.*, 1957b). By their nature and technical possibilities, ordinary electroencephalographic investigations are able to reflect only the synchronized electrical discharges of a great number of cortical cells. On the other hand, any increase in desynchronization leads to a lowering of the amplitude of the slow oscillations (suppression of the α -rhythm). In the case of maximum desynchronization, the electroencephalogram can, at a certain amplification, change into a straight horizontal line. This observation is of special importance in the case of the recording of the electrical oscillations of the cortex by means of ink-writing electroencephalographs whose sensitivity is usually sufficient only for the recording of highly synchronized high-voltage electrical oscillations.

It may be asked whether it is possible, by these technical means, to detect conditioned inhibition, which in its physiological essence is a dispersed process arising at synapses that are scattered over the entire cerebral cortex. Of course it is not. An exception may be those cases in which a very delicate and selective synaptic inhibition, for example, at the pyramidal neurons of the cerebral cortex, *can be accompanied by extensive and diffuse electrotonic changes that correspond to an involvement of the entire motor sphere into the process ("postural excitations" in our terminology)*.

Meanwhile, physiological literature abounds with descriptions of "conditioned inhibition" derived from electroencephalographic data.

There is no doubt that we have here a scientific error which appeared only because at one time the fundamental premises for electroencephalographic investigations of this kind had not been fully stipulated, although indications of this error had been repeatedly made.

Only by this can one explain, for instance, that the *slow* electrical waves in the cerebral cortex which accompany the state of sleep have been identified, contrary to all scientific data, with the state of active internal inhibition (Maiorchik, 1952). From the preceding chapter, we saw that there was no sufficient physiological basis for such an identification. This tendency to make comparisons on the basis of the similarity of

individual external features in states of the central nervous system which are by nature entirely different sometimes goes so far that it is even used for diagnosis in neuropathological, psychiatric, and neurosurgical practice.

If electric potentials are recorded from the cerebral cortex at a site next to a neoplasm, one may observe a shift of the frequency spectrum of the electric waves to the left, i.e., toward a decrease in frequency. This decrease in frequency of the electric waves in cases of cortical neoplasms has already become a well-established fact, and is therefore legitimately used in the solution of problems of topical diagnosis in neuropathology and neurosurgery.

However, the *nature* of these waves of a decreased frequency is, in our opinion, given an incorrect interpretation, and it is therefore essential to discuss it.

It must, however, be noted that in recent years the significance and composition of the slow electrical waves is becoming increasingly clear; therefore, the tendency to identify the slow waves with active inhibition is not so great. However, since there are still adherents of this point of view in both Soviet and foreign literature, it is quite important to demonstrate the unsound basis of this identification (Anokhin, 1926b).

Maiorchik (1957) has clearly demonstrated that if there is a sudden change from 10 flashes to 24 flashes per second during stimulation with flashing light, the electroencephalogram of the patient changes considerably. Changes appear even in the "normal" regions, but they are especially distinct in the region afflicted by the neoplasm. The changes are as follows: the dominant rhythm of the electric waves decreases, and the waves assume a high amplitude.

The *reliable* material available to the author is essentially limited to these observations. Further on hypothetical assumptions begin about the nature of the processes occurring in the pathological focus. As a result of the change in rhythm from 10 to 24 flashes per second, *a transformation of the rhythm and a transition to inhibition* begin in the cortical cells near the pathological focus which have a decreased mobility. These processes are responsible, in the author's opinion, for the appearance of the slow and high-amplitude electrical oscillations in the electroencephalogram.

These arguments appear to make quite likely the basic conclusion of the adherents of this point of view: *slow and high-amplitude electrical oscillations of the cerebral cortex indicate the presence of active cortical inhibition*. Gastaut *et al.* (1956) adhere, with certain reservations, essentially to the same point of view.

According to the theory of Vvedenskii and Ukhtomskii, the above considerations pertaining to the origin of the inhibitory process as a result of the transformation of the rhythm suggest the appearance of a *pessimal inhibition*, i.e., the most active form of parabiotic inhibition requiring the intervention of a strong inhibitory excitation. Continuing with this reasoning, one can draw the following conclusion: the *presence* of active pessimal inhibition in the cerebral cortex is accompanied by the appearance of slow, high-amplitude electrical oscillations.

The most important aspect in the modern interpretation of the nature of the electrical, so-called spontaneous, oscillations in the cerebral cortex is the concept of synchronization and desynchronization. According to this concept, the state of rest of the cerebral cortex, i.e., when it is not subjected to any external or internal stimulation, is mani-

fested by simultaneous or synchronized discharges of an enormous number of neural elements. Due to this synchronization the high-amplitude and slow oscillations arise, since a certain temporal dispersion of the discharges must occur during such a unification of millions of cellular elements.

Any impulses arriving at the cerebral cortex via the thalamus and the reticular formation make specific demands of the cortical elements, i.e., they drive them to operation independent of the other cellular elements. This circumstance, which is characteristic of the functioning cerebral cortex, must effect desynchronization of the electrical activity. Since the electrical manifestation of the operation of separate cortical elements will always be of lower voltage than the electrical manifestation of their simultaneous joint discharges, there will have to be a *lowering of the amplitude of the recorded electrical oscillations* in the general electroencephalographic picture. A typical example of such desynchronization is the suppression of the α -rhythm under the influence of the action of light on the visual analyzer.

Another example of desynchronization which any electroencephalograph can record is the arousal reaction, which appears in the cerebral cortex of a sleeping animal after electrical stimulation of the reticular formation of the brain stem (Bremer, 1935; Magoun, 1950; Moruzzi and Magoun, 1949).

On the basis of all the arguments presented above, we obviously have to accept the proposition that any active state of the cerebral cortex must inevitably have as its electrical expression an increase in the frequency of the electrical oscillations and a decrease in their amplitude. It is clear that this contradicts the above-presented conclusion that active cortical inhibition corresponds to a slow and high-amplitude rhythm.

Such a conclusion, and many others besides, leaves no doubt that in all such cases a decrease in the frequency of the electrical oscillations in the cerebral cortex is regarded as a criterion for transition to an inhibitory state. Emphasizing the dependence of diverse and even opposite reactions of the electrical oscillations of the cerebral cortex on the initial state neither eliminates nor alters the principal views presented above.

One may ask how such a contradictory interpretation arose, which is contrary to the very nature of the slow electrical oscillations in the cerebral cortex. The origin of this contradiction seems to be quite clear. The *a priori* assumption that the state of the cerebral cortex during sleep is identical with the process of active internal inhibition prevails among the adherents of this point of view. And since as a result of numerous investigations it has been established with certainty that slow oscillations of the electric potentials are recorded in the cortex during sleep, there automatically follows the erroneous conclusion that any transition of the cerebral cortex to a low level of electrical activity must be a symptom of a transition to a state of active internal inhibition.

As we have already seen above, an identification of the state of sleep with active internal inhibition would hardly be acceptable now in light of the latest advances in neurophysiology. Yet at the same time we must also recognize as entirely correct the proposition that sleep is a consequence of the development of active internal inhibition, as I have explained throughout the entire book.

For the neural elements of the hypothalamus to be "released" from cortical control,

it is essential that the continuous activity of the cerebral cortex be actively inhibited. This may be achieved by means of acute inhibition or by a gradual weakening (as in prolonged intense activity). This is the first phase in the development of sleep. The subsequent phase releases the active hypothalamic mechanism, which leads to the elimination of ascending activation. This mechanism does not involve active cortical inhibition. Consequently, any consideration of sleep as *active* cortical inhibition has no physiological basis.

This has led to the accumulation in recent literature of a large number of contradictory propositions which hinder the further elucidation of the physiological mechanisms of inhibitory reactions.

The recognition of active internal inhibition as a selective and complex process that arises at different microscopic sites of the synaptic formations precludes the possibility of detecting it by means of ordinary present-day electroencephalographs, especially those with ink recorders. It may be assumed, however, that those electrotonic changes which invariably accompany and promote the limited, and always precisely aimed, processes of the active inhibition of some activity could be diffuse. From the point of view of their electrical manifestation, however, these processes are something entirely different.

The electrotonic state creates the *conditions* for the origin of the inhibitory process and always involves more extensive regions of cellular elements. In spite of this broad electrotonic scope, however, the actual inhibition of the active nerve cells occurs in those regions which are receiving selective *impulses* at the given moment.

Cannot the electrotonic changes involving entire regions of cellular masses be an indication of the inhibitory state of individual synaptic formations?

This is highly doubtful since there still does not exist any definite concept of what kind of diffuse electrotonic changes accompany the formation of the selective synaptic inhibitions, which are the basis for active internal inhibition. These circumstances affirm that any use of the concepts of the "electrical indicator of internal inhibition" or the "biochemistry of conditioned inhibition" are not sufficiently well grounded with the presently available investigative techniques.

True, the refinement of the techniques of investigating *individual* neural elements by means of the finest microelectrodes has been fruitful (Eccles, 1953, 1964; Eccles, 1952a, 1952b; Moruzzi, 1954; Fatt, 1956; Malcolm, 1956).

One might have expected that an autocorrelational analysis of cerebral electrical phenomena would reveal some characteristics of self-regulatory apparatuses *within the brain* (Wiener and Schadé, 1963). However, because Wiener's premise is physiologically insufficiently clear, it seems unlikely that we will be able to understand the nature of the actual participation of the neural elements in the implementation of conditioned reflex activity by pursuing this line of thought.

It has become clear that, in attempting to understand the structure of the interactions of neural elements from the slow waves of the electroencephalogram, we are approaching the most delicate molecular processes which maintain their specificity and individuality even within a single synapse (see Chapter 5). There can hardly be any doubt that progress in the problem of the organization of the inhibitory elimination

of some activity is the result of the study of the structural and physiological interaction of complex and specific integrated activities on synaptic and axoplasmic levels.

The unraveling of this problem has been slow because of the difficulty of satisfying two essential conditions, without which no truly scientific conclusion is possible: a particular cortical nerve cell must actually be in a state of internal inhibition, and this particular cell must be under the microelectrode.

In recent years the simultaneous study of the conditioned reflex and the state of individual neurons has become quite extensive, as we have seen in Chapters 4, 5, and 6. "Inhibitory neurons" and "neurons of novelty" (Sokolov, 1958, 1959, pp. 5-76; Vinogradova, 1959, pp. 86-206) make their appearance. In other words, the participating neural elements are described separately, even though the end effect, i.e., the conditioned reflex, is apparently the statistical result of a multitude of participating neurons having different functions.

Conclusion

A RETROSPECTIVE evaluation of the entire material that has been presented, especially that in the initial chapters, convinces us that we are at the threshold of important changes in our concepts of both the biological nature of the conditioned reflex and its principal neurophysiological mechanisms. These changes, as is quite natural, are most intimately connected with the advances in related sciences, primarily with the advances in neurophysiology, which has made extensive use of the progress in electronics.

At the same time, as could be seen, all these changes in our concepts and fundamental hypotheses emphasize even more the most significant role of the conditioned reflex as a universal principle of living nature.

Indeed, living organisms originated during that phase in the development of our planet during which only the world of inorganic phenomena and principles was in existence. In this sense the first bit of living matter was essentially a particle of the inorganic world, though a particle which had slipped away from entropic inevitability....

A completely inviolable condition for the survival of this primordial life was its adaptation to the laws of the inorganic world, which had already arisen on our planet before.

We have seen (Chapter 1) that among these laws of our planet there has been one universal principle of space-time relationships—the principle of the repetition of sequentially developing external events. This principle served as the historical basis for the function of prediction from primitive protoplasm to the most refined activity of the human brain.

Only the means of prediction have changed, but its biological significance of adaptation to impending events remains the same throughout the entire history of living matter and in all representatives of life. The conditioned reflex is but the most differentiated form of realization and stabilization of sequentially developing external events, but the fixation of this temporary connection is, in the final analysis, brought about in the protoplasm of the cell in the same way as this was occurring billions of years ago in the protoplasm of the primordial organisms.

Nature was not very generous with respect to fundamental laws of life. After creating only a few of them during the critical period of life, it then, throughout the entire evolution of the animal kingdom and at all stages of its perfection, varied and perfected the implementation and manifestation of these laws.

In the final analysis, the question regarding how the signalization of impending events was implemented is quite immaterial; such signalization leads to better adaptation of organisms to the environment.

In the case of primitive organisms the sequential action of external factors may be implemented directly onto the membrane or even onto the protoplasm, while in higher organisms this action may be brought about by the peripheral receptors, the conduction of impulses over the nerves, and its transformation at the numerous synaptic formations. All these stages were an inevitable consequence of the complication of the organization of organisms and of their more perfect adaptation to the most delicate conditions of the environment.

In both cases, however, the cellular protoplasm has the decisive role in the patterning of the signaling connection. Evolution has only changed the "*means of delivery*" of the information, but its final processing is in all cases brought about on the same pathways and perhaps even by the same molecular processes.

At this point I would like to remind the reader of the experiments of McConnell, Hydén, and others (see Chapter 5).

It is therefore not surprising that such an authority on protoplasmic investigations as Crick would point out in summarizing the results of his investigations of ribonucleic acid metabolism in bacteria that the method of coding and utilization of RNA in the synthesis of protein molecules is amazingly uniform. One must keep this in mind, because sometimes one encounters the statement of the problem of the conditioned reflex in a somewhat simplified way, as in the question: "When in the evolution of life on earth did the conditioned reflex appear for the first time?"

An attempt is often made to confirm that the "appearance" of the conditioned reflex caused a certain qualitative change in the entire evolution of the adaptation of animals to the environmental conditions as well.

As can be seen, the point of view presented above denies the existence of such a sudden change related to the "appearance" of the conditioned reflex. It asserts that signaling interrelations as temporary connections have made their appearance already at the dawn of life on our planet, that they have taken part in the entire process of perfection of the organisms, and that they are an inherent property of every living thing.

This formulation of the question naturally presents the inborn activity in a somewhat different light too. As we have seen, in Pavlov's laboratories, the dog was chosen as the first experimental animal. Here the unconditioned alimentary reflex can be easily identified by the moment the food comes in contact with the mucous membrane of the tongue.

But how could this be done in birds, if they had been selected as the first object for the study of conditioned reflexes?

As we have seen, in the newly hatched rook there immediately appear clearly signaling, i.e., anticipatory, reactions to the action of the sound "kar-r-r" and to stimulation of the skin by moving air. The only difference is that in the case of the conditioned reflex in the dog the reaction to the signal is salivary secretion, while in the newborn rook it is opening of the beak. Nevertheless, in both cases the reactions are signaling and anticipatory, aimed at the intake of food.

However, in the case of the rook this reaction to the signal is *inborn*, while in the dog it is *acquired*, i.e., *elaborated*. It is clear that in a broad biological context "inbornness" is not a fundamental indicator of signaling adaptation to coming events, i.e., of the conditioned reflex.

If on the basis of the modern advances in neurophysiology a more thorough analysis of the unconditioned alimentary reflex were made, it would prove to be but a signal for more profound, future processes of tissue metabolism.

This neurophysiological mechanism explains primary satiation (in our terminology), i.e., satiation, which sets in at the dinner table. Actually the conditioned stimulus does not act any more now, but in the actual physiological essence the hunger has not been eliminated either, since the starved blood has not yet received the ingested alimentary substances and consequently continues to remain a stimulus for the hypothalamic structures.

What, then, is the unconditioned stimulus?

It, undoubtedly, is but an intermediate link in the chain of sequentially developing events, beginning with the onset of hunger, remote signals of food, food intake, "primary satiation," and, finally, the satisfaction of the true metabolic hunger, i.e., the "tissue hunger." The nature of these sequential events is such that the energy of the nutrients cannot be utilized immediately after the ingestion of these substances. A certain time is needed for the digestion, absorption, and assimilation of the ingested substances.

Actually the organism should be taking in food during all of this time (3-5 hours), until the starved blood ceases to be starved.

During prolonged evolution there appeared the process of *anticipatory* suppression of hunger excitation by means of the afferent impulses from the intake of food alone. This is "sensory satiation" in the true sense of the word.

Returning to the question of what the unconditioned stimulus is, we must answer it as follows: it is also a signaling, i.e., anticipatory, stimulus like the bell (conditioned stimulus), which signals the intake of food. The only difference is that the conditioned stimulus effects the signalization through the patterning of new combinations of neural connections, while the unconditioned stimulus effects the same kind of signalization through inborn connections. For higher animals this is accomplished most frequently by the sequential order of impulses *inside the organism*.

However, one must not assume, as do certain scientists, that in acquired signalization *new synaptic contacts are formed*. The study of the ontogenesis of electrical phenomena in the central nervous system shows that all the synaptic formations in the brain are formed on the basis of rigid genetic information.

The entire further enrichment of the brain with new connections and acquired reactions proceeds evidently merely through the facilitation of intraplasmatric protein rearrangements in the nerve cells. Thus, the problem of the unconditioned reflex can, from this broad biological point of view, be solved as follows.

There exists a universal characteristic of life: *signaling adaptations to sequentially developing series of events in the environment*. But in some cases, in view of the almost absolute likelihood of the subsequent events (mouth-esophagus-stomach-intestinal tract-metabolism), this signaling value proved to be fixed in the structures of the nervous

system of the organism during evolution, while other signaling values, in view of their historical newness and low probability in connection with the variability of the external events, still remain "acquired" reactions and are not yet hereditarily fixed.

It is most likely that a number of reactions of a signaling nature, even to stimuli that are remote but have a historically stable coincidence, can also become genetically fixed reactions. The signaling reactions of the newly hatched rook (to sound, to the movement of air) and of other animals can serve as an example of this. Are there inborn signaling reactions to remote stimuli in higher animals? Of course, there are, but they differ in connection with the characteristics of their ecology according to animal type and have altogether been too little studied from the point of view of the concept presented above.

The most reliable functioning of the organism is apparently secured by the functional system having all those characteristic properties presented in Chapter 6.

As is shown by comparative analysis, regardless of the level of development of an animal and regardless of the complexity of the functional systems in the same individual, all these functional systems have the same key mechanisms and, consequently, the same physiological architecture. This extraordinarily facilitates the process of investigation and determines the exact "address" of the question under study in the enormous variety of nervous processes of the entire organism. In fact, while studying, for instance, the discharges of a single neuron, we can characterize, as is usually done, its sensory modality, its relation to the strength of stimulation, and even its affiliation with the conditioned or the unconditioned reflex. However, this still does not determine what place this neuron occupies in the functional system as an integrated formation with mechanisms characteristic of it alone.

Therefore, until it has been established whether the discharges of a neuron pertain at a given moment to the triggering stimulus or to the streams of reverse afferentation, it is very difficult to understand the functional meaning of the observed discharges. This consideration, of course, does not rule out the study of the neuron as such and of its relation to stimulation, but still the investigation assumes the greatest functional significance when the location of the detailed process under study is exactly specified in the light of the entire functional system. By this I want to emphasize that the functional system can be not only an *object* of investigation, but also a *method* for formulating the problem and for the more effective gathering of experimental material.

In fact, the attempt to apply the principle of the functional system to the interpretation of the individual phases of the behavioral act shows the great advantage we obtain in the investigation by determining the significance of some processes in relation to the specific key mechanisms of the entire system.

Incredibly complex and as yet only little studied is the question of the fixation of acquired experience or, more simply, of the conditioned reflex. If its systemic structure is established, and if the place of its mechanisms within the integrated architecture is accurately established, the question must inevitably arise: exactly where and *which of its components* are stored in the form of memory about the experience?

When it was predominantly thought by investigators that a reflex is accomplished by a *linear process*, and this idea served as the basic concept, this question was not as

urgent. It was enough to say that *a new and temporary connection has been established between the neural elements.* This alone was an epoch-making discovery.

Now, however, when the physiologist refers ever more frequently to the level of molecular rearrangements in the functioning substrate, it is completely impossible to be confined by these descriptive characteristics.

The center of attention is no longer occupied by the actual fact of the "connection," but by its intimate molecular mechanisms. We know little about these mechanisms as yet, and it is therefore natural that for the time being this is a field of bold hypotheses, which indicate certain tangible paths of investigation rather than reliable information. Nevertheless, at this stage of the search these hypotheses undoubtedly are of great use.

Because of these hypotheses, the physiologist was given the opportunity to break the "barbed wire," which had been limiting his thinking and hindering any interpretation of neural mechanisms as soon as he wanted to construct something more integrative and specific than excitation and inhibition. The synapse of the nerve cell had always been such a "barbed wire." Any interpretation of neural connections ceased with it. The synapse was the point of contact of the most diverse excitations, and with this any interpretation of the neural mechanisms ended. But is this actually so?

It seemed to me that the neurophysiologist was somehow consciously avoiding the resolution of those agonizing contradictions which inevitably confronted him at this point in his investigation.

Let us, in fact, imagine (and this is quite realistic!) that at a given moment ten different impulses having a different origin and a different chemical specificity at the postsynaptic membranes converge onto the membrane of some cortical cell. Usually our ideas do not go beyond these membranes. But at the same time we know that under the influence of these impulses a pattern of cellular discharges takes shape at the generative point of the nerve cell (hillock). This pattern informatively and appropriately reflects the *sum total* of the ten impulses that have reached the cell at the given moment. Only under this condition will the neuron reflect its true significance in the integrative processes of the entire brain.

Here there arises a question which extraordinarily intrigues and at the same time frightens the investigator: *what occupies this "dead space," which extends from the postsynaptic membrane to the generative point of the cell?* Until recent years for the neurophysiologist this space was indeed dead. Actually, how are these impulses transmitted to the generative point, in what form and to what extent do they maintain their chemical specificity, by what mechanism does the synthesis of these ten different impulses proceed, which ends in the emergence onto the axon of one single impulse typical for the given neuron, and finally, in what chemical processes and molecular rearrangements of the protoplasm is this synthesis of impulses fixed?

It must not be forgotten that this fixed experience of the protoplasm must subsequently be instantaneously reproduced as soon as an appropriate behavioral or other situation occurs.

Moreover, the true memory of the entire brain is hardly the result of the fixation of experience in the molecular rearrangements of a single nerve cell. These rearrange-

ments undoubtedly occur simultaneously in millions, and may be even billions of cerebral cells, with a considerable variability of this fixation from cell to cell. Consequently, the brain's recollection of some event consists of the inscription of the microcosm of the cellular processes into some extensive macrocosm of integrative mechanisms of the entire brain.

From this it follows clearly that in this vast, newly opened field of interesting investigations any constructive hypotheses are legitimate and essential at the present time, as long as they promote the gathering of any scientific data. But none of them can make claims to exclusiveness until sufficiently adequate and convincing data are obtained. This is also how we evaluate our own hypothesis of the convergent coupling of the conditioned reflex (see Chapter 5).

According to the general concept of this book, the neurophysiological analysis of the conditioned reflex must, after reviewing the present concepts concerning the nature of the inhibitory process, turn to an analysis of the "accursed question" of the theory of higher nervous activity, i.e., internal or conditioned inhibition. All these characteristics are essentially synonymous and have developed during different stages of the differentiation of this concept.

Internal inhibition is indeed a difficult problem, mainly because the established traditions of thinking in terms of isolated processes of "excitation" and "inhibition" have, to a certain extent, set aside the profound integrative significance of the involvement of internal inhibition in the activity of the organism. Moreover, the assumption that internal inhibition was able to "spread over the cortex" or "move from the cortex into the subcortex" completely identified it with excitation. This, consequently, led investigators even further away from the study of internal inhibition as a *means* for the suppression of one activity by another activity. In this book I have first of all attempted to show that internal inhibition is a result of the interaction of extensive, distinctly integrated complexes of excitations. It is an essential tool for any interaction of two qualitatively fully defined activities.

Utmost attention in the analysis of the problem of internal inhibition was devoted to the development of logical schemes characterizing the general reactions of an animal. According to my data, these schemes must make the interrelations of the integrated complexes completely obvious and the idea of a direct inhibition of the conditioned alimentary reflex completely impossible.

As for the true functional reasons for the appearance of the conditioned inhibitory reaction, they fit entirely into the general architecture of the behavioral act as a result of discordance in the action acceptor at the moment of the first nonreinforcement (see below).

The most important factor characterizing our point of view concerning the origin of internal inhibition is that it attributes to the conditioned inhibitory stimulus its basic property: *the ability to pattern the integrated biologically negative activity characteristic of it with all the effectors specific for this activity*. This proposition has also a more general application which could be formulated as follows: every external stimulus which has reached a certain intensity must inevitably evoke some appropriate reaction, which must be a comprehensive indicator of the condition of the animal or man at the given

moment with respect to the given stimulus.

As had been noted (Chapter 9), the direct (appropriate) reaction for the conditioned inhibitory stimulus had historically remained obscure, and the phenomena of the collateral inhibitory effect of this negative reaction on the current alimentary activity had come to the fore.

This proposition leads us to a number of new investigations which must reveal the mechanisms of the patterning of these integrated activities with all their characteristic effectors. In order to understand the fundamental and methodological significance of this proposition, one must recall that large group of experiments in which some quite strong stimulation is applied and, *disregarding the actual appropriate reaction to this stimulus*, its collateral inhibitory effect on some other activity is used as the indicator.

Thus originate the conclusions: "nociceptive stimulation *inhibits* salivary secretion"; "inflation of the rectum *inhibits* gastric secretion"; "inflation of the cecum *inhibits* diuresis" (Miasoedova, 1956); "inflation of the small intestine *inhibits* the defense reflex" (Mikhailovskii, 1956); etc. [italics—P.A.]

By looking carefully at the logical basis of these and many other similar conclusions, one can see the universal significance of the concept we are presenting. From our point of view, one should make the following conclusions: a specific stimulus evokes a certain integrated reaction appropriate for it, and at the moment of its patterning this reaction inhibits the current or preceding activity. To demonstrate this mechanism, one only needs to study the action of those effectors characteristic specifically for the newly arisen inhibitory activity (respiration, cardiac function, etc.).

The formulation of the problem of the conflict between two activities, or of the "encounter of two excitations," which historically developed in Russian laboratories and is comprehensively discussed in this monograph with respect to internal inhibition, also opens up new tasks for investigation in various directions. For example, it was shown in Chapter 6 that any behavioral act is constructed according to a definite physiological architecture, which permits a purposeful analysis both of changes of every kind in the behavioral act and of restorative processes.

In particular, with any established conditioned reflex there inevitably arises a system of afferent parameters of the future result, which at the same time is a control mechanism: the action acceptor.

The absence of reverse afferentation about the obtained result, which is manifested upon the first nonreinforcement of the conditioned stimulus (e.g., upon extinction), immediately evokes discordance in the cyclic process and leads to the patterning of an orienting-investigative reaction. In turn, this reaction leads, due to unsuccessful repeated actions, to the formation of a biologically negative reaction.

Thus, the origin of internal inhibition in response to an unreinforced conditioned stimulus is a direct result of the conflicting interaction of two existing systems of excitation—the original conditioned alimentary excitation on the one hand, and the new integrated activities evoked by the discordance in the action acceptor on the other.

As was shown, the *conflicting encounter* of two systems of excitation is but the *first phase* in the elaboration of conditioned inhibition. The *second phase*, which proceeds without apparent conflict and without the mobilization of the vegetative components, is that

new and distinctive aspect which accompanies any acquisition of inhibitory experience and is the new action acceptor. Thus far, it is quite obvious that, during the process of extinction of the conditioned reflex, there occurs a definite change in the qualitative relation of the animal to the stimulus being extinguished.

This feature of the acquisition of inhibitory experience could only be discovered by taking into account the vegetative components of the conditioned reaction and, consequently, become the object of new physiological investigations. Formulating the question concerning this physiologically unique mechanism indicates the fruitfulness of the general concept, since it broadens the possibilities for the investigation of the mechanisms of higher nervous activity.

For the purposes of investigation this question may be formulated as follows: *by what mechanisms does any acquired inhibitory experience lose its initial nature of conflict and "become stored" in the cortico-subcortical connections as a process without visible signs of dominance of either the alimentary or the biologically negative reaction?*

Proceeding from the premise that every stimulus must evoke some kind of definite integrated reaction in the animal, we must ask *what reaction a well-established inhibitory stimulus evokes.*

This reaction clearly cannot be alimentary. But it is not biologically negative either, at least not to the extent to which it is manifested, for example, at the beginning of extinction. In some animals the biologically negative reaction continues for a rather long time, even after the complete extinction of the conditioned secretory effect. Here the picture is clear. The biologically negative reaction remains sufficiently strong, although, after repeated extinctions of the conditioned reflexes in these experimental animals, the zero secretory reaction is ultimately accompanied by a completely normal vegetative reaction.

The recent study of the characteristics of the action acceptor and its development in relation to the "expected results" has shown that the above-mentioned stage in the development of the inhibitory process may be explained quite satisfactorily; this was a rather happy occasion in the effort to decipher the "accursed question."

The behavior of the animal during the stage of "conflictless inhibition" is undoubtedly related to the *elaboration of a new action acceptor having afferent features of nonreinforcement*, which eliminated discordance and, consequently, the conflict nature of the reaction. In the behavioral sense, the animal passes from the state of *unexpected food deprivation* to the state of *already known and expected food deprivation*.

One of the most agonizing riddles of conditioned inhibition is the question: by means of what specific physiological mechanism is the entire integrated activity of the organism with all its numerous effector components simultaneously subjected to inhibition? This question pertains equally to internal and external inhibition. Therefore, in order to simplify the elucidation of the essence of the matter, it can be analyzed by using external inhibition as the example.

As is known, any integrated reaction is externally expressed in a number of effectors (motor activity, respiration, cardiac function, hormones, intestinal motility, etc.), and this is what indicates a central integration of any reaction of an animal as an integrated reaction in which the individual effectors are in harmony with each other. How

does a newly arisen stronger integrated activity, e.g., the orienting-investigative reaction, inhibit all the effects of the current reaction and manifest itself externally through its own specific distribution of excitations, partly *over the same effectors* but in a different arrangement of excitations?

If we consider that each one of the effectors of the reaction being inhibited is spatially related to a certain point in the central nervous system, and that these points can be considerably removed from each other, the mystery of this instantaneous inhibition of the current activity will appear even more remarkable.

Figuratively speaking, the existence of the complex positive activity of numerous points of the central nervous system can be compared to a huge city at various points of which there are various combinations of luminous dots. Let us assume that the entire city is suddenly plunged into darkness, and that after a few fractions of a second it is lit up again, but in a different pattern of illuminated points. By what means can such a change in the illumination of the city be accomplished?

It can be achieved in two ways. *First*, one can go to all the houses in the city and remove every light bulb. In order to do this simultaneously at all the illuminated points, one would have to send an entire army of messengers out over the city. *Secondly*, the same effect can also be achieved by a more economical method—the turning off of a power switch which controls all the illuminated points of the city.

If we use a comparatively simple device, which with the turning on of the necessary distribution of the illuminated points of the city makes it possible to turn the former distribution off automatically, we will have exactly the same effect of a change in illumination which was mentioned above.

It is quite evident that the turning off of the illuminated points of the city according to the first type cannot be accepted as a schematic expression of the mechanisms by which all the peripheral components of some integrated activity, e.g., the alimentary activity, are simultaneously “turned off.”

Meanwhile in the evaluation of the processes of higher nervous activity, our specific terminology makes us biased in many respects toward an understanding of the inhibition of some activity by this first type. We often say the “inhibitory point,” the “focus of excitation,” the “dominant center,” but essentially we never indicate the organic connections and spatial interrelations of these “inhibitory points” with the numerous components of the integrated reactions.

How, for example, can an “inhibitory point” in the cerebral cortex inhibit all the numerous components, both somatic and vegetative, of the alimentary reaction being inhibited at the given moment?

In this sense the second technical scheme can be a considerably closer figurative expression of the interrelations that develop in the central nervous system upon a sudden replacement of one integrated activity by another. It is most likely that the onset of the orienting-investigative reaction, which evokes the complete inhibition of the equally integrated current alimentary reaction, occurs by this type.

We are convinced by specific experimental investigations that the replacement of one integrated activity by another may occur within a fraction of a second. What other physiological mechanism could effect this instantaneous replacement of one integrated

activity by another? We see no other way to explain this replacement of numerous components other than by the second mechanism of "turning off" presented above. But then the question naturally arises: where is that power switch which enables the central nervous system to eliminate in one instant a complex nervous activity that encompasses an enormous number of excited points?

Many years ago, when we had our first doubts concerning the correctness of the generally accepted explanation of the inhibition of conditioned secretion, we were not able to indicate any specific mechanism for the inhibition of the integrated alimentary activity. On the basis of many experimental data, we could only conclude that this inhibition proceeds "over the entire vertical from the cortex down to the subcortical apparatuses" (Anokhin, 1932b).

However, recent investigations of the general physiology of cortico-subcortical interrelations have yielded such abundant material, especially about the activating effect of the reticular formation of the brain stem, that it has become entirely possible to gain a better idea regarding this mechanism.

As is now well known, the *ascending* action of the reticular formation on the cerebral cortex involves a continuous activation of the cortical cellular systems, thus determining a definite level of an active state. This activating effect on the cerebral cortex is naturally only energetic in nature and has been designated "nonspecific." Judging from all data, it maintains the activity of the complex of neural elements necessary for the given moment ("the blind force of the subcortex" according to Pavlov).

Since the initial information about this activating effect was later confirmed by many investigators, there arose a new possibility of explaining many known facts of nervous activity. The first consequence of the new concept is that in every integrated act we are now forced to clearly distinguish between its two constituent aspects: its architectural and its energetic characteristics.

The nature of the associations and their adaptive character are basically ensured by the higher levels of the nervous system, i.e., by the cerebral cortex. On the other hand, the energetic unification of the complex systemic connections of the cortex and the subcortex is evidently ensured by the subcortical apparatuses and primarily by the reticular formations of the brain stem and the hypothalamus.

This dual composition of every integrated activity had formerly not been taken into consideration by Penfield (1954, 1966), so that he came to the completely erroneous concept of the localization of consciousness in the "centroencephalic system."

Both these aspects of integrated activity are, of course, organically unified, and one cannot be conceived of without the other. However, the different spatial localization of the energetic maintenance of the functioning systems leads to highly important physiological consequences.

True, as had been shown above, under natural conditions this ascending activating influence is never nonspecific. It always bears the features of the selective effect of some specific biological modality, but its energetic consequences for the cerebral cortex remain the same.

Owing to this differentiation, any integrated activity, no matter how extensive it may be in regard to the number of its components, *can be immediately eliminated by the*

simple cessation of the influx of biologically specific activations from the hypothalamic and reticular apparatuses.

From our point of view, just such a mechanism is most likely for example, in cases of external inhibition upon the sudden action of some *new* agent which evokes a pronounced orienting-investigative reaction. The sum total of all the features in the development of the reactions of the organism compels us to admit that every functional system is subject to the action of a special type of "pacemaker" having a high energy charge. This is the only possible explanation for the fact that the numerous components of the functional system, which are often very remote from each other, are unified into a single integrated whole and continuously maintain this unity.

The destruction of this "pacemaker," for example, by coagulation of the hypothalamic nuclei, immediately eliminates the selective excitation of the cortical elements (Sudakov, 1965). The psychotropic effect of any drug is similarly manifested in all the components of the pathological system. The microinjection of various substances into the region of the reticular formation and the hypothalamus also evokes a widespread system of excitation appropriate for the injected substance (Anokhina, 1966a, 1966b). In this case, cortical elements also participate in the patterning of the complex.

All these data emphasize one principle of the organization of functional systems which may be called the *principle of the "pacemaker."* By accepting this principle, we make it possible to understand not only the mechanisms of the inhibition of integrated complexes, but also the mechanisms of the organization of psychopathological complexes and of psychopharmacological effects.

At any rate, this mechanism would solve those "agonizing riddles" created by the instantaneous inhibition of a complex integrated activity. We consider this mechanism to be one of the grandiose achievements of evolution, which has enabled the animal to rapidly replace one activity with another one. It is clear that this hypothesis changes many things in our previous concepts of the cortico-subcortical interrelations, and therefore it must naturally be checked in every possible way in special control experiments.

The proof of the inadequacy of the concept of the localization of internal inhibition at the analyzer is of course an advance. It enables us to formulate the goal of the search for those neural structures in which conditioned inhibition appears first.

Throughout the entire book I have repeatedly emphasized that without a definite concept of the mechanisms by which conditioned inhibition *originates*, the solution of the problem of its localization is doomed to failure, since it inevitably becomes mere speculation. The solution of this problem depends directly on how the mechanism of the origin of conditioned inhibition is explained. As we have seen, we cannot admit the development of internal inhibition in the cortical area of the analyzer. If one accepts, though, that it arises at the effector end, i.e., where the conditioned alimentary reaction as a whole has already been patterned, one is forced to encounter all those difficulties which I have discussed above.

Recent work aimed at a study of the localization of the inhibitory effect of the reticular formation on the linguomaxillary reflex has led to the conclusion that this

inhibitory effect cannot be exerted in the efferent part of the linguomaxillary reflex, but only on its afferent side (Hugelin, 1955).

True, the authors' concept of the "afferent part" of the linguomaxillary reflex is very indefinite: they attribute to it everything that cannot be attributed to the efferent part of the reflex, which is usually linked to the function of the *terminal neuron* alone. Meanwhile, even such a simple response as the linguomaxillary reflex *must be patterned as a whole, before its impulses emerge onto the terminal neurons.* Here it is also essential to recognize the presence of a zone of patterning of the reflex, to which the inhibitory effect of the reticular formation spreads. Such an assumption is all the more plausible since in the work of Hugelin cited above there were, in addition to inhibition of the linguomaxillary reflex, distinct volleys of impulses in the *motor nerve*, which is the nerve that should have effected the linguomaxillary reflex.

Thus, we have no doubts at this time that *conditioned inhibition is localized where the reaction to be inhibited is patterned.* In our opinion, the basic goal of the study of the localization of conditioned inhibition could be stated as a question: where does the inhibition of one integrated activity occur?

If we proceed from the concept of a "pacemaker" organizing any integrated activity, we must admit that, no matter by what pathways and in what order two integrated activities may interact, the "pacemaker" of the activity being inhibited must be inhibited first.

To this it must be added that a search for some single localization for all types of elaborated inhibition is hardly correct. We have already pointed out that the instantaneous inhibition of some integrated activity cannot have the same localization as the inhibition of some single component from a whole reaction without disturbance of its other components (i.e., inhibition of the activity of facial muscles). Probably, however, this difference is by no means the only one. There is reason to believe that there can also be other differences which presuppose a different localization of the conditioned inhibition. The study of the characteristics of each one of these forms of conditioned inhibition and of the localization of their origin is an interesting problem for further investigations in the physiology of higher nervous activity. Here it must be taken into consideration that the localization of conditioned inhibition at the beginning of its elaboration (stage of conflict) and at the end of the elaboration (stage of stabilization) will evidently be different.

The problem of the *spread* of inhibition is the easiest to solve. In its solution we must return to Sechenov's initial concepts, which had revealed for the first time the presence of an inhibitory process in the central nervous system. Historically there occurred a certain interference between two concepts which, even though they are outwardly similar, give different direction to the mind of the investigator. It has already become clear that the "spread of inhibition" is essentially a *spread of inhibitory excitation.* In spite of the apparent similarity of these concepts, they lead to different consequences. In the former case the inhibitory process itself appears to spread, and, upon reaching a certain point, it must inhibit some activity there. In the latter case, on the contrary, *only* an excitation is spreading, which can evoke inhibition only upon encountering some other system of excitation that is already being patterned, but is subject to inhibition.

In spite of this completely reliable physiological understanding of the "spread of inhibition," this subject is being presented in an extremely simplified manner in the literature of recent years, which wrongly orients the thinking of the investigator, and especially of the clinician, who wishes to apply Pavlov's theory on conditioned inhibition in practice.

The phenomenon known as the "Leão depression" cannot serve as a basis, as was thought by certain authors, for the explanation of all causes of the spread of inhibition both over the cerebral cortex and from the cortex into the subcortical structures. Quite aside from the fact that the rate of propagation of the "depression" over the cerebral cortex is too low for permitting it to explain conditioned inhibition, by its very nature it does not correspond to those conditions which accompany the origin of conditioned inhibition (Leão, 1944; Leão and Morison, 1945; Bureš, 1954, 1956; Bureš and Burešová, 1960a, 1960b). Above we were dealing with conditioned inhibition as the highest form of coordinative inhibition. As for *protective* inhibition, especially in relation to direct traumatic damage to the cerebral tissue, it has entirely different principles of propagation. The "Leão depression" may be one of the mechanisms of the propagation of protective inhibition; however, in connection with this the entire problem of protective inhibition must be specially discussed.

Naturally, the prospects for the further elucidation of individual problems of the conditioned reflex (such as its historical development and biological roots, the mechanisms of coupling, and internal inhibition) we have discussed by no means exhaust everything that can be successfully analyzed from the point of view of the concept we are proposing. For example, we believe that the study of the intimate physiological nature of conditioned inhibition can now be given a firmer physiological basis, since the qualitative nature as well as the composition and the spatial localization of the two competing integrated activities can be subjected to quite definite analysis.

The prospects for the *practical* application of the proposed concept of the origin of conditioned inhibition are especially diverse. First of all, one must ask the general question: what is the mechanism of the acquisition of vital experience on the basis of conditioned inhibition? And then, after solving this problem, it becomes easy to understand the physiological content of all those pathological emotional conflicts as well, which are the basic cause of an enormous number of "neurogenic" diseases, and also of "vegetative neuroses," the pathogenesis of which is not clear.

Among the problems which are solved on the basis of the concept presented above is the problem of the type of higher nervous activity. As is known, the characterization of the type of higher nervous activity is based on testing the excitatory process and the inhibitory process and their interrelations. But these interrelations constitute that "accursed question" for which a solution must be sought.

I would like to emphasize the hypothesis of the convergent coupling of a conditioned reflex. Having developed on the basis of new data obtained by our laboratory, it shows our dissatisfaction with both the electrical theories of the function of the neuron and the currently popular theories of memory. I am deeply convinced that the time has come when the investigator must leave the postsynaptic membrane and follow the little-known road which connects it with the hillock. On this basis we must try to

understand that abundance of specific structures (the postsynaptic substrate, the spine apparatus, the dendritic tubules, etc.), which have now been deprived of all their significance by the electrical theories of the function of the neuron.

Lately there have been indications of interest in the possibility of the development of learning in the form we proposed several years ago (Anokhin, 1965). Of course, the chemically based coupling within a single neuron is a hypothesis. However, we see in the formulation of such hypothetical propositions one of the fundamental conditions for progressive research work. The hypothesis is the spearhead of the scientific cognition of the material world. It guides the thinking of the investigator from experiment to experiment and replaces chaos in the collection of data by an organized and actively directed investigation of nature. Take away the right of science to the probable, to the hypothesis, and it will become a "gloomy temple of dogma," in which the scientist will retain but one single right—that of placidly pacing the stone slabs of the universally recognized.

In order for a hypothesis to become the moving force of scientific progress, however, it must without fail satisfy the following three requirements:

1. It must convincingly resolve the contradictions that have accumulated in the given field and are impeding further progress.
2. It must, on the basis of the latest scientific advances, explain in a more acceptable way the earlier reliable data that have not been explained before.
3. It must broaden the prospects for further investigations, open up new possibilities for experimentation, and enrich research by providing such new questions which could only have arisen as a result of the given working hypothesis.

In this we see how a working hypothesis benefits the elucidation of any problem. If a hypothesis does not meet these three requirements, it becomes useless to research.

At the same time it is generally known that even the working hypothesis most acceptable at a given time is *short-lived*. Sooner or later it must inevitably yield to a different hypothesis, which is more acceptable and still more perfect at the given level of knowledge.

With the rapid expansion of scientific concepts, enriched to an ever increasing extent by the advances in related disciplines, it is difficult to conceive of any working hypothesis that would for a long time fail to receive a new interpretation. What is more, any excessive stability of some point of view in individual scientific problems must lead to a justified suspicion of the investigator, whether his field of research is not falling behind the general advance of science and whether the investigators in this science have not frozen into cold complacency. This is the logic of the constantly changing stages of scientific cognition.

None other than Pavlov himself characterized this feature of scientific progress in an exceptionally profound way. In analyzing the problem of the cortical localization of the conditioned reflex, Pavlov wrote:

... all our classifications and laws are more or less conditional, and significant only for the given time, under the circumstances of the given method, and within the limits of the given material. Fresh in the minds of us all is a well known example—

the indivisibility of the chemical elements, which was considered for a long time as a scientific axiom [Pavlov, 1912c, see Pavlov, 1967, p. 195].

The necessity of the continuous renewal of our concepts of the fundamental physiological mechanisms of higher nervous activity could hardly be formulated more clearly. It is exactly in this sense that we are proposing in this book what is, in our opinion, the *most probable* approximation to an answer to the most difficult and puzzling questions of higher nervous activity.

One can hope that the discussion of all the problems dealt with in this book will promote the further creative development of the great scientific heritage left to us by I. P. Pavlov, which has now become the truly universal property of investigators.

Glossary of Pavlovian Terminology

Collision (*sshibka*). A technique for producing experimental neuroses in dogs, first reported by I. P. Razenkov from Pavlov's laboratories in 1924. After first developing stable conditioned responses to positive conditioned stimuli and differentiating inhibitory responses to negative conditioned stimuli, the animal is suddenly presented in rapid succession (without interruption) with positive and negative stimuli. This "collision" of positive and negative stimuli rapidly leads to the development of experimental neuroses, particularly in the two unstable dog types: the choleric (showing a preponderance of excitatory processes) and the melancholic (exhibiting a predominance of inhibitory processes).

In later experiments, Pavlov and his students extended the collision technique to include simultaneous presentation of alimentary and motor defense conditioned and unconditioned stimuli, the transformation of positive into negative signals and vice versa, and a number of other methods involving the manipulation of excitatory and inhibitory processes in the central nervous system.

Hysteriosis (*isteriozis*). A term used by Russian neurophysiologists to describe a pathological state of heightened excitability in the central nervous system resulting from sustained rhythmic stimulation of an afferent somatic or visceral nerve or receptor. This phenomenon was originally described by N. E. Vvedenskii (1912, see Vvedenskii, 1953, p. 325) in spinal preparations of frogs. Continuous tetanization of an afferent nerve for a period of 3-4 hours eventually failed to elicit reflex contraction of the corresponding muscles (due to pessimal inhibition, see *pessimal* in the glossary). Concomitantly, Vvedenskii observed decreased thresholds of excitability of other afferent nerves, indicating increased excitability of their corresponding centers. This is explained on the basis of positive intercenter induction.

Vvedenskii considered the phenomenon of hysteriosis to be related to the initial stages of strychnine poisoning and also to the somatic symptoms of hysteria. Vetiukov (1949) demonstrated that hysteriosis can also be elicited by periodic rhythmic stimulation (e.g., every 3 minutes) of two afferent nerves which elicit antagonistic reflexes. Hysteriosis can also be produced by prolonged stimulation of interoceptors. Some Soviet physiologists implicate the phenomenon of hysteriosis in complex functional disturbances in various tissues and organs. See also Airapet'iants (1957).

Parabiosis (*parabioz*, from the Greek *para*, near, and *bios*, life). In English physiologic literature, parabiosis has been used to denote the experimental or natural anatomic and physiologic union of two organisms. In Russian neurophysiologic literature, parabiosis has also been used to denote a form of nerve block resulting from strong or high-frequency stimulation. This is the sense in which the term is used in this book.

This term was originally introduced in 1901 by the Russian neurophysiologist N. E. Vvedenskii (Vvedenskii, 1901; see Bykov, 1952b), who studied this phenomenon in a frog nerve-muscle preparation. In English physiologic literature this phenomenon has often been referred to as Wedensky (German transliteration) inhibition. Vvedenskii conceived parabiosis in terms of a physiologic continuum according to the following scheme:

$$\text{rest} \rightleftharpoons \text{activity} \rightleftharpoons \text{parabiosis} \rightarrow \text{death}.$$

Parabiosis is thus the last reversible condition resulting from the application of strong or unusual stimuli.

Vvedenskii described several phases in the development of parabiosis: (1) equilibrating phase wherein the muscle (of the nerve-muscle preparation) responds equally to weak or strong stimuli; (2) paradoxical phase wherein the parabiotic region conducts weak but not strong stimuli; (3) inhibitory phase wherein there is loss of conductivity but not of excitability; (4) loss of conductivity and of excitability; (5) death.

Vvedenskii considered the parabiotic region of a nerve to have properties similar to those of a synapse. He demonstrated that the parabiotic region is always electrically negative with respect to the normal regions of the nerve fiber. Vvedenskii's student, M. I. Vinogradov (1952) reported that the application of positive polarization (anodic stimulation) to the parabiotic region removed or ameliorated the parabiotic inhibition. Further investigations by L. L. Vasil'ev (1953), D. S. Vorontsov, and V. S. Rusinov led to the conclusion that the parabiotic region exhibits persistent depolarization.

I. P. Pavlov applied the concept of parabiosis and of its equilibrating and paradoxical phases to events in the central nervous system and developed the concept of a persistent stagnant focus of excitation in the cerebral cortex. A. A. Ukhтомskii (1927) similarly developed the concept of a dominant focus as a form of persistent and stable excitation in the central nervous system which has an important function in the coordination of the activity of higher organisms. Pavlov postulated that a dominant focus can, under certain circumstances, become transformed into a focus of pathologically stagnant and persistent mental or cerebrovisceral disturbances.

Pessimal (*pessimal'nyi*). This term (from the Latin *pessimus*, meaning "the worst") was coined by the Russian physiologist N. E. Vvedenskii in 1886 (see Vvedenskii, 1951) to describe the decrease or loss of conductivity across the myoneural junction of a nerve-muscle preparation as a result of the application of stimuli of very high frequency or intensity. The same type of phenomenon takes place in a region of a nerve which is in a state of parabiosis (see above explanation). In Western physiologic literature the term "pessimum" is known as "Vvedenskii inhibition" (or the German transliteration "Wedensky inhibition"). This phenomenon has been described for other neural junctions such as the nerve endings in the submaxillary salivary gland and the sensory nerve endings in the spinal cord.

Supramarginal. Pavlov used the Russian phrase *zapredel'noe tormozhenie* to describe the central inhibition resulting from the application of strong, prolonged or frequently repeated conditioned stimuli. The word *zapredel'noe* literally means "beyond the limit." It can best be rendered in English as "supramarginal" or "supramaximal." Some Russian translators have rendered the word as "transmarginal."

In physiologic terms this phrase could best be represented by "supraoptimal inhibition." It implies that there is an optimal intensity of conditioned stimuli that evoke a conditioned response. The application of stimuli with an intensity or frequency above this optimal value leads to inhibition.

Speaking teleologically, Pavlov considered supraoptimal inhibition as a form of "protective inhibition," since it serves the function of protecting the cortical neurons from overstrain that may result from continuous impingement of unusually intense or prolonged stimuli.

Switching (*perekliuchenie*). This term is sometimes redundantly translated as "trans-switching." In these experiments the same neutral stimulus (CS) is reinforced with a different unconditioned stimulus (US) in different situations, e.g., with food in one chamber and with electric shock in another chamber; or different US are used as reinforcement at different times of day or by different experimenters. The same neutral stimulus thus acquires the property of provoking a different conditioned reflex (CR) under different circumstances.

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