THE PARABIOTIC NATURE OF THE REACTION OF THE NERVOUS SYSTEM DURING THE ACTION OF GAS GANGRENE TOXIN

S. V. Magaeva

Laboratory of Infectious Pathology (Head—Corresponding Member AMN SSSR Prof. A. Ya. Alymov, Scientific Director—Dr. Med. Sci. O. Ya. Ostryi) of the Institute of Normal and Pathological Physiology (Director—Active Member AMN SSSR V. N. Chernigovskii), AMN SSSR, Moscow

(Presented by Active Member AMN SSSR V. N. Chernigovskii)

Translated from Byulleten' éksperimental'noi biologii i meditsiny Vol. 49, No. 2, pp. 68-72, February, 1960.

Original article submitted February 18, 1959.

An analysis of the clinical picture of gas gangrene gives grounds for the assumption that the bacterial toxins have a paralyzing action on the centers of the medulla oblongata [1-3, 9, 10].

Several investigations have shown [4-7, and others] that the infectious toxicosis in gas gangrene is brought about by two fundamental nervous mechanisms: reflex and "automatic." The nervous origin of the toxic manifestations is shown particularly clearly by the extreme reactivity of the central nervous system to the bacterial toxin of the causative agent of gas gangrene and by the possibility of the prevention of the development of these toxic manifestations by surgical division of the reflex arc at any link, by lowering the reactivity of the nervous system by pharmacological methods or, finally, by protecting the central nervous system with specific antitoxic serum. The authors cited above largely investigated the reflex mechanism of the pathological process: The summational principle of its mechanism was revealed and the importance of the various divisions of the reflex arc in the development of the disease was demonstrated.

The results obtained dealt a severe blow to the widely held local hypothesis of the toxic manifestations affecting the organs in gas gangrene [8, 11, 12, and others].

It accordingly became necessary to investigate the nature and the special features of the reaction of the nervous system to the action of the toxins in order to develop further the study of the pathogenesis of gas gangrene, and this formed the purpose of our present research.

METHOD AND RESULTS

The work was undertaken on white rats and frogs. We used the toxin of one of the anaerobes of the main "group of four" (A. V. Mel'nikov)—vibrion septique (Series 405 and 406 from the N. F. Gamaleya Institute of Epidemiology and Microbiology).

The reaction of the nervous system to the action of the toxin was investigated initially in experiments on a peripheral nerve.

Liquid toxin (4 mg/0.1 ml) was applied to the sciatic nerve by means of a cotton wool swab or by injection of the toxin (0.4 mg in 0.02 ml) beneath the membrane of the nerve trunk. An insulating polyethylene film was placed beneath the nerve. The changes in the functional properties of the nerve were investigated in acute experiments by the method of parabiosis, as adopted by N. E. Vvedenskii's school. Recordings were made of the reaction of the gastrocnemius muscle to stimulation of the sciatic nerve by an induction current, using electrodes situated in the area affected by the toxin or proximally to it.

The action of the toxin of vibrion septique on the sciatic nerve was shown by disturbances of the afferent and efferent innervation of the limb, lasting several days. The muscles of the affected limb were atonic; the limb was not included in the act of locomotion. The animal did not react to nociceptive stimulation of the skin in the region of the 4th-5th digits.

The experiments showed that the changes undergone by the excitation of a peripheral nerve after the application of toxin to it have the characteristic three phases of the process of parabiosis. In the first phase, the excitation of the nerve fell by 7-10% in the course of 5-10 minutes; in the second phase it rose by 10-15% in the course of 10-15 minutes, and in the third phase it again fell, this time by 45-90% in the course of 40-60 minutes (Fig. 1, a).

The phase of the secondary fall in excitation was most characteristic of a nerve affected by toxin, and developed with the typical stages of parabiosis, of which

the most constant and prolonged was the stage of equilibration. The reaction of "inhibition immediately after excitation" was often apparent. The first two phases of parabiosis were inconstant and were not shown after injection of the toxin beneath the membrane of the nerve trunk.

Investigation of the functional properties of the nerve, affected by toxin, at various intervals after injection of toxin beneath its membrane showed the presence of lowered excitation and of stages of parabiosis for 8-10 days, with gradual restoration of the excitation and conduction of the nerve. Analysis of the changes in the physiological lability of the nerve in the third phase of its reaction to the action of toxin was undertaken by the usual method of electrotonic change in the functions. A constant current was applied by means of Dubois-Raymond nonpolarizing electrodes. The active pole of the current was situated in the altered area of the nerve, and the indifferent pole in the tibial muscles of the leg. A layer of insulating material was placed beneath the nerve.

The creation of an anode in the affected area of the nerve in 11 of the 19 experiments briefly restored the conduction of the nerve (at a current strength of 0.4-0.8 ma). The cathode intensified the parabiotic process (Fig. 1).

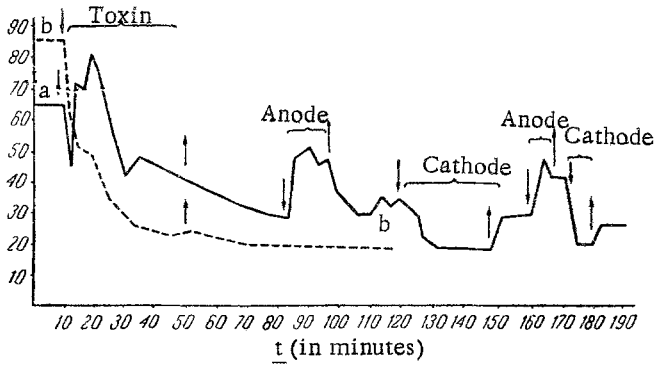

Fig. 1. Change in the excitation of a nerve when affected by toxin. a—Changes in the excitation of the sciatic nerve, and the effect of the electrode on the alteration of the properties of the nerve; b—changes in the excitation of the peripheral end of the undivided nerve. Along the vertical axis, the threshold of stimulation of the nerve (in divisions of the induction scale).

The character of the electrotonic changes in the functions of the nerve affected by toxin and the presence of stages of parabiosis were evidence of lowered lability in the most characteristic (the third) phase of the reaction of the nerve to the toxin of vibrion septique.

The experiments showed that the subordinating effect of the central nervous system and the anelectrotonic influence on the course of the parabiosis and in this particular form of nerve lesion were in the same direction. Parabiosis of the divided nerve developed much more quickly after the application of toxin than did the reaction of the subordinated nerve, and took place without the manifestation of the first two phases of the process (Fig. 1, b).

The reaction of the myoneural synapse to the action of the toxin was investigated in experiments in which toxin was injected into the proximal portions of the gastrocnemius muscle and the reactions of the muscle to indirect and direct stimulation were recorded. The experiments showed a rapid disturbance of the conductivity of the myoneural synapse under the influence of the toxin, while the excitation of the muscle was itself preserved for some time.

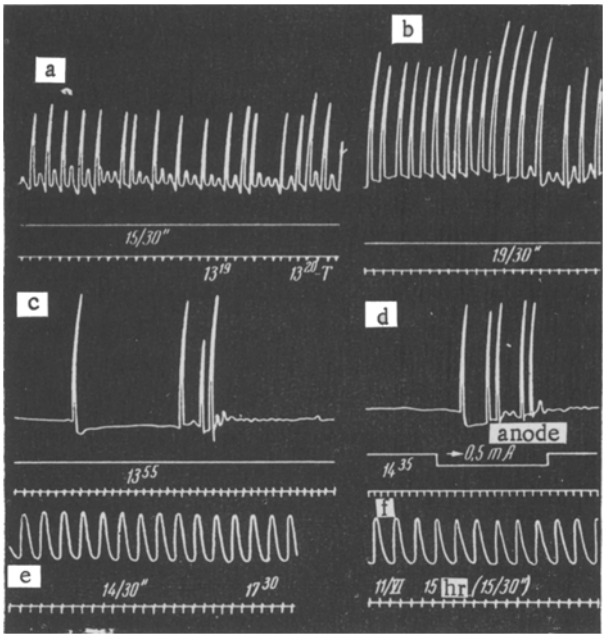

Fig. 2. Changes in the respiratory movements and the mechanocardiogram of a frog after the application of toxin to the medulla oblongata. a—Normal respiratory movements; b—changes in respiration 3 minutes after application of the toxin to the medulla oblongata; c—changes in respiration after 30 minutes; d—restoration of respiration after the creation of anelectro-tonus in the region of the medulla oblogata at the 32nd minute of cessation of pulmonary respiration; e—mechanocardiogram of the frog 3½ hours after cessation of pulmonary respiration; f—mechanocardiogram on the 3rd day after cessation of pulmonary respiration.

The reaction of the centers of the spinal cord and medulla to the action of the test toxin was studied in experiments on frogs.

The action of toxin on the centers of the spinal cord was brought about by applying the toxin to the outer surface of the cord by means of a cotton wool swab (2 mg in 0.1 ml). Recordings were made of the reflex reaction of the gastrocnemius muscle after stimulation of the central end of the tibial nerve with an induction current.

The experiments showed that, after application of toxin to the spinal cord, a parabiotic reaction developed, with features as described above.

The fact that the frog can cutaneously compensate for pulmonary respiration enabled us to investigate advanced stages of changes in the central regulation of respiration and the activity of the heart.

These investigations were carried out by applying the toxin (0.4 g/0.1 ml) to the exposed medulla oblongata or by injection of the toxin into the forebrain. Recordings were made of the respiratory movements of the buccal membrane.

After the action of the toxin on the brain, in several cases the rate of pulmonary respiration was raised and its strength was increased. In all the experiments periodic respiration developed 40-60 minutes after administration of the toxin, after which complete cessation of the respiratory movements ensued (Fig. 2).

The immobility of the animal, the atony of the skeletal musculature, and the absence of a motor defensive reaction to nociceptive stimulation were obvious evidence of irradiation of inhibition from the brain centers to the underlying divisions of the central nervous system.

After the complete cessation of respiratory movements, the activity of the heart, according to the data from the mechanogram, underwent no essential changes and its rate was gradually slowed on the 3rd-5th day. The frog could survive from 3 to 7 days, right until death, in a state of profound inhibition of the centers of pulmonary respiration. Analogous changes in respiration took place after injection of the toxin (2.8 mg in 0.1 ml) into the dorsal lymph sac of the frog, which indicated that some degree of similarity existed between the reaction of the animal to the application of toxin to the medulla oblongata and the effect produced by toxin circulating in the body. The rhythmic activity of the respiratory center, when inhibited by toxin, could be restored for a short time by stimulation of the skin of the animal in the first 5-7 minutes after cessation of respiration.

We also investigated the possibility of the electrotonic restoration of respiration. For this purpose the swab with the toxin was removed after respiration had ceased for 1-3 minutes; the active pole of the current was placed on the surface of the affected area of the brain and the indifferent pole on the skin in the region of the sacrum. The creation of anelectrotonus in the affected area of the medulla oblongata led to restoration of respiratory movements during the period of application of a current of 0.25-0.5 ma in 29 cases (6 of 14 experiments) (see Fig. 2).

The injection of strychnine into the lymph sac (0.2 ml of a 0.01% solution) 40 minutes before injection of the toxin into the brain prevented the cessation of pulmonary respiration and enabled survival in 17 of 20 animals whereas all the control animals died. We considered that the prophylactic action of strychnine which we observed was due to the labilization of the respiratory center. All the experiments described were accompanied by suitable controls of the effect of the nonspecific component of the bacterial toxin on the functional state of the nervous system.

The control experiments showed that the toxin, when destroyed by boiling or neutralized by specific antitoxic serum, did not cause the reaction described above. This was evidence that the parabiosis-producing properties were confined to the specific component of the vibrion septique toxin.

The parabiotic reaction of the central and peripheral nerve structures which we observed during the action of the toxin of one of the agents responsible for gas gangrene evidently reflected the "automatic" component of the toxic manifestations of this disease which we were studying. The distinctive features of the action of the vibrion septique toxin on the medulla was evidence of the decisive importance of the parabiotic process of the respiratory center in the pathogenesis of the toxicosis.

It may be postulated that, in ordinary circumstances, the development and outcome of the pathological process are to a large extent determined by the complex and dynamic relationships between the reflex and "automatic" components of the toxicosis, appearing in the form of a single parabiotic process of the nervous system.

SUMMARY

This work deals with the effect exercised by the toxin of one of the causative agents of gas gangrene on the functional condition of the nervous system (experiments on rats and frogs). The author demonstrated the parabiotic nature of reactions of the respiratory center, the spinal cord centers, the peripheral nerve, and of the myoneural synapse in their alteration with the toxin of vibrion septique.

The peculiarity of this reaction lies in the phase of decreased lability and excitability and the prolonged equalizing stage of parabiosis. As shown by experiments on frogs, the parabiotic process of the respiratory center is of especial pathogenetic significance. The function of the central nervous and peripheral nervous formations, disturbed during the process of alteration by the toxin, may be restored for a short period by creating an anelectrotonus in the area of alteration. Prophylactic administration of strychnine may prevent the development of a parabiotic process of the respiratory center in the frog.

LITERATURE CITED

[1] D. A. Arapov, Anaerobic Wound Infection (Moscow, 1950) [In Russian].

[2] V. Ya. Braitsev and S. P. Zaeva, Novyi Khirurg. Arkh. 30, 4, 472 (1934).

[3] A. N. L'vov, Gas Gangrene (Moscow, 1946) [In Russian].

[4] O. Ya. Ostryi and A. N. Aliev, Doklady Akad. Nauk SSSR 106, 1, 157 (1956).

[5] O. Ya. Ostryi and A. N. Aliev, Doklady Akad. Nauk SSSR 115, 2, 421 (1957).*

*Original Russian pagination. See C.B. translation.

[6] O. Ya. Ostryi, Z. I.Sobieva, and A. N. Aliev, Current Problems of Nervism in Physiology and Pathology (Moscow, 1958), p. 724 [In Russian].

[7] Z. I. Sobieva, Current Problems of Nervism in Physiology and Pathology (Moscow, 1958), p. 691 [In Russian].

[8] W. Frei, Ergebn. allg. Path. and Path. Anat. 31, 1 (1936).

[9] C. H. Kellaway, E. R. Trethewie, and A. W. Turner, Austral. J. Exper. Biol. Med. 18, 225 (1940).

[10] F. Klose, Munchen. med. Wschr. 64, 1541 (1917).

[11] M. B. Robertson, A System of Bacteriology in Relation to Medicine (London, 1929) 3, p. 225.

[12] W. Straub, Munchen. med. Wschr. 66, 89 (1919).