SOME NEW DEVELOPMENTS IN THE MORPHOPHYSIOLOGY OF THE CEREBRAL CORTEX

BY

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The study of the mechanism of the physiological and pathophysiological processes of the brain has for a long time occupied the attention of investigators. The work of I. P. Pavlov on conditioned reflexes has opened new ways to the understanding of the activities of the brain up to the most complicated ones—i.e., the highest nervous activities. There is no need to stress the importance of these experimental investigations, which furnish us with new ideas and methods for the better understanding of the cerebral processes, both normal and pathological, of man. A few examples of the work done will illustrate the position.

M. K. Petrova, one of the oldest pupils of Pavlov, succeeded in establishing in different dogs different types of nervous system with the precise characteristics of the various breeds. Petrova has furthermore ascertained that by inducing conditioned reflexes it is possible to produce experimentally in dogs nervous conditions which are characteristic of typical forms of neurosis. It is important to note, too, that she has ascertained that by the administration of a special dosage of bromine this experimentally produced neurosis can be completely cured.

Very interesting from the point of view of the influence of the cerebral cortex on the pathology of the organism are the experiments on conditioned reflexes in combination with the application of camphor. In the laboratories of Pavlov one of his pupils, Dolin, combined the use of the conditioning stimulant with the introduction into the organism of the dog of camphor, which, as is well known, causes convulsive epileptic fits. Having established the conditioned reflex through the introduction of camphor, Dolin succeeded, solely by means of the conditioning stimulant, without the introduction of camphor, in causing epileptic fits in the dog.

The investigations into the problem of the influence of the cerebral cortex upon the inner organs are, for medicine, in the broadest sense of the word, of particular importance. While up till now we have been able to speak only *a priori* of the influence of the "psyche" on somatic processes, the experimental investigations of K. M. Bukow and his pupils, using the methods of conditioned reflexes, have revealed definite physiological laws and the interdependence of the cerebral cortex and the inner organs—the heart, stomach, spleen, liver, urogenital organs, etc. These investigations show how, by causing certain conditioned reflexes in dogs, one can influence and alter the action of such organs as the liver, the kidneys, and the stomach. On the other hand, by a series of experiments, changes in the highest nervous activities of an animal, dependent on the condition of the inner organs, have been established. These experiments have shown the influence on the cerebral cortex of the impulses originating from the inner organs—in other words, the place which the most complex inner world of an animal has in its physiological behaviour has been established.

In these experiments it was found that, in causing conditioned reflexes or conditioned reflexive activity in an animal, new "temporary connexions" between the various sections of the central nervous system and the various organs and tissues of the organism are apparently created.

These investigations, in further developing the teaching of Pavlov on conditioned reflexes, have made it necessary to deal

with the question of the morphophysiological nature of these "temporary connexions" formed in the complicated processes of the brain. Knowledge of the mechanism of these processes and their morphophysiological relations would offer new possibilities for the identification of pathological symptoms in the brain.

Recent Electro-physiological Investigations

Of great importance for this research work are the recent electro-physiological investigations, particularly of the bio-electrical phenomena of the brain, and also the new data on the finest structural features of the cerebral cortex. Bio-electrical investigations (electro-encephalograms)—carried out in various laboratories of the Soviet Union by Sarkisov, Livanov, Russinov, and Steinberg; in England by Adrian, Matthews, Walter, Ultridge, and others; and in America by Lenox, Gibbs, Davis, and others—have opened up fresh possibilities of a dynamic conception of the delicate mechanism involved in brain activity.

The numerous investigations of the last 10 to 15 years have considerably enriched our knowledge of the electro-physiological mechanism of the various sections of the central and peripheral nervous system in both the normal and the pathological state. We have now definite conceptions of the chief characteristic peculiarities of the bio-electrical current curves of the cerebral cortex, of its various sections, of the finest laminae of the cortex, of the post-cortical formations, of the peripheral nervous system, and so on. A series of investigations have also been made on bio-currents in the state of waking, sleeping, hypnosis, and so on.

Very interesting are the investigations into the bio-electrical manifestations of the brain under different influences. We were able to establish, for instance, the laws governing the variations in these manifestations under the influence of various narcotic substances—e.g., strychnine, morphine, and others (Sarkisov). It is important to note, for instance, the following fact. As we know, morphine has a depressing effect on the central nervous system. Yet our electro-encephalograms have shown that it acts differently on each region of the cerebral cortex, and that in the different stages of narcosis the potentials of the various sections of the cortex and the post-cortex are dissimilar.

Our investigations, and those of others, have shown numerous changes of the normal brain potentials in cases of mental disease—e.g., epilepsy, schizophrenia, manic-depressive conditions, and so on—and also as a result of various changes in metabolism. Of great importance also is the study of the bio-electrical manifestations in the case of organic diseases of the brain. Characteristic alterations of the ordinary encephalogram occur, for instance, in cases of tumours of the brain. Of considerable and practical interest, in this respect, are the investigations of Grey Walter, who has suggested a novel method of using bio-currents for ascertaining the seat of disease in a case of brain tumour. Our investigations of the bio-electrical phenomena in the presence of artificially caused tumours of the brain in animals have produced curious results. It was found that the bio-electrical phenomena are directly dependent on the seat and also on the character or nature of the tumour. We have produced tumours in the brain of rabbits experimentally, and have carried out series of investigations on these animals by

means of electro-encephalograms. The tumours were muscular, "paraffinous," and "cancerous."

These investigations (Sarkisov and Penzik—published in 1940) revealed characteristic slow vibrations of the bio-electric potentials near the tumour. We noticed alterations of a somewhat different character at a considerable distance from the tumour, and it is particularly necessary to emphasize that the bio-currents of the brain vary according to the kind of tumour.

Fig. 1 shows an electro-encephalogram of a tumorous human brain with characteristically slow vibrations of 4 to 5 per second, instead of 10 to 12 vibrations in the normal state.

FIG. 1.—An electro-encephalogram of a tumorous human brain, 13/10/43. A, left temporal; B, right temporal.

FIG. 2.—Same brain as Fig. 1. A, left occipital; B, right occipital. Recording, 30/10/43; operation, 22/11/43. Follicular abscess in right parietal area. Restricted injury of the cortex and of the white substance of the upper temporal area. Time recording, 0.2 sec.

FIG. 3.—Same brain as Figs. 1 and 2. A, left central; B, right central. Time recording, 0.2 sec.

FIG. 4.—A, left occipital; B, right occipital. Deep injury of the left premotor region reaching the subcortical ganglia, with a metal fragment in the left frontal zone. Cicatrization not complicated by the purulent process. Time recording, 0.2 sec.

In our laboratories, Russinov, Livanov, Preobrashenskaya, and Lurya have during the war done a considerable number of electro-encephalograms (more than 1,300) in cases of various forms of cranium-brain wounds, and particularly of abscesses of the brain. The curves in Fig. 2 characterize the bio-electrical currents of the occipital regions of the brain in cases of various diseases of the parietal area. In Fig. 3 the curves depict the variations in the bio-electrical currents of the central region (right and left) of the same brain. Fig. 4 shows the curves of the right and left occipital regions of the injured cranium. The deep wound is in the left premotor region (reaching to the subcortical ganglia, with a metallic fragment), and in the left frontal region with a cicatrix (without abscess).

These examples should suffice to prove that the electro-encephalograms represent the separate nervous processes of the tissue of the brain in both normal and pathological states. However, it is necessary to emphasize that in each single case much in the electro-encephalogram is as yet obscure—that is, not accessible to analysis in the light of our physiological knowledge. Still, the data of the electro-encephalograms undoubtedly aid the examination of the various aspects of the complex brain processes. By means of the encephalogram we are now able, in a considerable percentage of cases, to pronounce on the character and periods of epilepsy, on tumours and abscesses, on the seat of a disease; and we can speak of a disease in the sense of its being local, and so on.

I have no space here to deal with another aspect of the electro-encephalographic investigation—the functions of the nervous tissue, central and peripheral, the laws governing the processes of excitation and inhibition, and other questions. Much has been done in this field in the Cambridge laboratories (Adrian) and in the Moscow Brain Institute (Livanov), and by others.

Physiology of the Brain

In connexion with our new ideas on the physiology of the most differentiated nervous activity and on the physiology and pathology of the cerebral cortex, our knowledge of the minute morphological organizations and connexions of the cortex is also broadening. We have now considerable knowledge of the brain, and especially of the cortical formations and the various architectonic cellular structures of the most highly organized matter of that organ. At the Moscow Brain Institute during the last 15 to 20 years specialized investigations in the phylogenesis (pertaining to a species) and ontogenesis (individual development) of the brain, and particularly of the cerebral cortex, have considerably extended our knowledge of its complex organization. Specific laws have been established governing the formation of the minute architectonic structures of the cortex and the cerebrum as a whole, in the various stages of their phylogenetic and ontogenetic development. The results of these investigations have been published in the form of separate works and monographs by the research workers at the Moscow Brain Institute—Philimonoff, Sarkisov, Kolonova, Blinkov, Preobrashenskaya, and others.

In emphasizing these achievements of modern neurology it may be said that our conceptions of the architectonic features of the cerebral cortex do not suffice to reveal the fundamental morphophysiological mechanism of the cortical function. In order to extend further our knowledge of the morphophysiological mechanism of the functions of the brain it is necessary to study the multifariousness of the cellular architecture together with the picture of the elaborate and complex intercellular connexions and their dynamics.

Structure of the Cerebral Cortex

The methods of architectonic investigation have been of great use in establishing the general features of the structure of the cerebral cortex, its division into separate areas and regions according to the character of the various cellular and fibroid laminae, and so on. These investigations play a particular part in solving one of the fundamental problems of modern neurology—i.e., the problem of localization. The data obtained in this way are the basis for further advancement in the study of the brain. It will be necessary, however, to ascertain how the formation of the neurons of the cortex in their entirety proceeds—i.e., to trace the development of the different types of neural cells of the cortex with all their appendices; that is, the dendrites and their axons. Furthermore, it is necessary to discover how in the process of development the connexions between the various groups of neurons establish themselves inside the individual cortical formations, as well as between the various cortical regions. What I have in mind is the significance of the most delicate connexions—i.e., the synapses in the cerebral cortex. The treatment of this question is indispensable to the understanding of the intimate physiological and pathological processes of the brain.

It is well known that the method of Golgi provides the possibility for this study. It is particularly necessary to emphasize that up till now the finest connexions between the neurons in the cortex, as distinct from the synapses of the peripheral

nervous system and, to a certain degree, of the lower section of the central (cerebrospinal) system, have been studied quite inadequately, if one leaves out of account the well-known work of Ramón y Cajal and others. This is due, in the first place, to the enormous difficulties arising in the study of the synaptic mechanism, especially in the cortex—as the most complicated part of the cerebral nervous system. These difficulties arise particularly in the study of the cerebral cortex of an adult. Therefore it should be expedient to study, by the method of Golgi, the cerebral cortex in ontogenesis, when the intercellular connexions and their structural features are comparatively simple and more easily accessible.

So far as we know, the study of the ontogenetic development of the cerebral cortex by Golgi's method has not yet been fully

in the shape of the cells, and particularly in the shape of the appendices, seems even more distinct.

The next differentiation of these connexions in an embryo of 8 months is of great interest with regard to those of the cortical structure. In Figs. 7 and 8 are shown the formation of the intercellular connexions of the frontal, lower-sinciput, and postcentral regions. One notices very fine cellular appendices of extraordinary multiformity and peculiarity in the three regions of the cortex in the embryo of 8 months; in the frontal region (precentral and motorial), strongly developed cells with significant vertical appendices. Contrary to this, the cells in the postcentral, and especially in the lower-sinciput (associatory), region of the cortex are considerably smaller and at the same time their appendices are distinguished by greater delicacy and multiformity. And, what is most important, they are distinguished by significant appendices extending laterally—i.e., in a horizontal direction—which obviously is largely

FIG. 5.—Four-lunar-months foetus. Above, formation of the precentral cortex (area 4). Below, formation of the optical cortex (area 17).

carried out. (Cajal investigated chiefly the brain of the newborn and in the first months after birth.) The first to start these researches was Dr. G. I. Polyakov, in the Moscow Brain Institute. It is not my aim to give a full account of his investigations into the study of the functioning of the cerebral cortex. Polyakov is about to publish his results in a monograph. Still,

FIG. 6.—Five-and-a-half-months foetus. Left, precentral area 4; right, postcentral area 1.

I would like to give at least a few illustrations from his studies, so as to convey some idea of the importance of the data obtained.

Fig. 5 shows the picture of the cellular structure in an embryo of 4 lunar months, where the upper lamina of the cells has been taken from the precentral region, and the lower lamina from the optical cortex—i.e., from the occipital pole of the brain. We notice here, in the earliest stage of the organization of the cortical cellular elements of neuroblasts, an apparently similar picture of the cells and their appendix in the precentral and optical regions. Still, it is not difficult, even to the naked eye, to notice, already in this stage, the differences in the shape of the cells and the characteristics of their appendices.

Fig. 6 represents the organization of the cortical structure in an embryo of 5½ months. To the left is the cortex from the precentral region; to the right, from the postcentral region. Here the difference

FIG. 7.—Eight-lunar-months foetus. Precentral agranular cortex (area 4).

FIG. 8.—Eight-lunar-months foetus. Middle part of the cross-section of the cortex. Above, lower parietal area 39; below, postcentral area 1.

characteristic of the receptive type of cortex. These fine neuron formations are obviously best distinguishable in the last month of uterine gestation.

Conclusion

I shall not dwell here on a full description of all the details of this amazingly diverse picture of the cellular structures and their appendices. They will be dealt with separately by Dr. Polyakov. Particularly important are the examination and the establishment of these structures in the adult. The examples given above convey some idea of the new data concerning the finest and most complicated structural features of the cerebral cortex. There is no need to prove that on these data the processes of the cerebral cortex in the normal and pathological state are based. Can one doubt the intimate physiological part

which these minute intercellular formations play? Can one doubt that in various pathological affections of the brain as a whole, and of the cerebral cortex in particular, these delicate intercellular structures are the first to be exposed to disease, being the most vulnerable? Of special interest are these data from the point of view of pathological changes of the brain in the so-called "functional diseases" of the nervous system. Obviously, in various "functional diseases," and also in many cases of psychosis, where we are not in a position to identify definite changes in cellular structure, one must assume first of all an affection of these intercellular connexions. The examination of these amazingly fine and diverse structural formations of the cortex presents us with more problems, the resolving of which is one of the chief tasks of modern neurology and neurophysiology. The work of the research staff of the Moscow Brain Institute is dedicated to the study of these questions.

Summary

The classical method of Pavlov in conditioned reflexes enriches considerably our knowledge and understanding of the part which the cortex plays in the most differentiated nervous activity and of the connexion of the cortex with the functions of the inner organs. The novel method of bio-electrical currents, and the exploration of the finest morphological structures of the cortex and its intercellular connexions, open new ways and opportunities for establishing the laws governing the fundamental morphophysiological mechanism of the complicated activity of the cerebral cortex.

DERMATITIS FROM WEARING ARMY SPECTACLES

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Although dermatitis due to the dye in artificial-shell glasses is fairly well known (Thistlethwaite, 1943; Gray, 1943) there has been little mention of a similar dermatitis resulting from the wearing of spectacles with metal frames, since its inconvenience is easily avoided under normal civilian conditions. Between December, 1941, and March, 1942, six cases of such a condition were seen by us at a military clinic in Scotland.

The Army spectacle frames (Mk. III) are made of "nickel silver" plated with nickel. Nickel silver has the advantage of useful corrosion-resisting properties; it is an alloy of nickel, copper, and zinc in the following proportions:

Part of Frame	Nickel	Copper	Zinc
Bridge ..	25%	60%-65%	10%-15%
End-pieces ..	25%	60%-65%	10%-15%
Cables ..	12%	60%-65%	23%-28%
Eye-wires ..	12%	60%-65%	23%-28%
Butts ..	10%	60%-65%	25%-30%

After manufacture the frames are given a solid nickel plating. It will be noted that the percentage of copper does not vary: the physical properties of ductility, hardness, etc., depend on the relative proportions of nickel and zinc. Common impurities—sulphur, lead, iron, and mercury—are all harmful in the alloy, and to avoid them the raw materials used in the casting consist only of pure nickel, electrolytic copper, and electrolytic zinc. Samples of each of these substances as well as the alloy, and alloy finally plated with nickel, were supplied by the metallurgists for the purpose of a patch test.

The physical state of the metal is of some interest. In the first place the raw material used is dead soft and therefore in an amorphous state. In the case of the eye-wires this condition is not greatly changed, as the only process is that of rolling and cutting. However, in the case of all other components, striking and reducing operations are carried out, and the metal must therefore be in a more or less crystalline state as a result.

A study of dermatological literature shows that dermatitis is not uncommon in the nickel industry (Blaschko, 1889; Landsteiner, 1924; Bulmer and Mackenzie, 1926; White, 1928; Jadassohn and Schaaf, 1929; Stauffer, 1931; Goldman, 1933; Stewart, 1933), but the first mention of sensitivity to spectacle frames containing nickel seems to be that of Lain (1931), followed by Fox (1933), Urbach (1935), Kristjansen (1937), and Löwenstein (1938).

Lain describes three cases of dermatitis occurring on the temples and ears of men wearing spectacles. In each case the frames were made of so-called "white gold," reported as an alloy of gold, copper, and nickel. In his first case the eruption occurred also across the bridge of the nose, but in the other two the bridge of the spectacles was of a different metal, and the eruption occurred only on the temples and ears. On his inquiry, the optical company manufacturing the glasses instituted a research in their laboratory and reported as follows:

"The trouble seems to be due largely to nickel that is found in white gold alloy. We believe that the action is largely electrolytic; that is, an electrolytic battery action is produced when there are dissimilar metals and an acid (or in some cases an alkaline) fluid is present and in contact with these dissimilar metals. When the perspiration, which is an electrolyte, acts upon the base, metal salts are formed, and such action is more pronounced in the presence of heat. It is probably a salt of the nickel that causes the irritation, which seems to be analogous to a trouble that is present in the nickel-plating industry called commonly 'nickel itch.'"

The case quoted by Fox (1933) was sensitive to both spectacle frames and a wrist-watch made of this white gold.

Goldman in 1933 surveyed the literature up to then and added two cases (not due to the wearing of spectacles) in nickel-workers. Citing the cases of Lain and Fox, he suggests that, in spite of strong presumptive evidence, the failure to perform eliminative patch tests had not positively incriminated the nickel. Both his cases gave a history of previous allergic disturbances (urticaria and hay-fever). Both gave strong responses to patch tests with nickel but negative to the closely allied metal, cobalt, thus showing a strong specificity to the nickel. This specificity, associated with the abnormally short latent periods in his cases (2 days and 3 days) before the appearance of the intolerance, suggests that the hypersensitivity may have been gained by: (1) inherited or congenital idiosyncrasy; (2) exceptionally rapid sensitization (the normal interval is 8 to 10 days); or (3) repeated brief contact with the metal (perhaps as nickel coins or suspender buckles) without appreciable clinical manifestation—the so-called "silent sensitization." Urbach (1935) described a case of sensitivity to nickel-framed spectacles. A patch test with an Austrian schilling, which contains a large percentage of nickel, gave a positive reaction. As the schilling contains other metals, this is of course insufficient as an eliminative test.

That this is not a very infrequent problem when the wearing of nickel-framed spectacles is necessary is shown by the fact that six cases were seen by us in a small area within three months and that similar cases (Bettley and Lyle, personal communication) have occurred in other parts of the country.

Case I

Pte. H. G.; Pioneer, aged 31; single. Received glasses Jan., 1941: myopia, -9.00 dioptres. Within a month a reddish patch developed where the spectacles touched the skin. After a time wearing the glasses for 5 to 10 minutes caused recurrence after a latent period of 15 to 30 hours. Since in spite of treatment it kept recurring on resumption of the spectacles, he was referred to us.

Examination on Dec. 2 revealed vesicular eczematous dermatitis wherever the spectacles touched the skin—behind the ears, over the temples and zygoma, on cheeks eyebrows, and sides of the nose where the pads touched. There was no history of drug sensitivity or other allergic phenomena. Mild pityriasis sicca capitis was present.

Treatment.—The skin healed with calamine lotion, but only when the spectacles were left off. A patch test was performed in the interscapular area with part of the frames, and gave a marked positive reaction in 48 hours. A control patch was negative. The following expedients were then tried: (1) A new pair of glasses: skin broke down in six hours. (2) Zinc adhesive plaster applied over parts of frames in contact with skin: lesion recurred. (3) Cellulose acetate varnish painted on to frames: successfully prevented recurrence, but started to peel off within four days. (4) Cycle-tyre valve tubing pulled over flexible ear-curls and pads, xylonite half-