THE INFLUENCE OF REMOVAL OF THE CEREBRAL CORTEX AND CERTAIN PHARMACOLOGICAL SUBSTANCES ON THE DEVELOPMENT AND COURSE OF FEVER*

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The present work is devoted to a study of the role of the higher divisions of the central nervous system in the development of fever. The role of the cerebral cortex in pathological changes in thermoregulation has not yet been satisfactorily studied; exact data on the role of the cortex in fever are almost completely lacking, both with respect to its "actuating" and its "adjusting" significance. There is, however, no doubt that in an intact organism, as well as under pathological conditions, the cerebral cortex plays an important role in the regulation of all of the physiological functions of the organism.

V. M. Bekhterev [1], S. P. Botkin [2], I. L. Stychinsky [6] et al. have admitted the existence of so-called "psychogenic" fevers; a febrile increase in temperature was even obtained during hypnosis [5, 8 et al.]. It is also well-known that even mild narcosis deprives animals of their pyretic capacity [4, 7, 10 et al.]. V. Skovronsky [9] observed a sharper temperature increase among decorticated rabbits in response to intravenous injection of β-tetrahydronaphthylamine in comparison with experiments on intact animals.

In the present research a study was made of the influence of removal of the cerebral cortex on the development and course of fever (at different periods after decortication). In a number of comparative experiments a study was also made of the influence of phenocoll, bromine and sodium amytal on the development of fever among intact (normal) and decorticated dogs.

EXPERIMENTAL METHODS

Experiments were conducted on 5 dogs with cerebral cortex removed (Dezi and Lisa, about 4-5 years old; Diana, Tsygan and Mars, about 1-$1^1/_2$ years old) and on intact animals (Tuzik and Rezvy). Previously the daily fluctuations in rectal temperature of each dog had been studied; the development of the fever reaction (according to P. V. Vasilyev's method [3]) was studied before decortication (control experiments) and at different periods after unilateral and bilateral removal of the cerebral cortex.

Phenocoll was given to the dogs per os (in a dose of 0.01 g) dissolved in milk diluted by half (by 50 ml) 30-60 minutes before fever was induced; sodium bromide was administered for a week prior to the experiment and on the day of the experiment (60 minutes before its start) in doses of 0.1 and 0.5 g, also per os in milk diluted with water. Sodium amytal was injected subcutaneously in the amount of 0.05 g per kg of the animal's weight. Decortication was performed in two steps; first the cortex of the left cerebral hemisphere was removed by the usual method, and that of the right hemisphere after 2-4 months.** The brains of the animals were

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subjected to a histological examination for a control of the completeness of the removal of the cerebral cortex.

RESULTS

The influence of removal of the cerebral cortex on the course of fever. The experiments of this series were conducted on 3 dogs—Dezi, Diana and Tsygan. The duration of life of the dogs after the second operation amounted to: 16 days (Dezi), 152 days (Tsygan) and 180 days (Diana). The animals finally died from general emaciation or during an attack of convulsive fits (Dezi). Following unilateral removal of the cortex, for the first month some hyperthermia was noted among the dogs, as well as greater than normal fluctuations in body temperature in the course of a day. The capacity for the pyretic state initially appeared somewhat reduced, but was quickly (after 1-2 months) restored.

Following bilateral removal of the cerebral cortex, during the first week severe motor excitation was noted among the animals, as well as a certain rise in temperature (initially), then a lowering (after 7-12 days) of temperature to the initial level. At first the animals did not take food (they were fed through tubes), did not react to the smell of meat or to sound and light irritations and moved (after 7-8 days) with a pronounced declination to the left (the animals executed a semicircle, striking objects encountered in the way). A rapid alternation was noted between a light sleep and being wide awake. On the subsequent days following the operation, an equestrian type movement was observed in walking; the animals reacted weakly to sound (a whistle or clapping of the hands) and found their food with great difficulty.

Upon dissection of Diana, for example, the following was detected: on the site of the occipital and frontal lobes—thickened connective tissue formations; in the region of the gyrus sylvioanticus and gyrus ectosylvius, the gyrus coronarius and gyrus suprasylvius—medial displacement of the internal surface of the temporal muscle; along the medial line (on both sides of the sinus sagittalis)—negligible scraps of cortical tissue delimited below from the subcortical formations by a thick connective tissue scar and above by a greatly expanded, thickened dura mater and pia mater, approaching cartilaginous tissue in consistency. Changes visible to the eye were not noted in the subcortical formations, in the mesencephalon, cerebellum and medulla oblongata. Microscopic examination (with Prof. Yu. M. Zhabotinsky's consultation) of a section from the cortical scraps (using Nissl's stain) revealed hyperemia both in all the cortical layers and in the adjacent white matter (the picture of stasis of the vessels). Altered nuclei were visible in a large portion of the nerve cells; in the pia mater a significant accumulation of hemosiderin was visible, the greater portion of which was located in macrophages, edematous modifications of nerve cells.

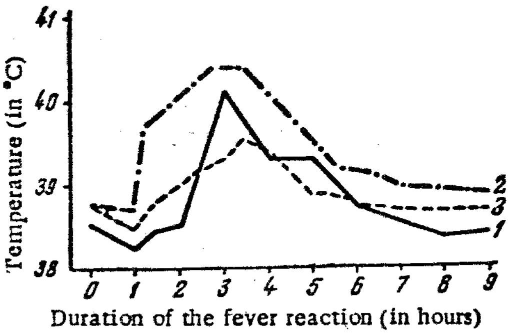

Fig. 1. The course of fever in the dog Tsygan. 1) fever reaction before the operation; 2) 10 days after bilateral removal of the cerebral cortex; 3) a month after the operation.

Following bilateral removal of the cortex, typical fever was observed 10-15 days after the operation; it was moreover, more acute (in Tsygan) in comparison with the fever in the animals subjected to unilateral removal of the cerebral cortex. When fever was experimentally induced 1, $1^1/_2$, 2, $2^1/_2$, 3 and 4 months after the operation, periodic observation revealed now the strengthening, now the weakening, of the course of the fever reaction (Fig. 1) down to temporary loss of capacity for the pyretic state. The most marked strengthening of the course of the fever was observed in experiments in which turpentine was injected into decorticated animals 2 and $2^1/_2$ months after the operation (Fig. 2).

The influence of certain pharmacological substances on the course of the fever reaction among decorticated animals. In all, 14 experiments were performed on the decorticated animals as well as 22 control experiments on intact animals: of this number, 5 experiments with phenocoll were conducted on decorticated dogs and 6 control experiments on intact dogs. The most conspicuous feature of these experiments was the difference in the behavior of intact and decorticated animals after injection of a single dose of phenocoll (10 mg): among the intact dogs there was mildly expressed excitation and a temperature rise of 0.2-0.5°; among the decorticated animals there was clearly expressed motor excitation (a revival of equestrian movements), loud barking directly after receiving the preparation, a sharper rise in temperature (up to 2.2° in Mars, for example). A more rapid and more acute development of the fever reaction was noted in the control experiments than in the experiments without phenocoll. The duration of the fever reaction did not change noticeably. These data confirmed the results of the special experiments of Daudova, who studied the influence of phenocoll and bromine on the development of fever reaction. In the experiments on decorticated animals phenocoll also exerted a stimulating influence on the development of fever, an even clearer one in individual cases (Mars). Previous administration of sodium bromide (in a dose of 0.5 g daily for 7 days and on the day of the experiment), as in Daudova's experiments, weakened somewhat the extent of the fever reaction among the intact animals; a 0.1 g dose of sodium bromide, on the other hand, somewhat strengthened its course.

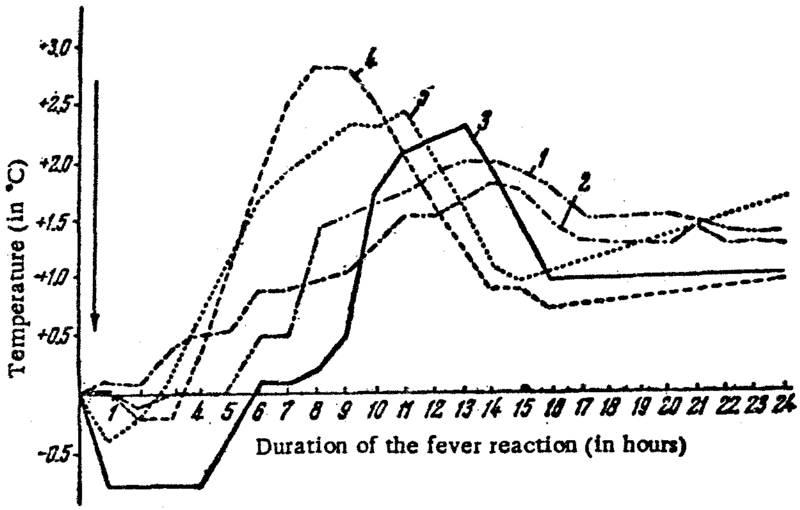

Fig. 2. The course of fever in dogs (Tsygan and Diana) when 0.5 ml of turpentine was injected subcutaneously.
1, 2, 3) fever reaction in intact dogs (Tobik, Rezvy and Lisa); 4, 5) the same in decorticated dogs 2 months (Tsygan) and $2^1/_2$ months (Diana) after the operation.

In two experiments on decorticated animals injection of sodium bromide in a dose of 0.1 g also increased the fever somewhat, while, on the other hand, there was observed a negligible decrease in fever when this substance was given in a dose of 0.5 g.

The experiments conducted with bromine are not, of course, sufficient for any conclusions to be drawn. If they receive further confirmation in the future, they could serve to point out that bromine can exert a known influence even directly on the subcortex.

Five experiments were conducted with sodium amytal on decorticated animals as well as 12 control experiments.

After injection of sodium amytal (subcutaneously in the amount of 0.05 g per kg of body weight) a lowering of temperature was noted among the intact animals (2° after 5-6 hours following injection); sleep began 1-2 hours after injection of sodium amytal and continued for 9-10 hours; injection of the same dose of sodium amytal into the decorticated dogs produced in them, at first, sudden motor excitation and a more rapid (within 15-30 minutes) onset of sleep; the sleep, however, was less deep, although more prolonged (up to 12 hours); hypothermia was also clearly evident, as among the intact dogs.

The difference in the reactions of the decorticated dogs stands out, particularly sharply in a comparison of the effect of the injection of a pyrogenic agent against a background of amytal sleep before and after the operation.

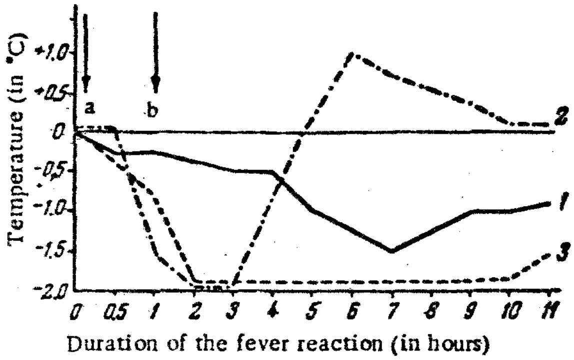

Fig. 3. The course of the fever reaction in a dog with cerebral cortex removed (Mars) against a background of narcotic sleep (sodium amytal – 0.05 g/kg of body weight subcutaneously). 1) temperature reaction in response to injection of pyrogen against a background of narcotic sleep before the operation; 2) the same after injection of pyrogen during amytal sleep after removal of the cerebral cortex; 3) the same after injection of sodium amytal without pyrogen; ↓ a) injection of sodium amytal; ↓ b) injection of pyrogen (B. mesenterium).

Thus in the dog Lisa the maximum temperature rise (after previous hypothermia) before the operation amounted to 0.2° above the initial temperature; after the operation it was 1.2°. In Mars before the operation the increase in body temperature, when pyrogen was given against a background of narcotic sleep, was clear, but the temperature did not attain the initial (prior to sleep) level; in two experiments conducted after the operation, Mars' body temperature rose above the initial temperature by 0.9 and 2° (Fig. 3).

Summing up the experiments studying fever among dogs with cerebral cortex removed, one arrives at the conclusion that the fever reaction, in principle an unconditioned reflex reaction of the subcortex, is at the same time, given an entire organism, under the substantial influence of the cerebral cortex. This fact is attested to by the significant changes in the course of the fever reaction which are produced by eliminating the functional influence of the cerebral cortex on the sections underlying it.

The instability of the course of the fever reaction (now a strengthening, now a weakening) in separate periods of the lives of decorticated animals is apparently explained by processes of necrosis and cicatrization, which develop continually on the damaged surface of the brain and interfere with the activity of the subcortex, i.e., by "secondary" disturbances to the activity of the subcortex (according to I. P. Pavlov).

SUMMARY

The influence on the development and course of fever during narcotic sleep in cases of extirpation of the cortex has been studied.

Studies of the influence of phenocoll, bromide and sodium amytal on the development and course of fever in intact and decorticated dogs prove the significance of the functional condition of the higher regions of the central nervous system in the development of fever reactions and indicate a possibility of a control of its course.

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