# Systemogenesis as a General Regulator of Brain Development

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## PRINCIPAL INTRODUCTORY REMARKS

In recent years it seems more and more evident that the investigation of the processes of nervous activity in ontogenesis gives us the opportunity to understand those nervous mechanisms which, in adults, could not otherwise be analyzed properly.

On the other hand, the investigation of nervous mechanisms in prenatal and postnatal ontogenesis helps us to understand the main principles of evolution of the adaptive activity of animals in relation to the outside circumstances. These deal with the mechanisms of creation and with an animal's descendants of those adaptive capabilities apart from parents and their descendants. That is what we must understand to solve the problems of an inborn behavior. The conclusion from the aforegoing is that the investigation of the ontogenetic period of life in the process of creation of nervous activity must combine two things: investigation of common evolutionary principles of adaptive activity; and the discovery of the real mechanisms in the species which are functional adaptations.

We must proceed from the fact that at birth an animal must already be equipped with adaptive activities capable of sustaining the newborn in its new environment. We also know that every species should be capable of adequately adapting itself to the particular features in its new surrounding ecology. Thus, for example, a newborn squirrel from the moment of hatching should have a complete set of proper adaptive abilities; a newborn monkey should have adaptive features but in a different combination, while a squab should be adapted to still other quite different circumstances of life. And even more, every kind of bird must have at the moment of its hatching a proper set of adaptive reactions characteristic only of this kind of birds. For example, immediately after birth chickens begin intensively to pick seeds, while a little rook is very passive in taking food which parents give it during a rather long period of time. But whatever special adaptive features a species may possess they *necessarily must be ready at the moment of birth.*

A very important conclusion can be drawn from the premise which to some degree has been our guiding principle during more than 30 years of investigation in the field of embryogenesis of nervous activity. The conclusion is: if forms of adaptive activity are different and individual animals adapt to different ecologies, then the mechanism of embryogenetic development of nervous activity in each individual animal is original, individual and specific for the species.

There naturally arise some questions: what is the mechanism which combines these different forms of embryogenetic development of nervous activities? Are there any *common principles* of development, which subordinate all kinds of adaptive reactions in different species? Many attempts have been made to give a proper formulation of such kinds of principles. The most important and popular is the theory of Coghill (1929), who postulated that the initial form of the organism's activity is the 'total' form of all the body's musculature, which we may call here 'mass action'.

It is this total form of activity which, according to Coghill plays the role of the original regulator of the whole development of differentiated forms of adaptive reactions. These differentiations of forms of activities are performed *inside* the total complex, by a process of 'individuality'.

Coghill's theory had many followers among both physiologists and pediatricians (Irvin, 1932a, b; Barcroft, 1938; Barcroft and Barron, 1939). At the same time the theory met objections, when new facts were discovered in respect to the process of development of the reactions of movement of a newborn child.

These new facts, were in the first place in contradiction with the principle of proximo-distal development, which inevitably must be concluded from Coghill's principle of 'pre-eminence of total pattern'.

It is very important to note that Coghill's theory was built up on the basis of investigations performed only on one species: *Ambystoma tigrinum.*

Our own investigations into the development of nervous activity in embryogenesis, performed on different species (fish, *Ambystoma tigrinum*, birds, mammals and human foetuses) showed that Coghill's conception was erroneous; this resulted from his investigating only one species of animal.

According to the basic premise of our report, *i.e.* that there are the same amount of embryogenesis as there are species, we, naturally, came to the conclusion that the common regularity of embryogenetic development can be formulated only after selecting from among large numbers of variations of individual embryogenesis a feature which all species have in common. These considerations were our guides throughout the process of formation of the conception of systemogenesis, which is to formulate the conceptions of 'organogenesis', 'morphogenesis', 'reflexogenesis', and at last, 'pre-eminence of total pattern'. It is not possible to present here all the experiments performed in my laboratory and published by me and my colleagues over the last 30 years. Therefore, we shall formulate initial premises and give some concrete results of our investigations. Only after this it is possible to present the last data, illustrating the theory of systemogenesis as exemplified by the ontogenetic development of ascending influences on the brain cortex.

## THE THEORY OF FUNCTIONAL SYSTEMS

The physiological theory of a functional system elaborated as a result of our investigation into the question of compensatory adaptations of disturbed functions of an organism is based on our works in the field of embryogenesis of nervous activity.

The investigations show that any compensation of disturbed functions, *i.e.* the restoration of final efficiency of the function, takes place only with the mobilization of the majority of the physiological components, which are often located in different parts of the central nervous system and in acting in the periphery they are united by the adaptive effect. Such a kind of functional combination of different organizations and processes on the basis of the achievement of a final effect has been called 'a functional system'. We can distinguish several types of functional systems, characterized by different degrees of changeability, *i.e.* by different capabilities to change the structural basis and to use *plastically* different parts of the central nervous system.

For example, the functional system of respiration, for the greater part composed of inborn and stable interactions, possesses very few features of plasticity in respect to choose from central and peripheral components (Anokhin, 1937, 1947).

On the contrary, the functional system regulating the locomotion of a body can have extremely variable contents of central and peripheral (muscles) components. In fact, the same place can be reached in different ways: by a jump, on foot, on all fours, lastly also head over heels, as for example, the rats did in Lashley's experiment, in which they approached the rack by barrel-like movements.

We considered that one of the most important conditions for the functional system as an integrative organization of an organism, including both central and peripheral structures, is the presence of an afferent feedback about the achieved final adaptive effect.

It enabled us to regard the functional system as a link between the physiological structure and a continuous flow of information about the status of action being performed (Anokhin, 1935). In this theory we had already anticipated all the main features of cybernetics. At that time we were mainly interested in the features of integrative activity of the nervous system, and that is why we used the principle of 'functional system' as the unit of selfregulation in the amount of variability of activities of an organism.

The following characteristics of a functional system as an integrative organization may be listed:

(1) A functional system is, as a rule, a central–peripheral organization. It maintains its entity on the basis of an amount of information flowing from the centre to the periphery and *vice versa.*

(2) The existence of any functional system is indissolubly connected with the final effect of adaptation. Thus this effect defines one or another distribution of points of excitations or activations throughout the functional system as a whole.

(3) Another sign of a functional system is the presence of a receptor apparatus, evaluating the results of its action. These receptor apparatuses may be innate, as, *e.g.* chemoreceptors of the respiratory system, or osmoreceptors of the vascular system, regulating the osmotic blood pressure. In other cases there may be receptors, registering the results of the action, created extemporaneously. They are fit dynamically in the process of building the functional system and adapting the organism to the special created situation.

(4) Every adaptive effect of the functional system, *i.e.* results from an action, forms a stream of feedback stimulations, which represent to the centre in details all important signs of the results.

(5) The most important central process of the activity of the functional system, is a juxtaposition of the feedback information, received from the periphery, with the receptor apparatus of that functional system. In the case of agreement of 'given' order and 'received' result, the action finishes; however, if there is 'disagreement' of both factors, then a special stimulus is created in search for another combination of excitations of the functional system until it receives a stimulus of an adaptive effect.

(6) The complex of functional systems, on which basis the inborn adaptive activity is created, possesses all the above mentioned features and becomes mature precisely on the moment of birth. It must be concluded that the consolidation of the parts of the functional system should be completed at some definite period in the foetal development prior to the moment of birth.

All the above formulated features of the functional system are quite fully developed at the moment of birth.

Taking this into consideration we then raise the following questions: what are the mechanisms underlying the numerous and complex components of the functional system, which are situated far from one another, and which combination of these factors makes the organism ready for the moment of birth?

Other parts of the report will be devoted to the analysis and characteristics of the concrete embryogenetic mechanism.

## THE HETEROCHRONY IN THE PROCESS OF THE GROWTH OF STRUCTURES AS A BASIS OF SELECTIVE MATURATION OF THE INBORN FUNCTIONS

The most important value of the functional systems in newborn at the time of birth is a categorical factor of survival. A functional system has to consist of the following components:

(a) The specific receptor apparatuses, receiving the ecological influences;

(b) The conductive apparatuses, bringing the peripheral information to the central nervous system;

(c) The central interneuronal (synaptic) relationships, defining the most important parts of the integration of the most valuable reaction;

(d) The combination of efferent pathways and their effectors;

(e) The combination of the afferent apparatuses, which all provide the feedback information about the degree of success of that vitally needed adaptive action of the newborn.

We regard as a biological peculiarity of embryogenesis, that defect of maturation of the functional system which in infrequent and differently localized connections evokes the law of natural selection that takes away the defective individual initial organization.

The heterochrony in arrangements and rates of development of different structural organizations of an embryo is the very powerful means, by which harmonical relationships between the different components of the functional system in foetal animals are established. Heterochrony is neither an epiphenomenon of development, nor its 'artefact', as some morphologists and physiologists think. It is the special regulating power by which the general demand of the survival of a newborn is accomplished, namely: harmonical relationships between the structure and the function of the organism together with the continual stream of the influences of specific ecological factors. Thus, heterochrony in the process of foetal development is a powerful tool in accomplishing the 'united law of ectogenetic development', as Severzev and his school properly realized (*cf.* Matveev, 1929). The heterochrony of the development of different foetal structures is one of the primary tasks of the evolution: to give to the foetus the most valuable and vitally needed functional systems. This selective and heterochronical growth of the foetal structures is not connected with the maturation of the organ as a whole, for it may be related only to a few of the subcomponents participating in extensive functional combinations far from the organ. Thus, the conception of the 'organogenesis', still playing a major role in the theories of evolutionary morphology, is unable to explain the systemic character of the morphogenetic processes of the foetal development. The conception of 'organogenesis' also cannot envisage all those variabilities of selective connections, which are created between different organs and tissues in the process of maturation of the functional system (Emelianov, 1963; Gause, 1941; Vasnezov, 1938). As a consequence of these conceptions we postulated in 1946 the new notion of systemogenesis, which more properly and completely characterized the above described regularities of the embryonic maturation (Anokhin, 1947, 1948, 1949a, b, c, 1958, 1961a, b).

We defined systemogenesis as the selective and temperature accelerated development in the process of embryogenesis of those structural organizations, which on the whole provide the survival of the newborn.

Such a selective combination of different kinds of structures in the organism with a single functional system, can only be realized on the basis of the principle of heterochrony, which acts during the initial structural organization and time of development and during the moment of consolidation of the structures during the whole period of embryonic development.

One of the general regularities of life is the continuous development and the changes in its functional systems, providing adequate adaptations of different steps of its postnatal development. In connection with these facts we distinguish as the main characteristics the heterochronic processes of structural development: (a) *intra*systemic heterochrony, and (b) *inter*systemic heterochrony.

The first type of heterochronic development means the unequal onset of the initial organization and the different moment of maturation of the components of the same functional system. The heterochrony is mainly defined by different degrees of complexities in the organization of the components of the functional system.

The second type of heterochrony is related to the initial organization and moment of development of those structural components, which constitute the basis for different functional systems, and which the organism will need at different periods of its postnatal development.

Of course there are many interrelationships between the two types of heterochronic development, but we have to distinguish at least these two individual types because it provides a proper perspective for future investigations into the regularities of heterochronic growth of different organisms.

Systemogenesis, as the general regulator of development, can be best realized by looking at the ontogenetic phase of development for, during that short period of time, the heterochronic maturation of many important functions of the organism takes place.

On the other hand, systemogenesis, being the result of a very long period of phylogenetic development and fixation by the inheritary forms of adaptation, permits us to understand the regularity of reconstruction organs and structures of the organism during the whole process of evolution (Golubeva, 1938).

## CHEMICAL PROCESSES DURING THE MATURATION OF THE FUNCTIONAL SYSTEM OF THE BRAIN

The functional system as a whole, as we have seen, comprises a great amount of variations of the individual components differing from each other in the complexity of structure, kind of tissue and chemical specificity.

These differences between the components of the functional system, are the basis for the unequal maturation of its parts in different periods of embryogenesis. The adaptive mechanism which starts functioning at the moment of birth is to be regarded as the stimulus, which during the process of evolution leads to the initial organization and accelerated growth of the individual structures. These structures, as a whole, define the intra- and intersystemic heterochrony. Experiments have shown that the structural heterochrony preparing the process of establishment of the functional systems of an organism is not really the initial form of heterochronic development. As a rule, it is preceded by the biochemical creation and acceleration of various prestructural components. This fact can be very markedly demonstrated by the maturation of synaptic organizations.

Working with adult animals we use to consider the fact that the conduction of excitation through the neuromuscular synapse of the striated muscle and the sensibility of that synapse to curare, could not be separated. Experiments performed during stages of ontogenesis have shown that there exists a phase in the maturation of the neuromuscular synapse, when stimuli may pass freely and still the animal performs its normal locomotion. At the same time, curare does not have its specific influence and that is why Ambystoma at the 32nd stage (according to Harrison) swims freely in a 1%-solution of curare. The same Ambystoma after 5 days more of development becomes completely paralyzed in the same solution of curare (Alekseeva, 1943).

This regularity can be better demonstrated in the process of action of sedative drugs on the central nervous system. During the postnatal ontogenesis of rabbit brain one can observe such a period in the cortico-subcortical relations. On the 10th–11th day postnatally the cortical electrical activity shows the phenomenon of

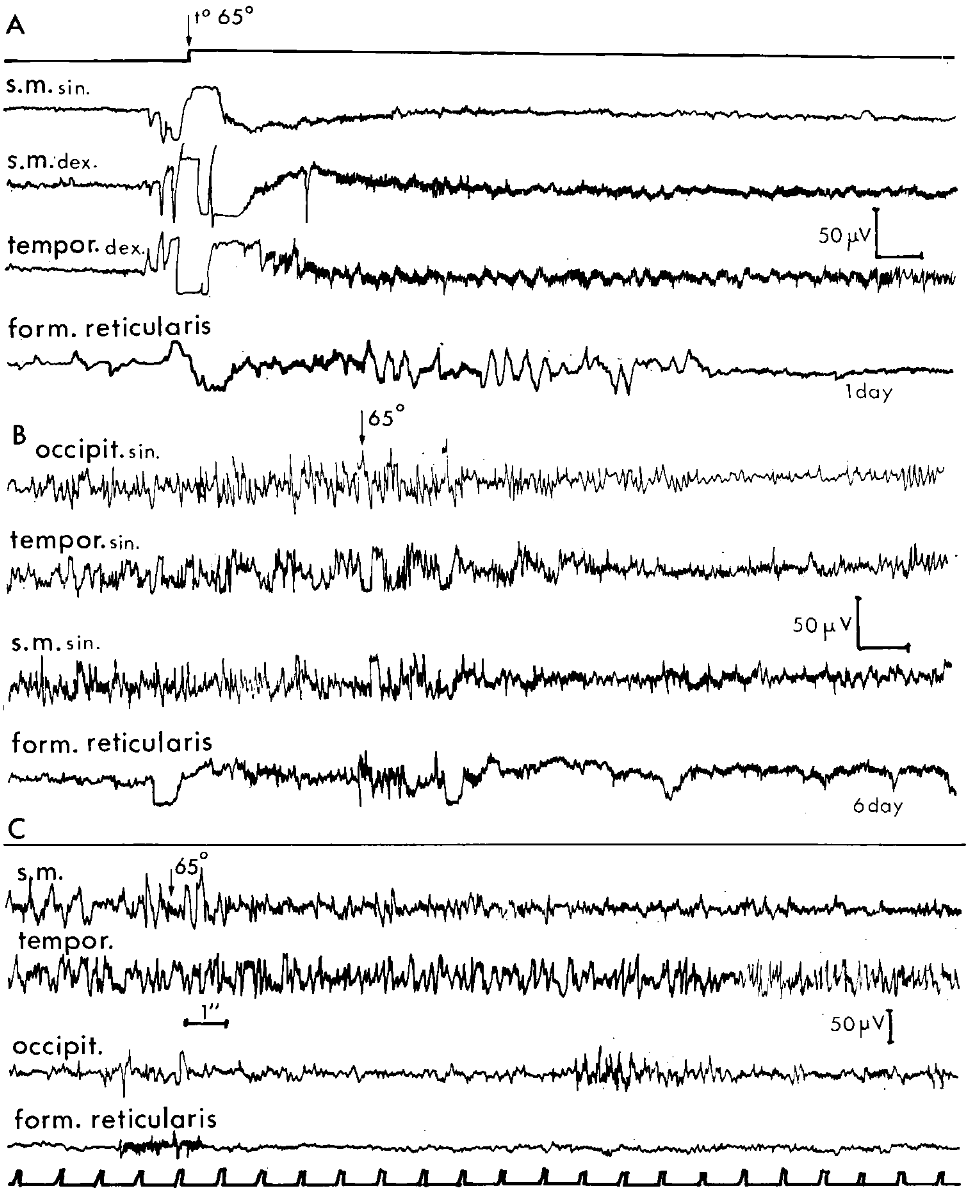

Fig. 1. Gradual changes in the electrical activity of the newborn rabbit and the appearance of subcortical reactivity to the action of chlorpromazine. (A) Electrical reaction to pain stimulation expressed as hypersynchronization in the first days after birth; (B) The reaction expressed as desynchronization in a later period of life when the blocking action of chlorpromazine is absent; (C) The appearance of the blocking action of chlorpromazine — the reaction to pain stimulation expressed as desynchronization is absent in the temporal area, but still present in sensori-motor and occipital areas.

desynchronization. An injection of chlorpromazine, which usually blocks the pain activation of the cortical electrical activity in adults does not exert such an action during this stage of the development. A few days later chlorpromazine in the same dosage will completely block the pain activation reaction of the cortex (Ata-Muradova, 1960a), as shown in Fig. 1.

The examples, mentioned above, show that during the process of ontogenesis the heterochronic maturation of chemical qualities, which are essential for the action of different pharmacological drugs, takes place at the molecular level.

This molecular heterochrony is one of the arguments, which suggest, that the structural heterochrony is preceded by a molecular heterochrony during the development of the conductive features of the synaptic organizations.

## EXAMPLES OF HETEROCHRONIC MATURATION OF THE COMPONENTS OF DIFFERENT FUNCTIONAL SYSTEMS

The maturation of different functional systems, was investigated in detail in our laboratory by means of morpho-physiological correlative studies of the functional systems for sucking, respiration, etc. Particularly, the reaction of food uptake by birds and the relation between swimming and moving in *Ambystoma tigrinum* were investigated. For all the investigations we used foetal animals. The results showed that those structures which are to constitute at the moment of birth the functional system begin to arrange and mature selectively and acceleratively. All those individual structures begin to make synaptic contacts with one another and to form a very marked functional system, which is able to provide the animal with the minimal adaptation, characteristic for that functional system.

The heterochronic maturation of the structures in the process of embryogenesis is a very powerful mechanism by which the evolution leads the components to a complex synchronism. Due to the regularity of the central relationships between the nucleus of N. trigeminus and N. facialis, the sucking mechanism, starts to develop already at the stage of the unclosed neural tube (Tilney and Riley, 1938).

However, the heterochrony of the development is not restricted to the early formation of nuclei of the cranial nerves. A more detailed examination of that process shows that countless variations of the development of certain elements of those nerves can be found. In this process everything is made subordinate to a single demand: to form the vital functional systems for the moment of birth and thus, to provide the survival of the foetus.

Thus, for example, the facial nerve is an isolated structure, but at a certain stage of the development a marked disproportion can be distinguished in the degree of maturation of separate fibers (Fig. 2). The fibers, projecting to M. orbicularis oris, providing the most important movement in sucking – are already myelinated and the contacts with the muscle fibers have already been established. At the same time no other facial muscles have such a marked organization of fibers and synapses (Golubeva, 1961b).

Analyzing the part of the N. facialis, situated in the medulla oblongata, we can observe that various cell groups develop and differentiate with a different velocity. The components related to the functional system of sucking are already completely differentiated, while, on the contrary, the parts which are the source of the frontal

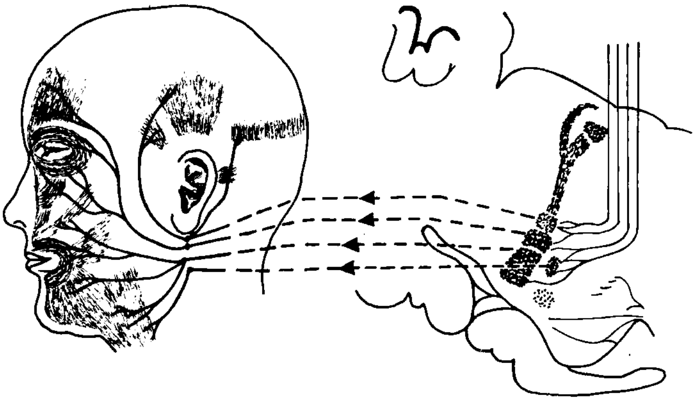

Fig. 2. A synthetic scheme of the N. facialis and its neuromuscular connections. (After Pearson, *Comp. Neurol.*, **85**, 461.)

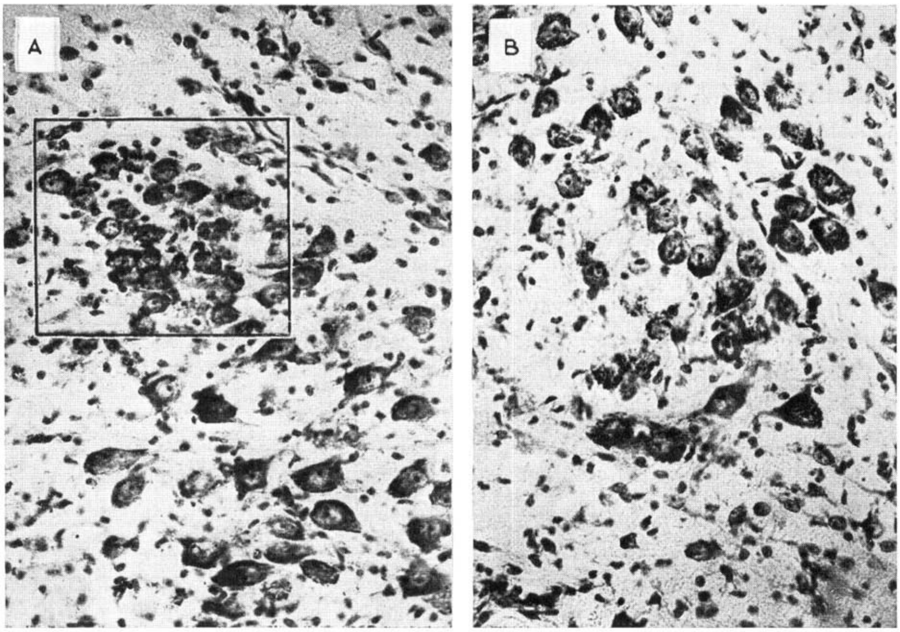

Fig. 3. Microphotograph of cell groups of N. facialis which are at different stages of differentiation. A = dorsal group; B = ventrolateral group.

branches of the N. facialis, are just beginning to differentiate (Fig. 3) (Golubeva, 1961a, b, 1962).

The accelerated maturation of the components, participating in the functional system of sucking, continues already to the limits of the nerve and also to its centre. There is no doubt that the same differentiation takes place in all parts of the functional system of sucking. The same phenomenon is observed in the maturation of the grasping reflex which can be detected already in the 5th month of prenatal development. The morphological basis of that reflex was investigated in detail by Shuleikina (1958) in our laboratory (Fig. 4). It was shown that the nerve of the forelimb, providing the

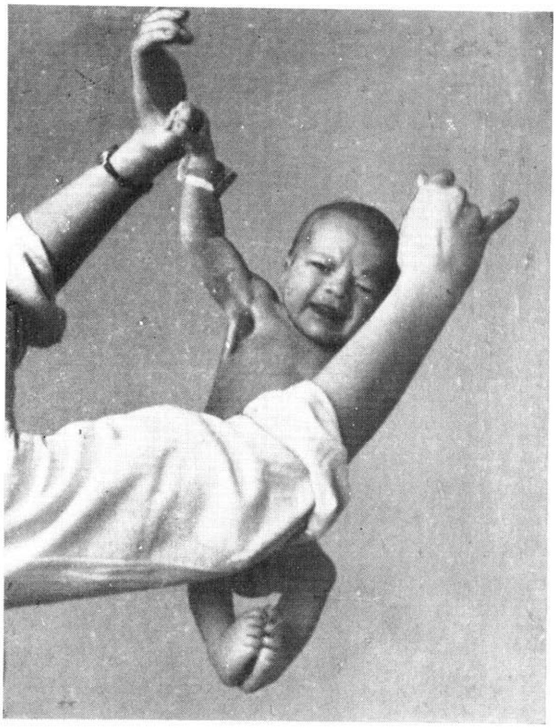

Fig. 4. The maintenance of the body in 'hand hanging' position in the newborn.

innervation of the M. flexor digitorum, is the first to become mature. During the stage, that the nerve of the M. flexor is already differentiated, others, as, for example, N. intercostalis, have not yet achieved that degree of differentiation.

Different components of the grasp reflex were investigated in detail. The cells of the cornu superior of $C_8$ are completely differentiated by the 6th month of pregnancy, while the cells of $C_5$ are not yet differentiated. One observes the selective maturation of the motor cells, directly related to the M. flexor profundis, *i.e.* to the grasp reflex. Morphological investigation on the descending control of the motor neurons of $C_8$, showed, that there is a special fasciculus, descending from the midbrain, to the cells of $C_8$, *i.e.* the motor cells innervating M. flexor profundus. This fasciculus is, at that stage of the development, the only one which ends at the spinal level and is, therefore, called 'the primary fasciculus' (Fig. 5). Its accelerated growth suggests the selective maturation of a functional system which for monkeys would provide the mechanism in the first hours of life for holding onto the mother's back.

The embryonic and postnatal maturation of birds may be the best example of the selective and accelerated maturation of the structures of vital importance for the animal.

We have been investigating for a period of 12 years the behavior of the rook (Milijagin, 1954). The birds are a good example to show the maturation of those nervous structures responsible for adaptive reactions to ecological factors. As is well known, the rook after being hatched immediately responds to the sound 'kar-r' and to a stream of air by opening the beak. Both stimuli are necessary to receive food under natural conditions. An analysis of the capacities of the ear just after birth, shows that only those receptor elements have maturated which are able to receive the components of the sound ‘kar-r’. An analysis by means of pure tones showed that other receptor elements are still immature. This example demonstrates very clearly the selective maturation of the receptor apparatuses and their synaptic connections in the central nervous system in correspondance with the ecological factors (Milijagin, 1951, Fig. 6).

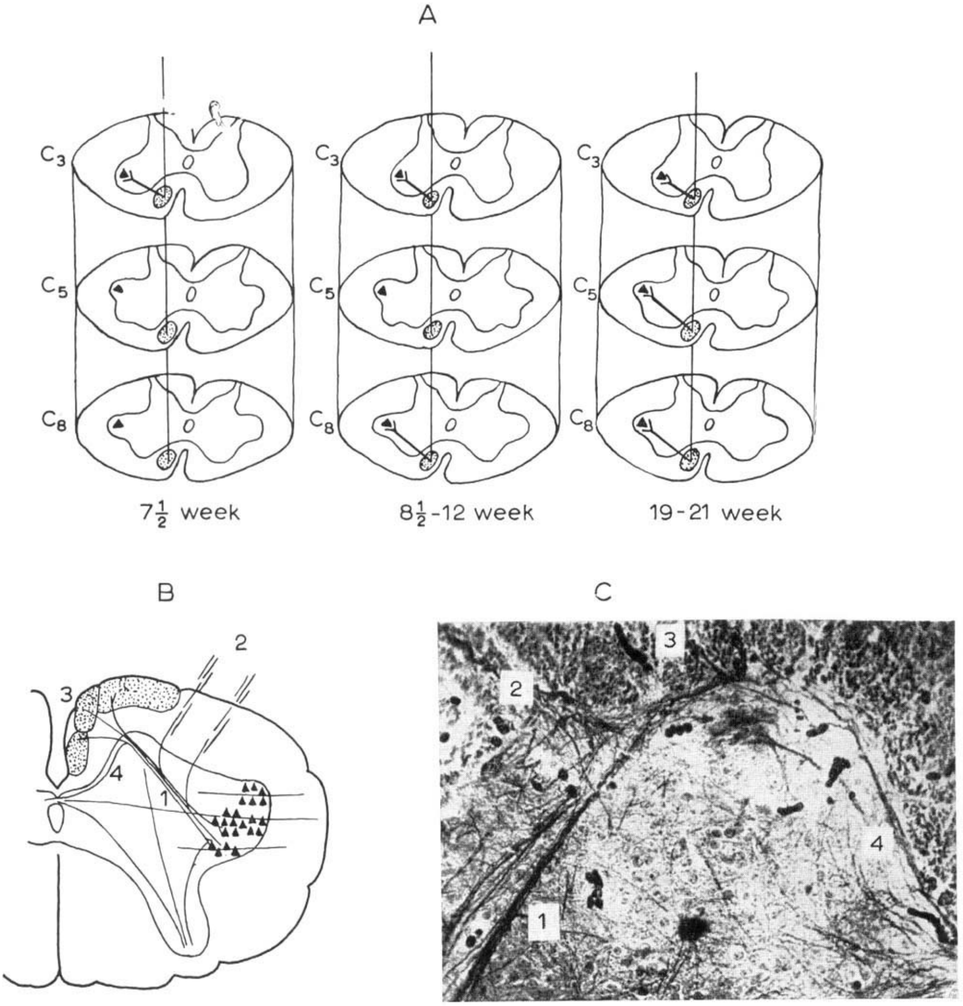

Fig. 5. (A) Heterochronic growth of the fasciculus descendens. The control on the motor neurons of $C_3$ begins to act much earlier than the connection at the $C_5$ and $C_8$ level. (B and C) Horizontal section of the spinal cord at the $C_8$ level. The ‘primary fasciculus’ is noticeable; which goes from the anterior horn to the motor cells of the flexor muscles.

We have compared the behavior of the rook with the behavior of newborn birds living in hollows, such as *Muscicapa hypoleika*. This bird lives under different ecologi-

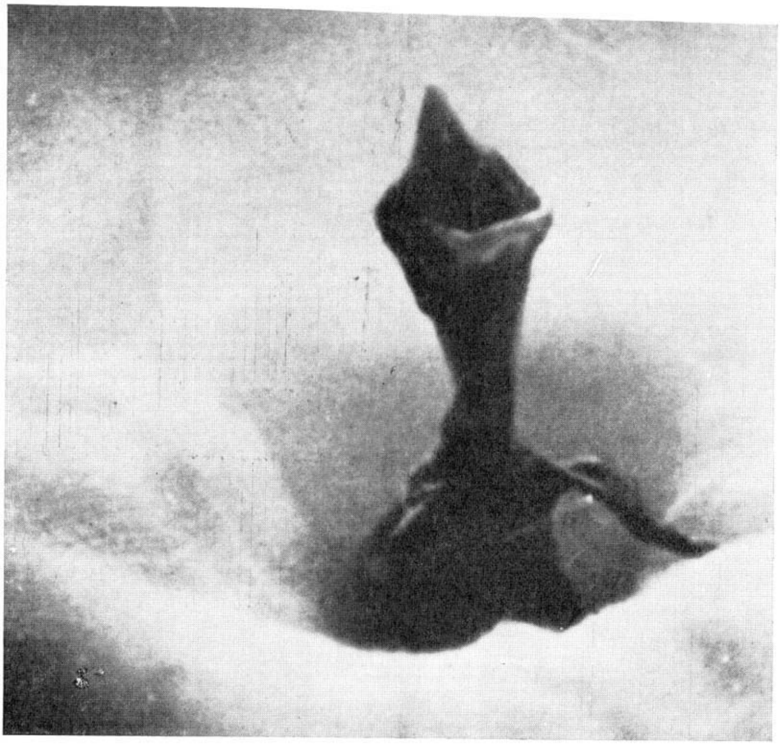

Fig. 6. Effect of the arborized functional system in the process of food uptake by little rook immediately after hatching. The exact coordination of numerous components maturing at the time of hatching is needed for the successful uptake of food.

cal conditions. The question arose what kind of stimulus is needed to open the beak for food-uptake.

We discovered a very interesting fact that darkening the hollow, when the mother arrives with the food and thus shuts the 'window' through which the light can enter, appears to be the active stimulus. It seems clear that at the moment of birth the selective maturation has only been provided for those synaptic organizations which provide the reception of changes of light and for those which make up the opening of the beak (Fig. 7) (Chajutin, 1963).

All the above mentioned facts permit us to postulate the general rule which seems to operate for the preparation of all vital systems in the newborn during the process of embryogenesis.

The rule runs: against the background of the maturation of different structures of the organism during the process of embryological development those structures are selected which provide the most vital functions for the newborn. The selected functions show an accelerated and differentiated growth.

An organ does not mature simultaneously as a whole in all regions. Only those parts and structures of an organ which are necessary for performing the vital functions at the time of birth, mature selectively and with a higher speed.

It should be stressed that all the components of different organs, often at some

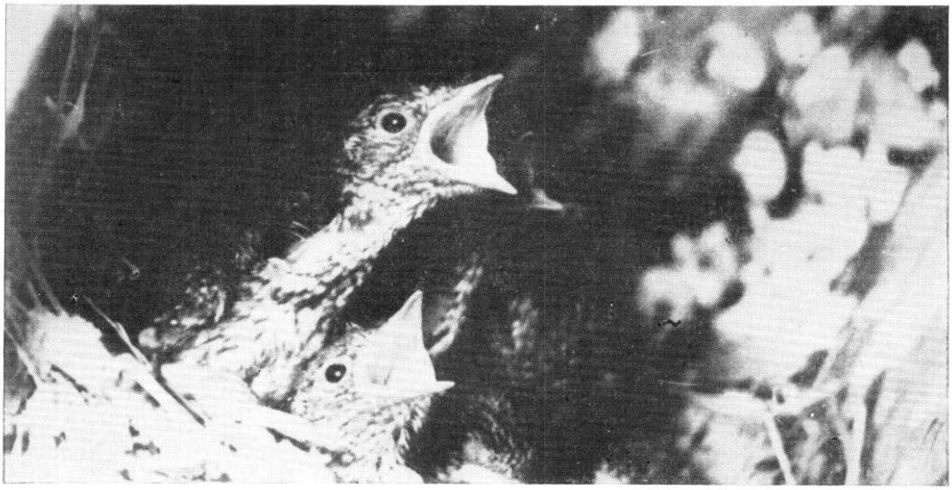

Fig. 7. A photograph of the reaction of the squab (*Muscicapa hypoleika)*, living in a hollow. The active response of the squab to the darkening of the hollow is seen.

distance from each other develop during the first stage somewhat isolated, but become consolidated in their further development and arrange themselves into an integrated functional system. The selective growth and maturation of the structures are subordinated to the law of development of the system, vitally for the inborn.

This kind of development of an embryo differs radically from the rules of organogenesis, which propose a proportional maturation of the organs as a whole. We postulate, on the contrary, an accelerated and selective maturation of those parts and structures of the organs, which are to compose the functional systems and are independent from the maturation of the organs on the whole.

This new form of development is called the *systemogenesis.*

## SYSTEMOGENESIS AS THE REGULATOR OF THE DEVELOPMENT OF NERVOUS ACTIVITY

From what was mentioned above it may be seen that metaphorically speaking in the 'mass' of embryo there are invisible processes of selective and accelerated growth of substrates which in future will combine to create a fully developed and arborized functional system with positive adaptive effect for the newborn. The great number of the investigations, performed over a 30-year period, have convinced us that this growth of structures, and this combination of the selectively matured components have a clear systemic character since at the end of that process a fully developed functional system is available. One can see finally an absolutely coordinated pattern of maturation, the last step of which is the formation of a functional system. This type of regulation of maturation is called by us *systemogenesis.*

We think that the term reflects the idea of a process by which a function, but not a mature organ, is developed. For example, the hand or forelimb has not yet matured, in particular, the innervation of many forehand muscles has not been completed at the time when the innervation of the flexors necessary for swallowing has already been finished. The illustrations from the experiments described above suggest a regulation of the development of function. The specific principles of systemogenesis served as guides throughout all our investigations and we believe that these principles are based on the specific regulation of development which can be seen in all the experiments performed on different species.

It seems that these principles may also be used by other scientists for the solution of the common questions of the brain development which depend upon embryological and postnatal development of functions.

We should, therefore, like to state the general principles which determine the ontogenetic development of an organism from the moment of the first signs of a component in the whole system to the appearance of the fully developed adaptive function in the newborn.

### *(a) The principle of the asynchronic arrangement of the components of the functional system*

This principle rules that irrespective of the complexity or simplicity of the structural components of a functional system, these components should act together as a functional unit at the moment of birth. Analyzing the relationships of certain components, for example, in the locomotor function or sucking function, or respiratory function, we can say that any working arrangement of the muscle in the periphery demands for each of those three functional systems an extremely fine integration in the central nervous system. The action of the central nervous system as a component of each of these above mentioned functional systems is to integrate the act as a whole in its spatial and temporal relationships. Thus, for example, if in the act of sucking, the peripheral face muscles, forming a vacuum in the mouth cavity, begin to contract before the mouth closure is air-tight due to the contraction of M. orbicularis oris, then quite naturally the functional system does not create any positive effect. Thus, the central excitation must be programmed very exactly by means of the finest organizations of the synapses of the nerve cells of the appropriate centre.

Taking all these factors into consideration we want to state that the finest regulation of either the functional sucking system or of the respiration derives from its central component. Thus the fact that the nerve centres are combined in groups and begin to mature in the most cases earlier than their innervated substrates, the muscles, must be regarded as an expedient phylogenetic adjustment (Fig. 8). In this same sense the formation of the muscle tissue is much simpler and occurs more rapidly than the central apparatus which integrates muscle function. Our observations show that the creation of synapses with their fine selective relationships is the most important part of the integration process. One can see that the entire complex consisting of the organs and tissues combined in action for the performance of a function will be immediately and dangerously incoordinated if even a small disturbance in relationships of the central parts should occur.

A systematic investigation of the times of appearance of the various components

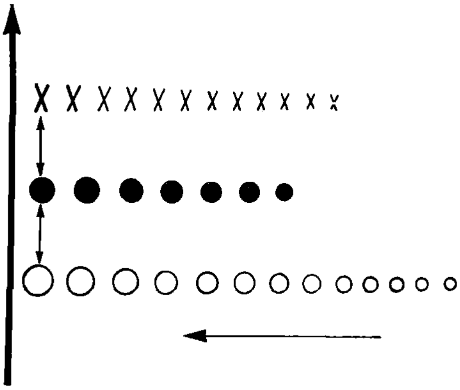

Fig. 8. A scheme demonstrating different moments of the initial organizations and different times of maturation of various components of the functional system. The components of the functional system are denoted by different symbols: circles = central integration; black circles = muscles elements; crosses = nervous truncs. The vertical thick arrow shows the moment of birth, the enlarged symbols before the moment of birth demonstrate the readiness of the components and their consolidation into the whole functional system.

of different functional systems of all species was not performed. Therefore, it seems very important to stress the regulation by which the necessary functional systems either of sucking or of respiration arrive at full maturity at the moment of birth. It seems probable that many cases of prenatal defects may be connected with insufficient development and arrangement of individual components of the functional systems of sucking and respiration.

### *(b) The principle of the fractionation of an organ in the process of the embryonic development*

The systemogenetic type of development assumes a necessarily heterogenic composition of an organ at every moment of its development. Those components of the organ will develop first which are necessary for the organization of the essential functional system for survival after birth. This principle is well seen in the example of development of innervation of the facial muscles. Of the nerve nucleus involved only those cells necessary for peripheral nerve mature, the rest of the nucleus being subordinated to the same regulation. Thus, during ontogenesis the organ (in this case the nucleus of the 5th nerve) as a whole has a differential initial organization and a differential rapidity of the development of its individual parts (Fig. 9).

Another good example is the case of the maturation of Corti's organ in the rook which is at hatching limited to those sounds which are present in the mother's sound 'kar-r'. Certainly all the parts of the Corti's organ will be fully matured in the adult life of the rook but at the moment of hatching the maturation is fractionated in such a manner as to satisfy the immediate demands of postnatal adjustment. Also in comparative analyses of the time periods of development of the cells of a spinal cord in the embryos of the chicken and the rook, one can see that the differentiation of the cellular elements in the cervical and lumbar segments proceed at different rates.

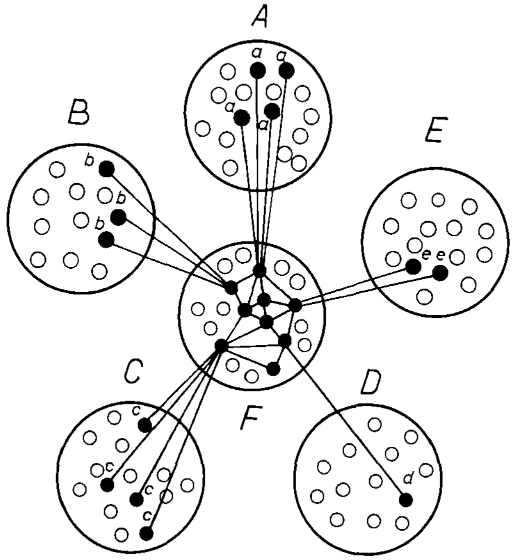

Fig. 9. Scheme of minimal provision of the functional system by the necessary structural components. The scheme demonstrates the organized maturation of the functional system which at each stage of the development provides the minimal adaptive effect. It illustrates the process of fragmentation of organs during the development of certain functional system. A, B, C, D, E = different organs and the accelerated differentiation of the structural elements; a, b, c, d, e = undergoing accelerated growth and consolidation.

In the chicken the cellular elements and the interneuronal connections differentiate earlier in the lumbar segments than in the cervical, while in the rook the differentiation occurs first in the region of the cervical segments. Thus, one can see the evident developmental fractionation of the spinal cord as an organ in the two species and that this fractionation is intimately connected with the ecological peculiarities of each species of bird.

We would like to stress a peculiarity in the disproportional development of organs that the irregularity in the process of arrangement in the times of maturation may be so profound that the 'local reflex activity' will appear. It is concluded, however, that the so-called 'local reflexes' are only fractions of the functional system which have selectively matured at an accelerated rate.

### *(c) The principle of the consolidation of the components of the functional system*

The moment of the consolidation of the entire functional system is a critical point in its development. To illustrate those processes which take place inside the functional system, I would like to describe a functional system studied in our laboratory in great detail, that is, the functional system involved in jumping by the guinea-pig. The biomechanic architecture of that act is characterized by unequal work being performed by the different limbs because the body moves by means of pushing off and the main work is, naturally, done by the hind-limbs. At the same time the observations on the guinea-pig embryos at the 23–25th day of the development show that tickling the guinea-pig's face by a bristle evokes immediately the highly coordinated act of pushing off by means of its hindlimbs with, at the same time, very limited participation of the rest of the body. We subjected all steps in the development of that functional system, and especially at the moment of its consolidation, to detailed morphological and physiological study. This could be done easily because of the position of the fore- and hindlimbs at the opposite ends of the body.

In fact, the descending pathways from the cells situated in the brain stem grow step by step down to the lumbar segments and begin to make contact with those motor lumbar elements which have already acquired marked differentiation and connections with the periphery. Thus, the brain stem having finished the arrangement of the finest synaptic connections in which the architecture of the future function of jumping is reflected, gradually takes control of lower spinal cord segments. These descending pathways do not form all the synaptic connections but only the selective ones required for individual motor neurons of the lumbar segments. This event creates special conditions which radically change the relationships previously formed in these segments. The components of the segmental neuronal combinations under the influence of the descending control acquire a definite position in the functional system integrated on the brain stem level. It is suggested that the 'descending' brain stem neuron on arrival at the lumbar segments changes radically the relative prominence of the components of the system. Thus, for example, during the development of the spinal segments of the guinea-pig the rule of the axis gradient plays a certain role, *i.e.*, the radial segments are formed and differentiated a little bit earlier than the lumbar ones, although both accelerate at different times in their development than do the other structures in the spinal cord.

The axis gradient is apparent until the moment when the descending pathways, arising from the brain stem centers, arrive at the key lumbar segments. After this occurs the relative maturation in the lumbar cord changes abruptly as the lumbar segments acquire special strength and play the leading role in the functional system of jumping. Such abrupt re-evaluations of individual fractions of the functional system at the moment of their consolidation is a real consequence of the architectural peculiarities of that functional system. We observed many examples of such a re-evaluation of the usual proximo–distal regulation of the development at the moment of consolidation of the functional system. Thus, for example, the initial stage (8 weeks) of the development of the human embryo is characterized by the growth of the neurons through the plexus brachialis to the forelimb reaching the muscles in exact accordance with the law of a proximal to distal acceleration of development of the flexor nerves discussed above. Still, the predominance of flexion as a division of the functional system begins to appear only when the descending brain stem pathways, the primary fasciculus, reach the motor elements of the 8th segment. From that moment the relative value of the hand as a whole in the system of distal–proximal parts of the hand changes radically. The act of grasping and gripping by the fingers, although taking place in the distal part of the limb nevertheless acquires the leading role in maturation of the whole functional system in hanging and maintaining the body in a hanging position. Thus, one can see that the moment of consolidation of the discretely maturating components of the functional system is the crucial time at which the central components of the system, giving the final physiological architecture to the system immediately acquire the control of the system. Due to the importance of this final consolidation it must be analyzed in detail in terms of various behavioral manifestations in order to uncover the individual peculiarities of the important functional systems and their order of entry into function of the different component parts. First of all arises the question as to which parts of the functional systems are maturated sufficiently for consolidation, and what parts cannot yet begin to be consolidated. The next part of the report will be devoted to these questions.

### *(d) The principle of the minimal provision of the functional system*

This regulation of the timing of maturation noticed by us in examples given above of the development of certain functional systems represents from our point of view a great achievement of evolution, and expresses probably one of the most perfect adjustments in the struggle for the ability to survive. The essence of that regulation is as follows: the functional system as represented in an adult animal does not appear from the beginning in mature form. First those structural parts of single components of the system which have been already matured at the moment of the consolidation combine with one another. Because of this the functional system which has been consolidated is to some degree already completely functional from the time somewhat before all its links were structurally created. As a result, the functional system begins to play an adjusting role in the life of the newborn long before its complete and definite maturation.

We are reminded in this regard of the action of curare on the *Ambystoma tigrinum*. In that case the conduction of excitation throughout the synapse begins before the structure of the synapse becomes mature. It is of interest to stress that at the time when curare begins to paralyze the gills and the anterior part of the body the Ambystoma nevertheless continues to swim by means of movement of the posterior part of the body which still lacks synapses. It is clear that due to the accelerated and differential consolidation of the front of the body, only a mere fragment of the total functional system, the animal escapes the risk of being unprepared in the case of the abrupt interruption of embryonic development.

We were lucky to observe over a comparatively long period of time the immature embryo of a human being which was born alive weighing only 560 g. This human being was immature from all points of view but it was able to make coordinated sucking movements and to suck 10 $\mu$l of milk. This immature child lived for a period of 42 days, and during that period we were able to observe certain improvements of its functional system of sucking. It was clear that in this case the consolidation of individual components of the functional system had already taken place. Some of the central cells had combined and some of the peripheral nerves related to the act of sucking had formed functional connections with appropriate muscle fibres. Yet we know that the same act was accomplished by a normal child with much more strength and with more evident adaptive action. Therefore, in that immature embryo only some parts of the possible connections were formed at the time of the premature delivery.

By comparison of the data one can notice one interesting fact which is conspicuous in the process of evaluating the principle of the minimal provision of the functional system: the consolidation of the functional system does not begin chaotically, and the components do not mature simultaneously nor do they consolidate synchronously. On the contrary, a few structural units mature at a given time and maturation occurs in such a way that they are ready to combine and form certain simple, very imperfect but at the same time architecturally fully functional fractions of the mature pattern (Fig. 9).

It seems to us that the principle of the minimal provision has an extremely deep biological importance because all further improvements of the functional system arise from these minimal provisions for function of the system. By means of this regulation the animals have the opportunity of surviving even in those circumstances when they must be able to live independently from birth. Because of the great importance of these mechanisms the principle of minimal provision continues to be under investigation in our laboratory.

## THE ONTOGENETIC DEVELOPMENT OF ASCENDING INFLUENCES ON THE BRAIN CORTEX

Until now we have been studying the rules for the development of whole functional systems, which are the basis for successful adaptive activity in newborn animals and thus, the basis for successful survival.

The central integrative component is localized as a rule in the central nervous system. Among the components of the essential functional system it is the general key for the creation of the architectural peculiarities of the functional system in terms of distribution in space and time of the activities of its components. The distribution of activities in terms of time must be such, that the activity of the functional system as a whole is completed for a positive adaptive effect which is specific for that functional system. A little discordance in the time entry of the different components may lead to the complete disintegration of processes on the scale of the whole functional system and to a complete loss of the final adaptive effect.

The conclusion from the discussion above is that the heterochronic processes of growth and maturation, which take place in the central nervous system are the signs of an intersystemic heterochronicity. The brain and especially the brain cortex are the sites where thousands of different functional systems of different adaptive meanings interact. Due to this complexity it is very difficult to study individually the structures in the cortex corresponding to each of these functional systems. For example, it is relatively easy to distinguish the functional system of sucking because of its early maturation and comparatively simple structure. It is much more difficult to do the same for functional systems of an organism completed at a later time as, for example, the gross behavioral acts appearing during transitional periods of life as exemplified by the erect position or the development of speech.

That is why it is much more important in the case of functional systems of behavioral character to select key forms of growth and maturation which combine all the acts and parameters of the integrative activity of the whole organism, both local and generalized. We think that the maturation of the subcortical connections of the cortex in the process of their dynamic interaction, is carried out to the greatest degree by such key features.

These parts of the brain are very markedly divided by their functional features and their phylogenetic growth, which can be traced clearly in the investigations of Herrick (1948). This author showed the structural transformation of the cortical areas in the process of the growth and the complexity of the sensory analysis and synthesis of environmental events under the influence of the increasing necessity for adaptive behavior (Fig. 10).

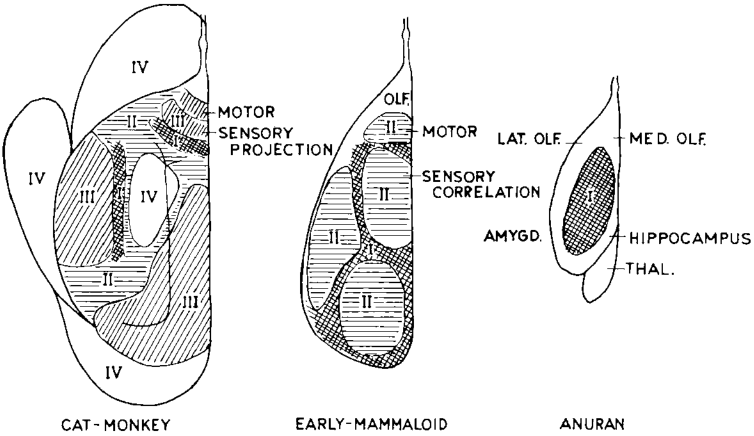

Fig. 10. Schematic representation of the specialization of the sensory areas of the brain (from Herrick 1948).

Certain questions arise from that premise: what is the form of the heterochronicity, which is created in the process of maturation of the ascending pathways and what are the influences of different phylogenetic histories? What is the form of division of the 'specific' and 'unspecific' ascending influences on the brain cortex in ontogenesis? All these questions acquire special meaning, if we take into consideration that such a beginning of participation cannot be heterochronic due to the fact that cortical-subcortical components must start to act in a certain sequence.

The same timing must apply to the influence of different phylogenetic 'ages' on the elements of the brain cortex which ascend from the neuropil integrative substrate to the special sensory fields and accomplish the discrete sensory activity of the cortical cells.

The investigation of the ontogenetic ascending influences on the brain cortex is very important because of other considerations to be discussed below.

The scientist, investigating the character of the ascending influences on the brain cortex in an adult, works with mature synaptic organization both in the subcortical nuclei, and at the level of the different cortical layers. The synaptic delays are different in quality of the ascending influences in the immature organism but in an adult one they have already become equal and therefore, on the surface of the cortex one can observe, a response which is 'finished' and summated in its electric expression.

There is quite a different situation in the process of the early postnatal development. Due to the heterochronic growth of the structures at the cortical and subcortical levels one can see a kind of filtration of the influences. Because of this fact one can create a complete picture of multiple character of the influences, ascending to the brain cortex, which are reflected in its electric responses.

Our recent studies have shown, that the research into the process of systemogenesis, on the basis of which the individual activities of the newborn organism are created is not complete unless the rules of the maturation of the cortical-subcortical relationships are examined for that specific aspect.

The next part of my discussion will be devoted to that question.

There are three electric indicators of different degree of specificity for the physiological evaluation of the ascending influences of the brain cortex:

(1) The electroencephalographic record. Slow activity, which in spite of its extensive usage in solving neurophysiological problems is still even at this time *terra incognita.*

(2) An evoked potential, which appears during the electric stimulation (single stimulus) of some receptor surfaces.

(3) Discharges in single neurons due to some disturbance, which takes place in the nervous system.

We have investigated the possibilities of the first two methods in detail but the microelectrode recording and the characteristics of the discharges from single neurons are the subject of our current investigations and, I expect to present these results at some meetings in the near future.

We have already said that the chemical groups in the central synaptic formations which are responsible for the perception of the action of different pharmacological agents mature at the last stage of the development of the nerve cells. They appear as a result of protoplasmatic features sufficiently developed to be able to conduct excitation.

In this case I would like to stress the sequence in the maturation of different kinds of the ascending influences on the brain cortex. Thus, for example, in the first hours after birth, electric stimulation of the sciatic nerve evokes a marked reaction in the sensori-motor cortex in the form of high amplitude oscillations. This form of reaction is not characteristic of an adult, in which the reaction in the sensori-motor cortex is always expressed by a marked desynchronization. The same sciatic stimulation in a slightly older animal, for example, 7–8 days old, evokes some signs of desynchronization which are well established by the 11th day.

Let us try to see what has happened during this 10-day-period in the cortical cells. The most probable explanation of the phenomena is the creation of new ascending controls on dendrites. In fact the high amplitude rhythm observed in the newborn cannot be the basis for the desynchronization. Undoubtedly, the desynchronization is the result of special ascending influences on the cortical cells, perhaps, of the type, which has been recently discovered and investigated in detail by scientists in Pisa (Moruzzi, 1960).

On the other hand, desynchronization is also a specific form of the activation of the cerebral cortex and is undoubtedly connected with the individual specific in quality, ascending 'impulse' of excitation, which terminates on the dendrites of the cortical cells. Thus, one can see the presence of heterochronic growth of two ascending influences on the brain cortex, and these two influences differ demonstrably in their phylogenetic origin.

The primary evoked potential was investigated simultaneously both morphologically and electrophysiologically in our laboratory. As it is well known from the works of Scherrer and Oeconomos (1954) the photic or sound stimulation used in the newborn rabbit or a kitten, evokes only a slight negative deviation. At that stage the typical form of an evoked potential, which normally consists of positive and negative components, does not occur. The authors described the phenomenon of the isolated existence of the evoked potential during the first days after birth, but did not connect this paradox with the current theory of the origin and formation of the primary cortical potential. This may have been because it contradicted the existing view. It was necessary therefore to solve the contradiction in one or another way.

Professor Purpura in his physiological and morphological investigations also met the fact of the isolated existence of only the negative component during the first days after birth. Therefore, the fact was evident, that the positive component does not appear first. Ata-Muradova (1960a,b) in our laboratory also found the isolated appearance of the evoked potential in newborn rabbits during sciatic stimulation.

Most likely, we also should not doubt the validity of the classical representations of the origin of the evoked potential from a single, homogeneous ascending impulse arriving at the cortex through the above described pathways. Still, the conception of systemogenesis elaborated in our laboratory several years ago from our experimental observations and the hypothesis of heterochronic growth of the nervous structures, logically connected with that conception, forced us to suspect that the paradoxical appearance of only the negative potential may be due to the heterochronic character of the evoked potential itself. Further experiments performed with many control variations led to the conclusion that our surmises were quite reasonable.

Thus, for example, it was shown, that the negative component of the evoked potential has several features, a point which contradicts the idea that it is the result of the pre-existing processes and in the adult animal changes to the positive component of the evoked potential. The use of different narcotic drugs, electric currents of different strength, a heating of the cortex surface and other treatments, showed that the negative component has undoubtedly an independent character. Even before the appearance of the positive potential it has a characteristic growth of amplitude and an enlargement of the zone leading from the focus of maximal activity situated in the sensori-motor cortex. All these facts point out that the isolated negative potential during the first days after the birth is created in the large hemispheres of the cerebral cortex by an independent impulse which passes through pathways independent of the positive components.

Direct morphological studies performed by Ata-Muradova and Chernischewskaya (1961) showed that the isolated negative component arises in the plexiform layer due to discharges arriving at the axodendritic synapses, since at that time the presence of directly ascending fibres arising from the white brain matter to the plexiform layer was found. These ascending fibres could be demonstrated at the time of complete maturation; they ascend directly to the brain cortex and to the area which is the focus of the maximal activity where on the first day after birth the isolated negative component can be elicited (Fig. 11).

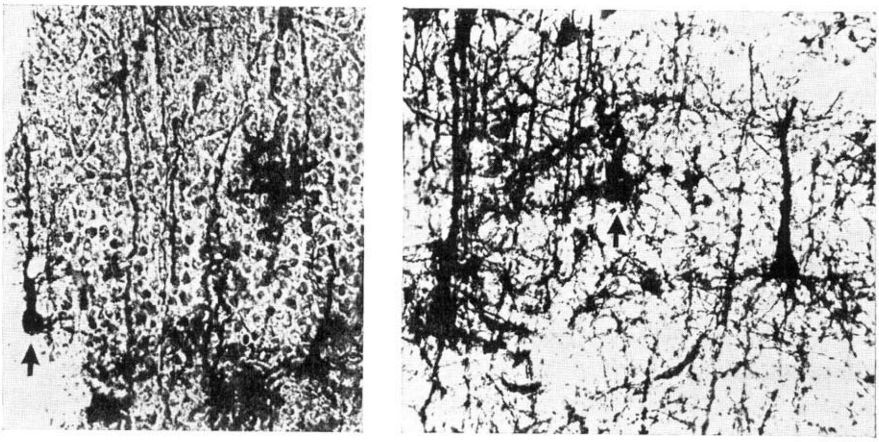

Fig. 11. Microphotograph of the ascending fibres branching in the plexiform layer of the sensori-motor area in newborn rabbit. Note the absence of other ascending pathways to the first cortical layer. The cells in the IVth layer correspond to those in the IIIrd at 15 days postnatally. Note the evident progress in the increase of the amount of dendritic organizations.

The combination of all these facts together with the data available in the literature specially the results of Purpura (1959) concerning the heterochronic maturation of synaptic apparatus in the brain cortex, led us to the conclusion, that both components of the primary evoked cortical potential have discrete anatomic origins and belong to two different systems of ascending influences on the brain cortex. The illustration (Fig. 12) shows the common scheme of the maturation of the both components due to the maturation of the synapses of axodendritic and axosomatic character.

In order to decide the problem of the nature of the individual components of the primary evoked potential one inevitable question to be answered was, do all evoked potentials have multiple genesis, and acquire a common fused character depending on strength, interval and localization?

First control experiments were performed to characterize the physiological features of the positive and negative components of the primary evoked potential. We thought that the positive and negative components differed undoubtedly in their features depending on the frequency of the stimulation and the rate of conduction. The positive component is the fast one, while the negative component, on the contrary, is the slow one, and is more susceptible to the tetanic stimulation. It is quite evident that we are dealing here with an extremely interesting paradoxical case in which two components appear after the birth in inverse relation to their physiological quality; that is, the slow component appears earlier, and the fast one much later.

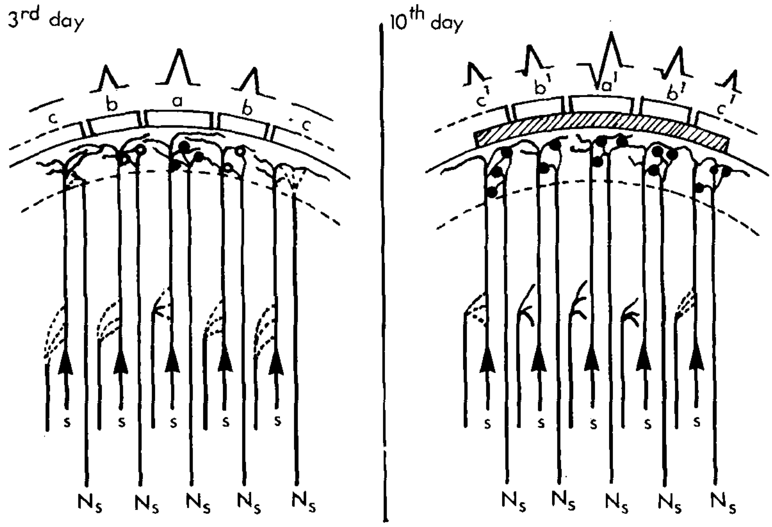

Fig. 12. Synthetic schema showing the order of heterochronic growth of axodendritic synapses in newborn rabbit. Note the correlations between the synaptic connections with the changes of the evoked potential in the sensori-motor area during the first days postnatally. The mature synapses are denoted by black circles; the immature synapses are denoted by empty circles. The dotted lines denote immature synaptic organizations which do not give discharges to sciatic stimulation. s = the specific ascending pathway; $N_s$ = ascending fibres from the nonspecific nuclei in the thalamus; a, b, c, = indicate the localization of the recording electrodes. The electrode at (a) is just above the stimulation point, at (b) and (c) at equal distances from the point of maximum stimulation.

It is clear that in view of such paradoxical relationship in the process of the maturation of both components, there would inevitably have to be a crossing of function during their maturation if we draw the curves based on their time of growth, and their physiological lability (Fig. 13).

Such experiments were performed in our laboratory by Sun-Ven-In. We used the

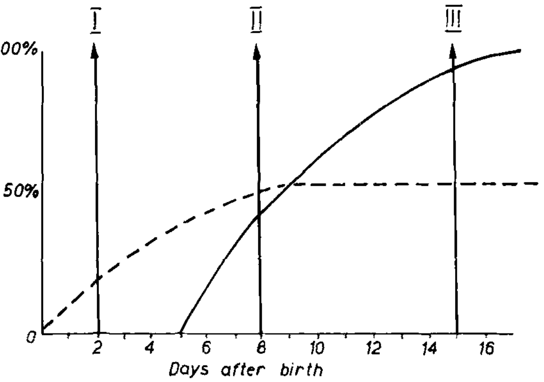

Fig. 13. Schema of the time correlation of excitabilities of negative and positive components which appear as the result of the second stimulation. Solid line = maturation of the structures for the positive component of the evoked potential; dotted line = maturation of structures for the negative components of the evoked potential. Vertical arrows I, II, III, show the moment of stimulation of the sciatic nerve.

well-known method of paired stimulations with gradual change of intervals between stimulations. In view of the above mentioned curves, we thought, that the most interesting times for the examination of paired stimulations were those marked with the Roman numerals I, II, III (Fig. 13).

Let us try to visualize what we could expect with the change of the interval on these different stages of the development. Applying the stimulation on the 4th day after birth, *i.e.* in the period, when we have only the one negative component, the shortening of the interval between stimulation or conversely the delaying of the second stimulus of a pair will give with different intervals the first signs of the negative component, and delay between the two stimuli will increase the amplitude of that component. It is apparent that, using such a method of the stimulation in the first days after birth, one can find a very long threshold and an optimal interval for the second stimulation which is a good characteristic of low lability or slowness of the component. The most interesting fact obtained from using such pair of stimuli was in the second zone. As it is shown by the arrow II it is that zone where the negative component has almost achieved its complete maturation, while the positive one is yet on the stage of formation (Fig. 13).

It is evident that at any given time the maturation of both components is quite different in conditions. The positive component on first appearing must have an extremely low lability (high threshold) as does any maturating substrate; the negative component, on the contrary, has almost its maximum lability (low threshold). Using the paired stimulation method we found a point when after the second stimulation, *the negative component alone, without the positive one, could be registered*. These experiments completely followed assumptions described above as can be seen in Fig. 14. The fact that this period is very short explains why it had not been discovered previously.

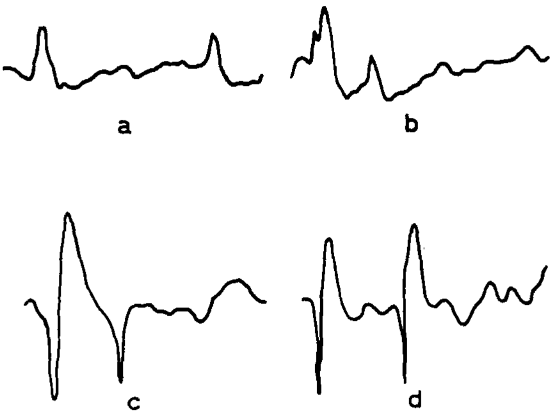

Fig. 14. Results obtained in the experiments with coupled sciatic stimulation in newborn rabbits. (a) two sciatic stimulations applied at the 2nd day after birth at the stage when only the negative component of the evoked potential is present; (b) stimulation applied at the 8th day after birth. Note the predominant negative component of the evoked potential. The positive component is completely blocked; (c) sciatic stimulation at the 20th day after birth. Note the predominant positive component of the evoked potential; (d) the adult animal, control (for explanations see text).

In the third zone we evidently have inverse relations. The fast positive component has acquired its definitive qualities of fast spread and short duration. It, therefore, depends much less on any refractoriness, remaining after the first stimulation. On the contrary, the negative component, still not being completely mature, because its qualities depend much more on the refractoriness remaining after the first stimulation. For this reason, the inverse relationship will take place with a change of interval between stimuli. The positive component will be most stable, the negative one — the less stable; *i.e.* such relationships as are present in the adult animal. The experiments suggested the form of the relationships shown in Fig. 14c, the positive component occurring even in the case of very short intervals between paired stimulations (Anokhin, 1964).

The experiments can be decoded very easily, if the dual characters of the evoked potentials and both components are taken as the basis of our representations. Let us suppose: (1) that the impulse for the positive component arises from the so-called specific thalamus where it has certain 'fast' parameters of origin and conduction; (2) that the negative component is generated by other cells, nonspecific cells of the 'specific' thalamus (Whitlock and Nauta, 1954), or 'nonspecific' nuclei of the thalamic system. If this is the case then the conduction of excitation to the cortex during the sciatic stimulation, will have direct dependence on the rapidity of the development of processes in the synaptic relays in each of these pathways (Fig. 12). If stimulations appear one after another then naturally both excitation streams are conducted, the rates depending upon the traces of refractoriness which remain in each system. All variations of the above mentioned results can be easily assumed from the correlation of the physiological properties of both these conductive pathways, especially from the disappearance of the negative component of the evoked potential under the influence of urethan. Urethan may act selectively on the sensory subcortical structures which create the negative potential, at the same time being without influence upon the structures responsible for the positive potential, which are more resistent to its action. The action does in fact take place (Anokhin, 1961a).

A more profound and detailed analysis of the negative component shows that it is itself a very complex phenomenon, and is not formed as the result of the single ascending impulse. At a certain stage of development the examination of that isolated negative component can be performed using stimuli of different strengths. If this is

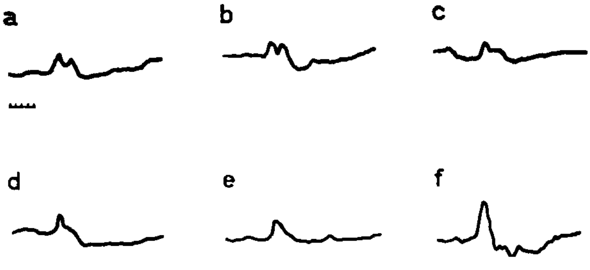

Fig. 15. Tracings demonstrating during the first days after birth the dependence of the configuration of the evoked potential on the strength of the stimulation. The double negative potentials are converted into high amplitude single negative oscillation when the strength of the stimulus increases from 5 V to 10 V (a–f).

done, the potential which at first seems homogeneous, dissociates into several potentials clearly showing its multiple nature (Fig. 15).

In this figure one can notice that the additional and secondary negativity does not cease immediately with increase of the strength of the stimulation, but it is 'swallowed up' step by step as the stimulation of the sciatic nerve is gradually increased. This fact explains all the variations in the form of an evoked potential which we have often observed in these experiments (Ata-Muradova, 1964).

In accordance with the scheme described above explaining the separate genesis of the negative and positive potentials we can draw the same schema for the explanation of the phenomenon just described of the confluence of the two negative potentials into one of higher amplitude (Fig. 16).

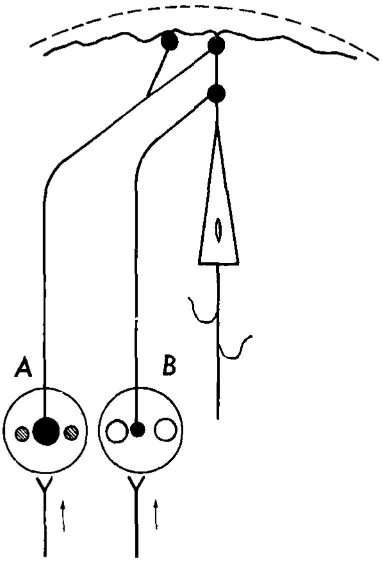

Fig. 16. Schema illustrating a mechanism for the dissociation and combination of two streams of excitations. A = subcortical structure with the presence of almost mature synaptic connections. B = subcortical structure with the heterochronically delayed maturation.

Let us assume that a single given cortical area but different apical dendrites receive fibres from a given thalamic formation. In the thalamic formation, itself, there are different cell bodies with different functional meaning and with different relationships to the surrounding nervous formations (Fig. 16: A and B). Let us suppose, that the complex A, due to systemogenetic regulation matures earlier by a very short interval than does the cell complex B. In the experiments described above there is a stream of impulses arising from the sciatic nerve as a result of weak stimulation. After several preliminary relays excitation arrives at the both complexes A and B, but due to their different degree of maturation the excitation, arriving at the same point of the cortex, but at different apical synapses evokes the form of potential, which is shown first in Fig. 15a. Now if the strength of the stimulation is changed quickly, for example, from 5 V to 10 V, then the velocity of the conduction throughout the both complexes A and B is to some degree equalized and both streams of the excitation arrive at the plexiform layer almost simultaneously, and as a result, a homogenous and single negative potential appears. This potential can be seen in Fig. 15f. Thus our concept of the multiple character of ascending influences to the brain cortex can be clearly illustrated by these experiments.

In recent years we have begun to use only this method for decoding the evoked potentials, and the results are very encouraging. The amplitude and the time constant of the evoked potential seem to be registered as a result of limitation of the positive component by the negative one which appears immediately after it as the result of an impulse. On this basis all the configurations of the evoked potentials can be explained.

If the negative component of the evoked potential is in any way removed (by GABA or urethan), then one can see an immediate augmentation of the time constant of the positive component (Ata-Muradova, 1960b). The explanation of this event is as follows: in the usual situation the mature positive phase can never be seen since the negative discharge is obscured in the plexiform layer very soon after it appears. Metaphorically speaking the negative component 'goes close on the tail' of the positive one and consequently reduces the positive phase since it depends upon the interval between two ascending streams of the excitation (Anokhin, 1961a,b).

The negative component of the evoked potential may be removed in another way; for example, by the treatment of the sciatic nerve with novocaine. As is well known novocaine blocks first fine unmyelinated fibres. The single sciatic stimulation applied at this stage of anesthesia evokes in the brain cortex only one positive potential instead of the usual well-developed two phase one. This positive potential develops completely and thus appears as a potential augmented to the utmost in amplitude and time constant (Poljakova, unpublished data).

All these considerations arose in connection with the investigation of the systemic and heterochronic maturation of nervous structures and gave extensive opportunities to regard all the variations of the cortical evoked potentials as a result of many ascending influences according to their time of spreading within the brain, the intervals between them and the spatial relationships between different electric phenomena.

Until these experiments the heterochronic growth of the cortical structures was considered only in connection with the genesis of the electric phenomena and their relationships. The studies show that there exists only one opportunity to disperse the electric phenomena into their component parts; that is, a change in the strength of the stimulus reveals the multiple genesis of what otherwise appears as a homogenous electric phenomenon. More demonstrative methods of showing that such a kind of dispersion exists are made available by the local application of drugs to the cortical surface at the focus of maximal activity of the evoked potential. If a piece of paper soaked in the GABA solution is applied on the cortical surface at the time the two-phase potential is first evoked (15th day), then one can see very easily the evolution of the evoked potential phases. The second negative phase begins gradually to augment simultaneously with the gradual disappearance of the first negative component. This event usually takes place in an adult as a result of the GABA action. It is evident that

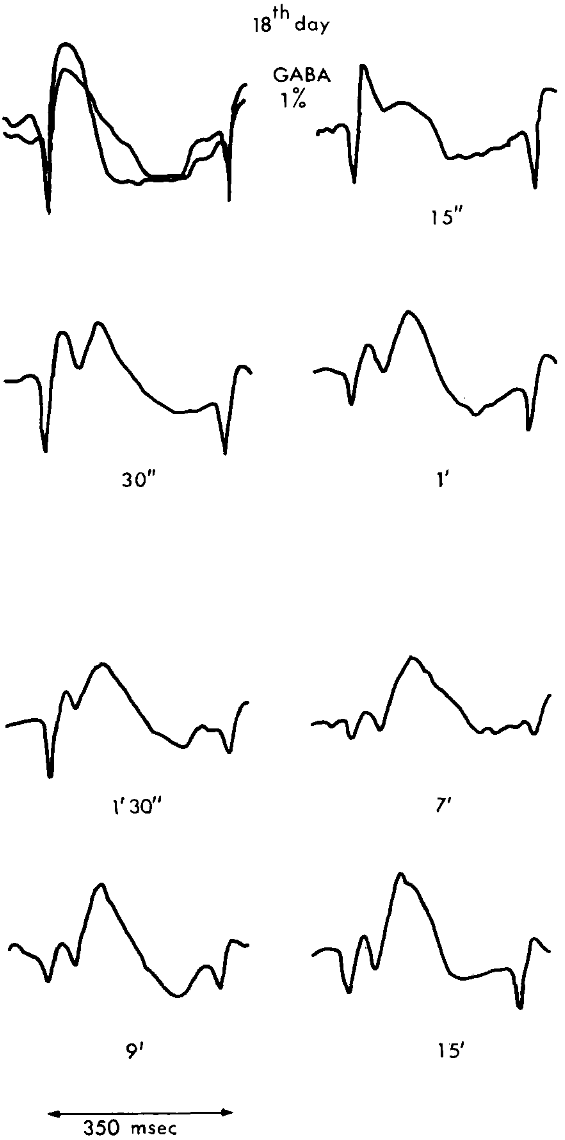

Fig. 17. Four tracings demonstrating the gradual course of the action of GABA on the evoked potentials, the correlative blocking of the primary negativity and the gradual increase of the secondary negativity are shown.

the negativity increases and decreases only because of GABA. As you can see in Fig. 17 the primary negativity and the secondary one change their amplitude reciprocally, exactly in accordance with the time of GABA action (Ata-Muradova, 1963). The most noticeable change is increase in amplitude of the secondary negativity which can be observed after GABA application (Fig. 15f).

Probably, this second negativity is not a phenomenon characteristic of early postnatal ontogenesis for in some cases it may appear after GABA application in an adult

(Serbinenko, 1963). The fact is without question that in the early stages of postnatal ontogenesis (15–20 days) the secondary negativity may be revealed in its most marked form which is again, the result of the heterochronic growth of the synaptic organization of cells of the brain cortex.

We have focused our attention on another fact: how one can explain such dual action of GABA. Why does GABA block the only one negative potential while it activates the other one? From the point of view of current concepts about two types of synapses, depolarizing and hyperpolarizing, we would expect only blocking effect and in no case an activated one, *i.e.* the activation of the negative process. We did not find in the current literature any suitable data, so we have tried to form a theory as to nature of that phenomenon.

Our usual classification of the synaptic organization of the brain cortex is based on the parameter of the cell membrane polarization; but polarization, and depolarization especially of synaptic organizations depends completely on the metabolic process which develops in the membrane itself, as well as in the axoplasm. There arises then the question: are those metabolic processes which maintain polarization in different nervous cells and synapses, and which possess always the same electric signs always equal in their chemical nature? Our usual evaluation of these phenomena stops at the level of electric signs. Is that really enough?

The comparative physiological data convinced us that the chemical specificity of the synaptic activity may be essentially different in the presence of the same electric phenomena (Koshtojants, 1941). Thus we have data that the same electric phenomenon can be based on quite different metabolic processes with individual and specific chemical sensitivities.

From that very broad metabolic point of view, the paradoxical fact of the existence of different behavior of the two negative electric components in reference to the influence of the one and the same chemical agent, GABA is an interesting one.

Schematically these relationships may be represented as the following: there are two synaptic organizations with different specificities of chemical processes in the bodies of different cells or even on the membrane of the same cell. Such an assumption is

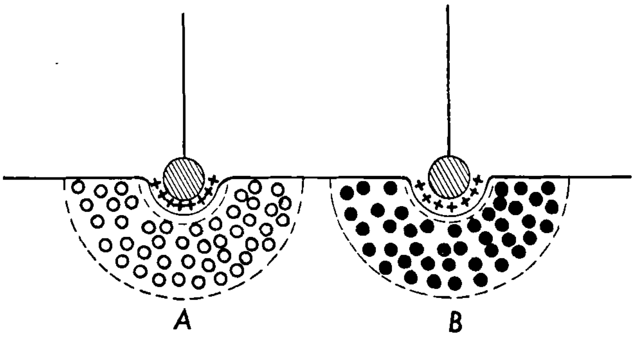

Fig. 18. Schema of the metabolic development of the subsynaptic processes providing the same negative electric effect on the cortex surface. A and B represent two examples of synapses with different specificities of cortical processes. + and — signs indicate membrane polarization; ○ and ● indicate different transmitter substances.

not difficult to accept if we take into consideration the extreme heterogeneity of the nervous cell membrane and its different synaptic organizations (Fig. 18).

It is also very important to stress that these facts give us a real opportunity to investigate those protoplasmic variations, on the basis of which the finest associative processes of the central nervous system are performed.

One may think that variable sensitivities of the nervous system toward pharmacological agents have in their nature the metabolic heterogeneity of different synaptic organizations. All these questions await solutions by investigations of neurologists, neurochemists and neurophysiologists.

## SUMMARY AND CONCLUSIONS

The data collected in our laboratory over a number of years gave us an opportunity to suggest that systemogenesis is a real regulator of the development of the brain structures and functions.

The development goes on all the time selectively and is accelerated in accordance with the earliest needed adaptation to the outside surroundings by the newborn animal. We see that the well-timed consolidation of the vitally needed functional systems of the organism is continuously monitored by the systemic initial arrangement, the growth and consolidation of the components of the functional system.

We also see that this heterochronic maturation of different components of the functional system takes place everywhere including the finest organizations — on the

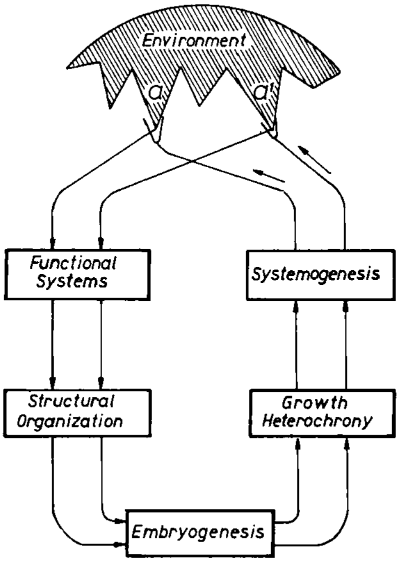

Fig. 19. Schema demonstrating the place of the systemogenesis in the evolutionary development of the adaptive functions of the newborn satisfying the demands of its ecology. Note that the ecological factors form the phylogenetic factors of the development in which embryogenesis performs correspondence of the newborn reactions to the peculiarities of its environments; 'a' and '$a^1$' symbolically express those ecological factors which demand immediate adjustment just after birth.

level of molecular combinations and in the processes of the selective and successive maturation of individual synaptic organizations, in particular, on the cortical level.

It is true that the systemogenetic type of the maturation and the growth is the most marked for those functional systems of the organism which must be mature exactly at the moment of birth. They are evidently inborn, the preparation for their consolidation is preformed, and in fact, in the process of the ontogenesis, they correspond demonstrably to the ecological factors of that species of animal (Fig. 19).

The combination of the components of later and finer organized functional systems on the basis of which different behavioral acts are formed is less easily demonstrated. In that case maturation and formation of new synaptic organizations of the brain in the presence of the completely mature peripheral working apparatus begin to play a leading role. Our first experience in the field of the investigation of the time of maturation, localization and quality of the synaptic organizations reveals opportunities for extremely inspiring investigations.

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