ON THE PATHOGENESIS OF TYPHOID FEVER INTOXICATION IN DOGS AT VARIOUS STAGES OF GROWTH

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A.D. Speransky and his coworkers established the role of the nervous system in the pathogenesis of a number of infections, both under experimental conditions and through clinical observations. The importance of the nervous system in the process of development of the principle symptoms of disease is shown most clearly by experimental analysis of toxin intoxication at various stages of growth.

The work of our laboratory has established that the absence of so-called typical symptoms of a disease during toxin poisoning at an early age is due to the inactivity of those reflex mechanisms which produce these symptoms in adults [1-4].

The problem which was attacked in the present investigation was the characterization of some principle symptoms of typhoid poisoning in dogs at various stages of growth, especially with respect to the intestines.

EXPERIMENTAL METHOD

The experiments were conducted on 38 adult dogs: 3 puppies 5 days old; 2, 8 days old; 3, 14 days old; 2, 18 days old; 2, 22 days old; and 4 puppies 3 - 4½ months old. We used a diphasic antigen, which had been prepared at the Gamaleia Institute of Epidemiology and Microbiology, in order to produce the typhoid intoxication. It was a concentrate of the entire culture: the liquor and killed bacteria. We were able to use two antigens which had been prepared from two different varieties of typhoid bacteria. We established the lethal dose of Anitgen No. 1, the more toxic one, to be 10 mg/kg; the lethal dose of Antigen No. 2 was 15-20 mg/kg. The antigens, which had previously been dissolved in physiological salt solution, were introduced subcutaneously and, in a few experiments, intravenously. We observed the clinical condition of the animals carefully; we took electrocardiograms to register changes in heart action and noted changes in breathing and temperature. After the animals died or were killed a certain length of time after introduction of the antigen, the pathological anatomy of the intestinal tract was studied.

EXPERIMENTAL RESULTS

Adult dogs die during the first, or more rarely, the second, 24 hours after the administration of a lethal dose of the antigen. The first signs of recuperation appear on the third day (with Antigen No. 1) and in some cases on the second day (chiefly with Antigen No. 2) after introduction of a sublethal dosage. In only an hour or more, depending on the dosage and method of administration, vomiting begins (more frequent with Antigen No. 2). Later, diarrhea, usually bloody, is observed (especially true with Antigen No. 1). During the acute stage of the intoxication the temperature rises to 40°. Prolonged bradycardia occurs in adult dogs.

Animals whose intoxication was not lethal were killed from several hours to five days after the first symptoms of illness. Autopsy revealed the typical progress of changes in the lymphatic system of the intestines which has been described for human typhoid fever. During the first hours after administration of the toxin, es-

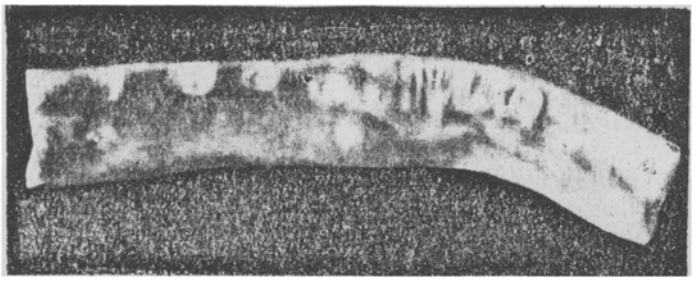

Fig. 1. Upper portion of the jejunum of an adult dog (weight, 12 kg), two days after intoxication produced by administration of 10 mg/kg of typhoid fever Antigen No. 1.

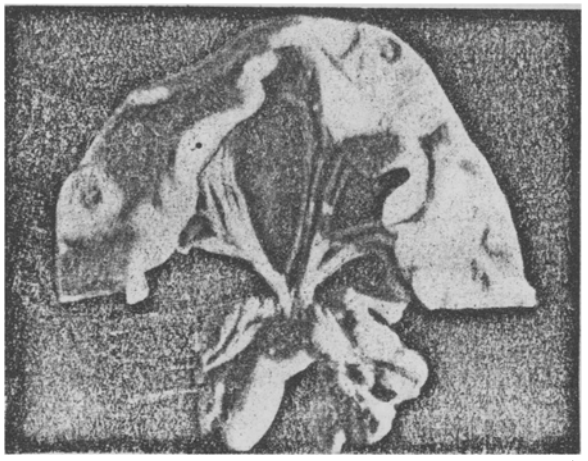

Fig. 2. Ileum and mesenteric lymph glands of an adult dog (weight, 9 kg), 5½ hours after the beginning of intoxication produced by administration of 10 mg/kg typhoid Antigen No. 2.

pecially of a lethal dose, swelling of Peyer's patches and solitary glands could be observed, together with hyperplasia of the lymphatic tissues, i.e., the first stage of proliferative inflammation. Peyer's patches were swollen the whole length of the intestines, especially in the region of the ileum and, slightly less, in the duodenum. The first stage was replaced by the second – necrosis, followed by ulceration and sloughing of the necrotic tissue.

The area of the patch became deeper as a result of the necrosis, reaching the serosa in individual cases. 24 hours and, in individual cases, two days later, autopsy revealed extensive necrotization and ulceration, together with swelling of Peyer's patches (Fig. 1). When sublethal doses of the antigen had been administered (especially in the case of No. 1), hyperemia was evident primarily in the ileum and duodenum. On introduction of lethal and, especially, larger doses, swelling of the mucosa and a very evident diffuse hyperemia of it throughout the length of the intestine could be observed. The intestine became soft and practically fell apart under the scissors. In these cases, the hyperemia was evident in the area of the lower part of the stomach and, to a lesser extent, in the large intestine. The liver, and especially the spleen, were full of blood. Petechial hemorrhage was observed in the lungs and, occasionally, in the

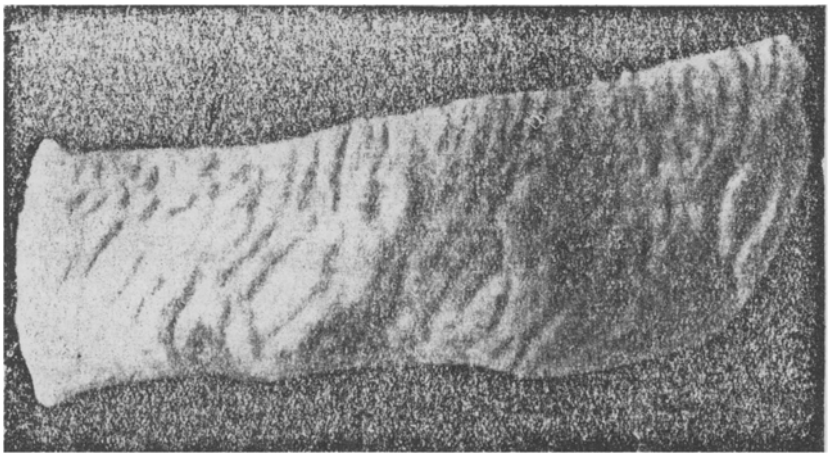

Fig. 3. Duodenum of an adult dog (weight, 7.5 kg), two days after the beginning of intoxication produced by administration of a dose of 7.5 mg/kg of typhoid fever antigen to the atropinized animal.

heart muscles, also. The mesenteric lymph glands showed lymphadenitis at various stages of intoxication. At this time, the glands became large, swollen, and grayish-red (Fig. 2).

Thus, we succeeded in fully reproducing the intestinal symptoms characteristic of typhoid fever in the adult man. Since the antigen was administered subcutaneously and intravenously, the reactions described above could only have been the result of its effusion through the vascular system of the intestines.

According to general opinion, typhoid fever agents are excreted through the bile tract where they may be held up for a more or less prolonged period of time. Periodically entering the intestines, the microorganisms again act on the lymphatic system of the intestines, producing changes which are typical of typhoid fever.

All of these changes, which have been thought to require the action of the bacteria from the mucosa of the intestines on its lymphatic system, were reproduced in the dogs by means of typhoid toxin, administered subcutaneously.

How are the reactions of the intestine as described above produced in the case of typhoid intoxication? The work of our laboratory has established that the typical inflammatory reaction on the intestinal mucosa which is produced in adult dogs by dysentery intoxication is not produced in puppies until they are 25-30 days old. Analysis has indicated that this is the result of the absence of those reflexes which produce inflammation in older dogs [2,3,4].

Our experiments were conducted on 12 puppies ranging in age from 5 to 22 days. They indicated that subcutaneous administration of typhoid fever Antigen No. 1 (5-10 mg/kg), in doses which were lethal in all cases, did not cause those typical changes in the lymphatic system of the intestine which were found in adult dogs. The puppies died within the first 48 hours. Autopsy revealed that the intestinal mucosa either differed in no way from normal, or showed diffuse hyperemia – in those cases when large doses of antigen were administered. Not one puppy showed necrosis, nor ulceration of Peyer's patches. A scarcely perceptible swelling in the area of Peyer's patches could be observed only in the case of 18 and 22-day-old puppies.

Our data do not establish the age at which the intestinal symptoms of typhoid fever intoxication, typical of adult dogs, begin to appear in puppies. By analogy with the data obtained from dysentery intoxication, we can only suppose that the first typical symptoms appear in puppies about 30 days old. Four puppies which were 3-4½ months old responded to subcutaneous administration of lethal doses of typhoid fever antigen with the same changes in the lymphatic system of the intestine as did the adult dogs.

The work of our laboratory on dysentery intoxication established that the appearance of the inflammatory reaction in the intestinal mucosa coincided with the beginning of parasympathetic regulation of intestinal activity, characteristic of adults. Later, it was shown that the vascular component of the inflammatory reaction in the intestinal mucosa during dysentery intoxication is produced by the sympathetic innervation. As regards the motor component of the intestinal reaction (spasms, reflex gaping of the anus, and frequent stools), it is produced by the parasympathetic innervation. If the parasympathetic influence is blocked with atropine in adult dogs, thus excluding the possibility of the realization of the motor component of the intestinal reaction during dysentery intoxication, the complete inflammatory reaction is also prevented.

We carried out two series of experiments in order to analyze the role of the neural mechanisms in the production of intestinal symptoms during the typhoid fever intoxication of adult dogs.

In the first series using 9 dogs, the typhoid feve antigen was injected subcutaneously 20-30 minutes after the parasympathetic system had been blocked by the subcutaneous administration of a dose of 0.1 mg/kg of atropine.

Three of the five dogs which had been given a dose of antigen known to be lethal remained alive. The course of the intoxication was somewhat easier in these dogs, as well as in four which had been given sublethal doses. The pathological changes in the small intestine differed considerably from those described above. External examination revealed that the entire small intestine was not soft and hyperemic, but, on the contrary, firm and white, with clearly defined annular musculature. The mucosa of the intestine was thickened, swollen and pale. The intestine cut with a slight crack. Small areas of hyperemia and hemorrhage in the region of the duodenum and ileums were found in four dogs. Peyer's patches were large, firm, swollen, and projected above.

In the second series of experiments on 6 dogs, the typhoid fever intoxication was produced after intravenous injection of 8-10 mg/kg of sympatholytin an hour before administration of the antigen. The three dogs which were given lethal doses of the antigen died. Three dogs were given sublethal doses of the antigen.

On autopsy, Peyer's patches were found both in the first and second stages of change in all the animals. However, there were more patches in the stage of proliferative inflammation than there were in the next stage of necrosis and ulceration.

Experiments carried out with atropine, especially experiments on young puppies, demonstrate the role of the nervous system in the mechanism producing the macrophagous proliferative reaction of the lymphatic system of the intestine during typhoid fever intoxication. Further analysis of a more detailed nature is necessary, however, of the effect of the nervous system on the production of the defense reaction to the typhoid fever agent. The data obtained permit some understanding of the clinical findings with regard to the atypical course of typhoid fever infections in small children.

The course of typhoid in children, especially under one year old, is usually similar to intestinal dyspepsia and enterocolitis. The pathological changes which are typical for adults are either completely absent or so insignificant that an accurate diagnosis can only be made on the basis of clinical bacteriological examination, not through pathological anatomy [5,6].

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