CARDIAC ACTIVITY CHANGES IN TYPHOID FEVER IN DOGS

A. S. Taraban

From the Laboratory of Pathology and the Physiology of Aging (Head — Professor I. A. Arshavskii) Institute of Normal and Pathological Physiology (Director — Active Member of the AMN SSSR V. N. Chernigovskii) AMN SSSR, Moscow

(Received October 23, 1958. Presented by Active Member of the AMN SSSR V. N. Chernigovskii)

Experimental analysis of the physiological mechanisms controlling the course of dysentery, staphylococcal infections, and diphtheria in dogs of different ages has revealed a cyclical reaction, whose features are correlated with age. In the previously mentioned infections, the cyclical reaction displays characteristic changes in the different phases, which are particularly well shown in the reaction of the nervous centers controlling the cardiovascular system [3, 4, 14].

In the present investigation, we studied the action of the typhoid toxin with a view to understanding the characteristic symptoms and changes in cardiac activity in human typhoid patients of different ages.

METHOD

The experiments were carried out on 38 adult dogs, 12 puppies less than 22 days old, and on 4 ages 3-4½ months. Typhoid was induced by using a two-phase antigen prepared in the N. F. Gamaleya Institute of Epidemiology and Microbiology. This consisted of a concentrate of a whole culture (liquid portion and dead bacteria).

In a previous communication we have shown that typhoid toxin produces precisely the same intestinal symptoms in adult dogs as are found in adult human subjects [15]. Two antigens were available, prepared from two different typhoid strains. Antigen 1 was the most toxic, the lethal dose being about 10 mg per kg body weight, while for antigen 2, it was 15-20 mg per kg. The antigens, diluted in saline , were injected subcutaneously or intravenously. Careful observations on the condition of the animals were made. Temperature and respiration rates were recorded. Cardiac changes were recorded from lead 2 of an EKP-4 electrocardiograph. The ECG was first taken several hours before the injection, and subsequently at frequent intervals during the whole course of the illness, until recovery or death, according to the dose of toxin given. The animals were not anesthetized or restrained. Four of them were given a preliminary injection of 10 mg/kg of morphine.

RESULTS

From the results obtained, the animals may be divided into two groups. The first consists of puppies less than 22 days old, and the second of adult animals of 3 months or above. We will first describe the results for the older age group. In all of them, both antigens (1 and 2) produced the same quantitative reaction. The only difference was in the size of the dose required to produce a particular reaction. Antigen 1 was the stronger of the two (see 'Method'). The typhoid toxin was injected after the normal resting heart rate, which varied from 70 to 90-100 beats per minute, had been established. In the resting condition, respiratory arrhythmia might be present in greater or lesser degree.

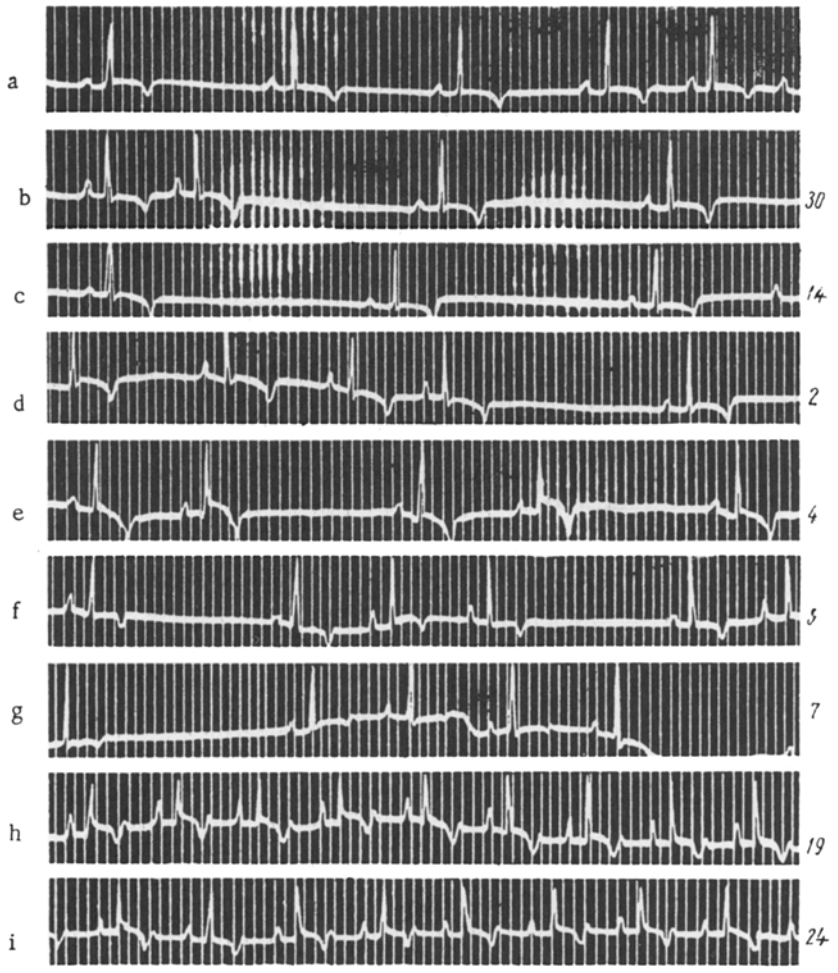

Fig. 1. Electrocardiogram of an adult dog infected with typhoid. a) Before the injection of typhoid toxin; b, c, d, e, f, g) first phase of the reaction; h, i) second phase.

If a sublethal dose of 4-6 mg of Antigen 1, or 6-10 mg of Antigen 2 was now injected, after 10-20 minutes there was a marked slowing of the heart rate, and marked respiratory arrhythmia. The rate fell to 60 or even to 50 beats per minute. Respiration was also slowed. In addition, there was a marked reduction in the amplitude of the P and T waves, and, simultaneously, some increase in the R wave. In the resting condition, the T wave was given negative, and after the injection, it remained negative and increased in amplitude. This first phase of the reaction lasted from 6 to 12 hours, and in some cases as long as 20 hours. The greater the dose of toxin injected, the shorter the duration of the first phase; however, in all cases, this first phase lasted longer than has been reported in staphylococcal infections, dysentery, and diphtheria.

The second phase follows immediately after the first, when there is an increase in heart and respiration rate. The heartbeat rises to 120-150 per minute. Respiratory arrhythmia ceases. The amplitudes of the P and T waves increase, while the R wave is reduced. This phase may last any time from a few hours to several days; the greater the dose, the greater the duration (Fig. 1).

When phase 2 has been completed, there is once more a marked reduction in heart rate to a value 15-30 beats per minute below the original resting rate. The respiration rate is also greatly reduced. A marked respiratory arrhythmia also returns. The P and T waves become reduced, while the R wave is greatly increased. This phase corresponds to the condition described by A. A. Koltypin [10], who referred to it as the vagus phase in the acute stage of several infectious diseases in children. The occurrence of this phase indicates the cyclical nature of the reaction to typhoid toxin. Subsequently, there is a gradual return to the initial resting condition.

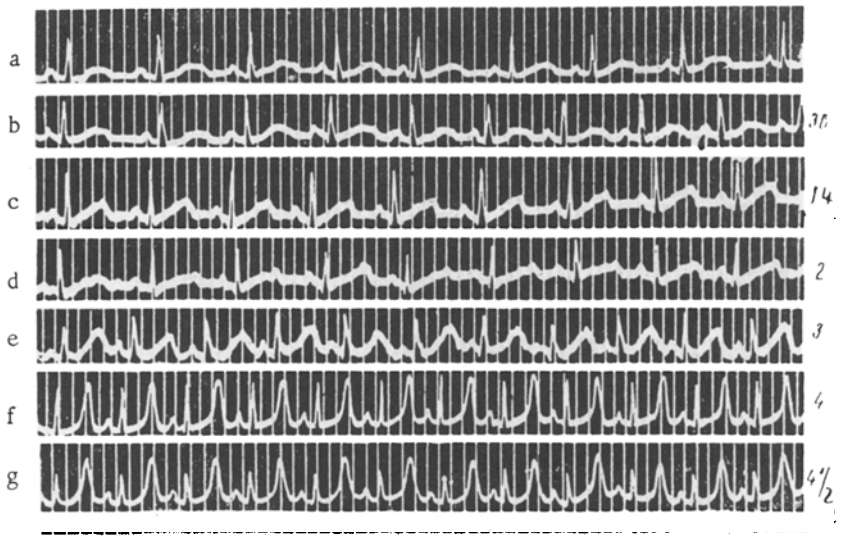

Fig. 2. Electrocardiogram of 22-day-old puppy injected with typhoid toxin. a) Before injection; b, c, d, e) initial stage of first phase of reaction; f, g) phase 1 maximally developed.

The duration of the whole cycle varies from 2 to 4 days. When small doses of 2-3 mg/kg of Antigen 1 are given, the reaction does not extend beyond phase 1.

We must now consider the cause of the change in the heart rate and in the amplitudes of the ECG waves. Information on this point was obtained by giving an intravenous injections of 0.1 mg/kg of atropine to 9 dogs, 30 minutes before the injection of the toxin; this dose of atropine was sufficient to block tonic cardiac vagal impulses. During the course of the infections of small amounts of atropine were given at intervals of $2\frac{1}{2}$ - 3 hours. In the atropine treated dogs, the phasic changes in heart rate and ECG waves were completely absent. During the whole period of observation, the heart rate remained constant.

Thus, the natural conclusion is that just as has been shown for staphylococcal, dysenteric, and diphtheretic infections, in both the first phase and in the phase when the changes in heart rhythm and ECG waves recur, the tonic action of the vagal cardiac center is in a condition of increased activity (first optimum reaction of this center).

In the second phase of the reaction, in which the heart rate is increased, there is an inhibition of vagal cardiac innervation (first pessimum of the reaction of this center). The amount by which the heart rate is increased in the second phase depends on the degree to which the vagal cardiac center is inhibited. When lethal doses are injected, the first phase is considerably shortened. Also, the second phase shows a more marked heart rate increase, up to 160-200 per minute.

The third phase follows immediately after the second. Unlike the phase 3 which has been described, it consists of a short cardiac spasm, or syncope, lasting from 3 to 50 seconds. Finally, the heart again begins to beat at the very slow atrioventricular rhythm (vagus escape). The R wave is enterely missing from the ECG. The whole of this phase, comprising syncope and the subsequent transition to the atrioventricular rhythm, does not last more than 3-7 minutes. At this period, breathing usually stops for a period before the last breath is taken.

The third phase is also vagal in origin, and is due to a marked increase in the tone of the vagal cardiac center; it does not occur in atropinized dogs. By analogy with the corresponding phase in other lethal bacterial infections, the third phase may be considered as the second optimum of the reaction of the vagal cardiac center. At the end of the third phase, the heart goes over to the sinoauricular rhythm, which does not change after section of the vagi (second pessimum of the reaction of the vagal cardiac center). In some experiments, in the third phase, fibrillation of the heart occurred.

In puppies of the younger age group, subletal doses of typhoid toxin do not cause a slowing of the heart rhythm, as in the older animals, but an immediate increase of 30-60 beats per minute. The increased rate is

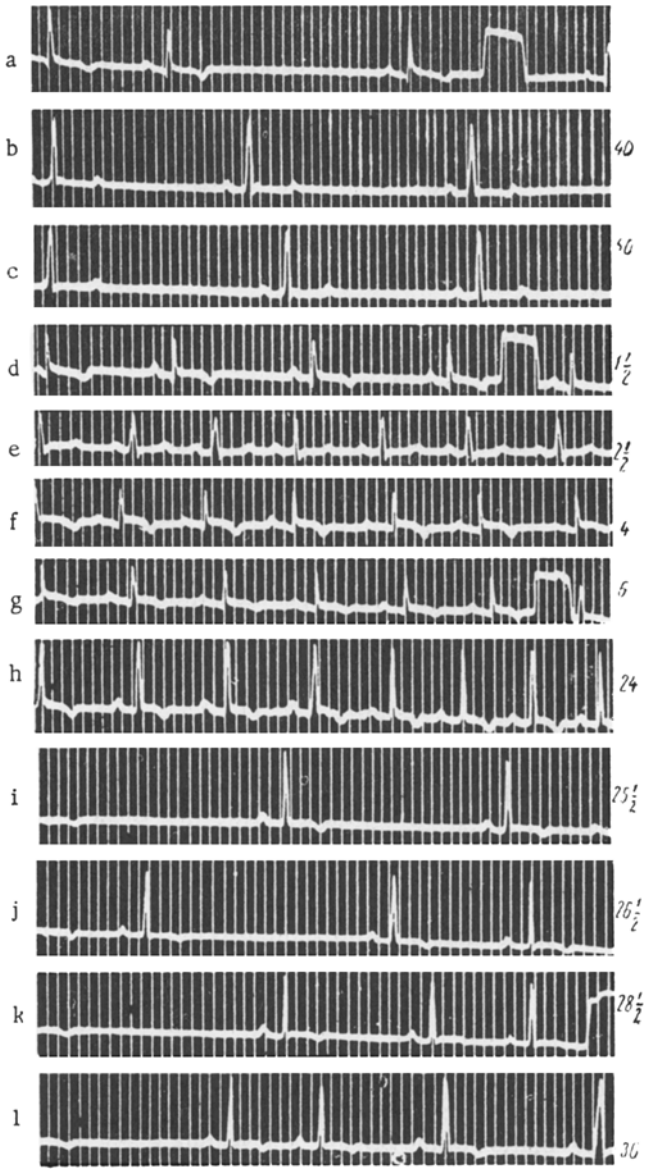

Fig. 3. Electrocardiogram of an adult dog injected with dysenteric toxin. Reactions; e, f, g) second phase; h) beginning of phase; a) before injection of dysenteric toxin; b, c, d) first phase of recovery; h, i, j, k) recovery phase.

maintained for the whole period of the toxin action, and may last from 8 to 30 hours according to the dose of toxin given; subsequently, there is a gradual return to the initial condition. Fig. 2 shows a series of ECG recordings taken from a 22-day-old puppy, before and after injecting typhoid toxin.

Thus, in young puppies given a sublethal dose of toxin, the whole of the reaction is confined to the first phase. This result is readily understood when it is appreciated that in young puppies, the heart rate is not controlled from the vagal center, but from the center for cardiac sympathetic innervation [1, 6]. The increase heart rate caused by the injection of typhoid toxin into young puppies must be attributed to a stimulation of the cardiac sympathetic center.

If young puppies are given a lethal dose of typhoid toxin, then immediately after the phase of raised heart rate, there is a progressive slowing of the cardiac rhythm, and this represents one of the components of protracted

collapse, as frequently described by I. A. Arshavskii and his co-workers in many cases of bacterial and chemical poisoning. In adult dogs, in the raised heart rate induced by large amounts of typhoid toxin, there is an inhibition of the vagal cardiac center, whereas in young puppies, the slowing of the heart rate caused by large doses is due to inhibition of the sympathetic center.

The results obtained in the experiments on young puppies explain why the bradycardia which is so typical of typhoid in adults [5-9] fails to develop in young children, especially in those of preschool age. We must ask, then, whether the typical adult bradycardia represents a specific effect of typhoid toxin acting as a stimulus. Were this to be the case, then evidently bradycardia would occur in the young also. The particular form the reaction takes depends not only on the nature of the stimulus, but also on the age of the human or animal infected.

It was shown above that bradycardia in adult dogs is the primary response not only to the action of bacterial toxins, but also to that of many chemical substances. We require to know what features are specifically induced by the bacterial toxin.

Injections of His-Flexner dysenteric toxin were given subcutaneously to 6 adult dogs; 3 received a sublethal, and 3 a lethal dose. With the sublethal dose, the typical phasic reaction occurred, there was a bradycardia, tachycardia, and then a return of the bradycardia, and the corresponding changes in the ECG waves occurred at each phase, just as we have already described for typhoid infection (Fig. 3). When lethal doses were given, the same sequence of four phases of the reaction of the vagal center, as has already been described for lethal doses of typhoid toxin, was observed.

The results of this set of experiments are in line with the changes in cardiac activity observed to occur in dysentery [4, 14].

What are the distinctive features of the reaction of the heart to typhoid and dysenteric toxins ? From his own results, and those of his co-workers, I. A. Arshavskii [2] concluded that they consist essentially of a variation pf the nonspecific normal parabiotic reaction. It was shown above that when sublethal doses of typhoid toxin are given, the first phase of the bradycardia lasts for from 6 to 20 hours. With sublethal doses of dysenteric toxin, the duration of the first bradycardial reaction varies from 30 minutes to $1\frac{1}{2}$ hours.

The specific feature of the typhoid toxin on adult animals is the unusual length of the initial bradycardia.

SUMMARY

Characteristic changes in cardiac activity due to the action of typhoid toxin in full-grown dogs and young puppies are described. The response of adult dogs to the intravenous or subcutaneous injection of sublethal doses of typhoid toxin takes the form of a cyclic reaction involving the following phases: first bradycardia, second tachycardia, and third a restoration of the original bradycardia which terminates in a return to the initial condition. All these phases reflect the changes in the intensity of the tonic excitation of the vagus center of cardiac innervation. In previously atropinized dogs the above phases of the reaction are absent. In young puppies the cyclic reaction to intravenous or subcutaneous injections of the toxin is limited to the tachycardia phase only, which reflects the rise in the intensity of the tonic excitation occurring in the center of the sympathetic cardiac innervation. The action of the typhoid toxin in lethal doses not only alters the correlated duration of the reaction phases cited, but also gives rise to additional ones, both in full-grown dogs and in young puppies.

LITERATURE CITED

[1] I. A. Arshavskii, Nervous Regulation and the Activity of the Cardiovascular System in Ontogenesis* (Moscow – Leningrad, 1936).

[2] I. A. Arshavskii, Reports of Researches*, 176 series biology, issue 37, 68-85 (Leningrad University, 1954).

[3] I. A. Arshavskii, Zhurn. mikrobiol. epidemiol. i immunobiol. 10, 104-110 (1955).

[4] I. A. Arshavskii and V. D. Rozanova, Arkh. pat. 4, 83-84 (1955).

[5] M. G. Danilevich, Handbook of Infectious Diseases in Children* (Leningrad, 1949).

* In Russian

[6] S. I. Enikeeva, Fiziol. zhurn. SSSR, 25, 1-2 , 102-111 (1938).

[7] S. I. Enikeeva, Fiziol. zhurn. SSSR ,30,3,339-345 (1941).

[8] S. I. Enikeeva, Fiziol. zhurn. SSSR, 2 , 227-232 (1955).

[9] S. I. Ignatov and S. D. Nosov, Typhoid and Paratyphoid in Children* (Moscow, 1954).

[10] A. A. Koltypin, The Pathogenesis and Clinical Classification of the Acute Infectious Diseases in Children* (Moscow, 1948).

[11] V. D. Rozanova, Fiziol. zhurn. SSSR, 34, 1, 49-60 (1948).

[12] V. D. Rozanova, Fiziol. zhurn. SSSR, 35, 2, 242-252 (1949).

[13] V. D. Rozanova, Fiziol. zhurn. SSSR, 4, 440-452 (1949).

[14] V. D. Rozanova, Transactions of the First Scientific Conference on the Morphology and Physiology of Aging*. 125-131 (Moscow, 1954).

[15] A. S. Taraban, Byull. éksptl. biol. i med. 41, 1, 38-42 (1956).* *

* In Russian

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