

# A STUDY OF HIGHER NERVOUS ACTIVITY IN EXPERIMENTAL TUBERCULOSIS

## Communication I. Conditioned Food-Secretory Reflexes in Dogs on a Background of Tuberculosis Infection and during Streptomycin Therapy

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Many clinical and clinicophysiological observations have established that disturbances of higher nervous activity develop in tuberculosis. There are also data indicating that these disturbances play an important pathogenic role in the development of the tuberculous infection.

It should, however, be stressed that many aspects of this problem remain unexplained. Specifically, although there are several works [1, 2, 3] investigating the influence of the tuberculous infection on the higher nervous activity of experimental animals, there are many sides of this question which remain unexplored (the comparative resistance of positive and negative conditioned reflexes to tuberculosis, the significance of the type of conditioned reflex, the reversibility of the changes which develop in higher nervous activity, etc.).

This article presents results obtained in a study of conditioned food secretory reflexes in dogs infected with tuberculosis during the diseased period, during the treatment of the experimental animals, and at the end of the course of treatment.

### EXPERIMENTAL METHODS

The conditioned reflexes were investigated in a soundproof chamber by the food-secretory method. A stereotype of conditioned reflexes was developed in the dogs to the following stimuli: a bell, a light, a positive tone, a gurgle, a negative tone and a bell. The experiments were performed on six dogs, two of which (Chilka and Oka) served as a control (the dogs were infected with tuberculosis, but we did not investigate their conditioned reflexes or administer treat-

ment to them). A total of 247 experiments were performed on four dogs. All the dogs were mongrels. Orsha, Seraya and Moroshka had nervous processes of average strength, were even-tempered and rather lively; Pyatnistyi belonged to the strong, inert type. The infection was produced intravenously with a culture of the Valle strain in a dose of 0.5 mg/kg (Orsha, Moroshka and Chilka) or 0.75 mg/kg (Seraya, Pyatnistyi and Oka). Streptomycin was injected intramuscularly in a dose of 20,000 units per 1 kg of weight, 30-60 minutes after the work with the dogs in the chamber ceased.

### EXPERIMENTAL RESULTS

As soon as the second day after the infection, the sum of the positive conditioned reflexes of the dogs of the first group was observed to decrease 70-75% of the original level (Fig. 1). Unconditioned secretion began to decrease significantly towards the end of the first week following infection (by 50-64%), although in one dog (Moroshka), its decrease began at the same time as the decrease in the conditioned (Fig. 1 and 2).

The conditioned secretion to the weaker stimuli decreased before that to the stronger. Increasing sequential inhibition was observed. Two weeks after infection, the total amounts of the dog Orsha's conditioned reflexes had decreased an average of 85% of the original level, in some experiments equalling zero. Unconditioned secretion continued decreased. During this period, one could observe the delayed development or even the complete lack of the conditioned reflex motor food reaction. In several experiments, the dogs fell asleep between the different stimuli. Slight dis-

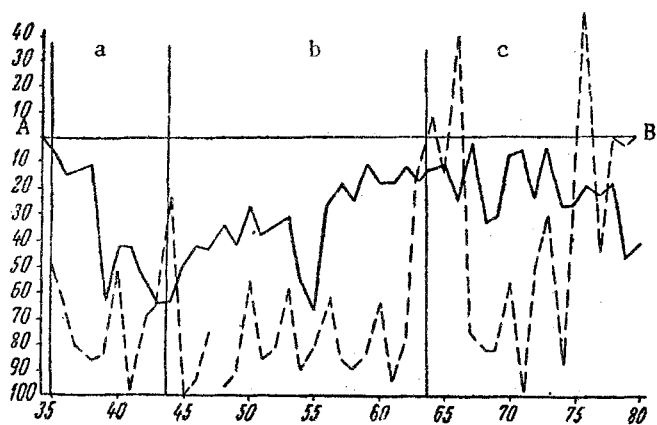


Fig. 1. Relative changes (in percent) in amount of conditioned and unconditioned secretion in the dog Orsha during tuberculosis. Axis of abscissa) number of experiments; axis of ordinate) percent: a) Before streptomycin treatment; b) on background of treatment; c) after treatment ended; A-B) Average initial level of amount of conditioned (---) and unconditioned (—) secretion before infection.

inhibition of the differentiation was observed in both dogs in a few experiments.

Streptomycin treatment of the dogs in this group was started the third week after infection. During the first 3-3½ weeks of treatment, conditioned reflex salivation remained at the same low level and, in several experiments on one of the dogs, decreased even further than before the treatment. Except in a few experiments, the differentiation was total. The amount of unconditioned secretion began to increase slightly on the 17th-18th day (Orsha) and at the end of the treatment had almost regained the original (before infection) figures. In the second dog (Moroshka), restoration of the unconditioned secretion began somewhat later and proceeded parallel with restoration of the conditioned.

According to the conditioned reflex indices, relative normalization of the condition of higher nervous activity occurred later than the improvement in the dogs' clinical condition; it was not observed in Orsha until the 50th day or, in Moroshka, until the 40th day of treatment. At this time, the amount of Orsha's conditioned secretion equalled 81%, the amount of Moroshka's, 75% (of the original, taken to be 100%); in one experiment, the amount even exceeded the average original level. During this period, the antibiotic injections were discontinued. The tendency of the amounts of the conditioned reflexes to level off continued after the treatment was stopped, but they still did not equal the original level. One of the dogs, Moroshka, died accidentally seven days after the last streptomycin injection. The second dog, Orsha, was sacrificed a rather long time after the treatment was stopped. The autopsy performed on Moroshka showed a mildly expressed tuberculous process—colorless miliary tubercles

in every lobe of the lungs and single tubercles in the kidneys and spleen, while the autopsy on Orsha showed only single miliary tubercles in the lungs.

The dose of the tuberculous culture administered to the second group of dogs was 1½ times stronger in order to induce a more serious process. As early as the end of the first week following infection, we observed in the dog Seraya that the sum of the positive reflexes decreased an average of 35%; some disinhibition of the differentiation (1-2 scale divisions; Fig. 3) was also observed. At this point, unconditioned secretion had decreased an average of 8-10%. At the end of the 2nd week (and thereafter), we observed a sharp decrease in conditioned reflex salivation, sometimes coming to (in a few experiments) a total lack of reflex to the weaker stimuli. Sequential inhibition became more intense. The conditioned reflex motor food reactions to the same stimuli were also absent. In addition, there was a sharp decrease (68-70%) in the amount of unconditioned reflex salivation. Unconditioned secretion and the sum of the positive conditioned reflexes then continued to remain at a low level. The dog stopped eating the meat-sugar powder.

During the first eight days of the infection, the sum of the dog Pyatnitski's positive conditioned reflexes decreased an average of 55%; no disturbance of the differentiation was observed. The decrease in the amount of saliva representing unconditioned food secretion was much greater in the case of Pyatnitski than in the case of Seraya, reaching 95% of the original level by the 9th day of the disease. The dog began to refuse food as early as the first week after infection; the conditioned secretory and the conditioned motor food reactions "split" (the first was greatly diminished

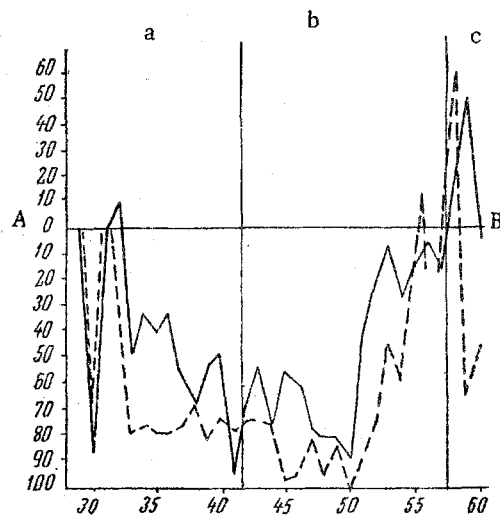


Fig. 2. Relative changes (in percent) in amount of conditioned (---) and unconditioned (—) secretion in the dog Moroshka during tuberculosis. Symbols the same as in Fig. 1.

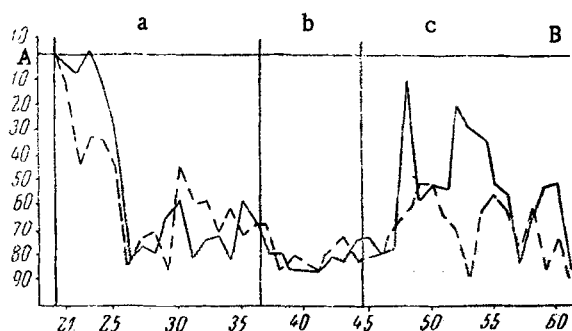


Fig. 3. Relative changes (in percent) in amount of conditioned (---) and unconditioned (—) secretion in the dog Seraya during tuberculosis. Symbols the same as in Fig. 1.

while the second was active). Progressive deterioration of the dog's general condition was observed the 3rd week of the infection; the animal lost weight and became weaker. The differentiation was noticeably disinhibited. At this time, the level of conditioned reflex secretion was 75-80% lower than the original. Sequential inhibition had increased.

We began to treat the dog Pyatnystyi the 33rd day of the disease, and the dog Seraya, the 42nd day. The course of treatment lasted 3½ weeks. Throughout the course of treatment, the conditioned and unconditioned reflex saliva secretion of the dog Seraya continued to remain at a low level; conditioned salivation to the strong stimulus (bell) decreased, and the conditioned reflexes to the weak stimuli were particularly inhibited. During the streptomycin treatment of the dog, we noted progressive disturbance of its motor coordination and an ataxic gait. In view of this, the streptomycin injections were discontinued on the 25th day of treatment. The indices of conditioned reflex secretion were low. A tendency to restoration was noted in a few experiments in relation to the unconditioned reflex secretion, but as the animal's condition deteriorated, it too again fell to 85% of the original level. The dog died 4½ months after infection and 68 days after treatment ceased. The autopsy disclosed cachexia, serous exudate in the pleural and pericardial cavities and numerous miliary tubercles in the lungs, liver, spleen and kidneys.

After streptomycin treatment of the dog Pyatnystyi began, conditioned and unconditioned reflex activity continued to decrease. The differentiation was stably disinhibited. Considerable deterioration of the dog's condition was noted about the 30th-35th day after infection: the dog lost weight progressively and died, showing symptoms of increasing weakness. The autopsy disclosed serosanguineous exudate in the pleural and abdominal cavities, many miliary tubercles in the lungs and a solitary focus in the spleen the size of a hazelnut.

The control dogs (Chilka and Oka) were also infected with culture of Koch's bacillus (with 0.5 and 0.75 mg/kg respectively); they were each sacrificed and subjected to pathologico-anatomical examination on the day that we began treatment of their related group of experimental animals. We found a microfocal tuberculous process in the lungs and kidneys of both dogs. Miliary foci were also observed in Chilka's spleen and in Oka's liver.

The data obtained from the autopsies on the control dogs indicated that the treatment of the experimental animals was started on a background of developed experimental tuberculosis in both experimental groups. The experimental results have shown that considerable functional disturbances of the sections of the cerebral cortex participating in the formation and realization of conditioned food secretory reflexes occurred in the experimental dogs under the influence of the tuberculosis infection. This was very clearly indicated by the decrease in the value of the conditioned positive salivary food reflexes. Intensified sequential inhibition was also regularly observed in all the experimental animals.

Another phenomenon observed was disinhibition of the differentiation. This phenomenon, however, was less regular in character. In the first place, it usually developed later than the decrease in the value of the positive secretory conditioned reflexes; in the second, it was less pronounced; thirdly, disinhibition was not by any means observed in every experiment, and, finally, as the tuberculous infection progressed, it did not increase as regularly as did the decrease in the positive secretory conditioned reflexes.

Treating the animals of the first group with streptomycin had a marked therapeutic effect; improvement of the animals' general condition was observed which, judging from our observations on the dog Orsha, continued after treatment ceased. Restoration of the clinical indices was the first improvement effected by the continuous streptomycin treatment; normalization of the conditioned reflex food secretion did not occur until later. One can therefore assume that the disturbances which develop in conditioned food secretory reflexes during tuberculosis infection are reversible in the event of successful treatment.

The results of the treatment administered to the dogs of the second group were quite different. The course of the process induced by the more massive doses of the Koch's bacillus culture used in this instance was extremely severe, attended by acute intoxication and terminating in death, notwithstanding the active treatment of the animals. The issue of the disease also determined the dynamics of the pathology of nervous activity; during and after treatment, we observed in Pyatnystyi and Seraya progressive, acute, and, by this time, irreversible disturbances of the conditioned and unconditioned salivary reflexes.

#### SUMMARY

The author studied conditioned secretory reflexes in dogs in experimental tuberculosis prior to treatment and during streptomycin therapy. As established, tuberculosis provokes considerable disturbances of the brain function, manifested in depression of the positive conditioned salivary reflexes and in intensification of the process of sequential inhibition. The disturbance of differentiation was less regular in character. It was possible to reverse the functional changes occurring in

the cerebral cortex by streptomycin therapy. However, normalization of the indices of the conditioned reflex salivary secretion took place later than normalization of the clinical indices in the sick animals.

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