

# FUNCTIONAL CHARACTERISTICS OF EXPERIMENTAL STREPTOCOCCAL ALLERGY

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Increasing attention has recently been paid to the investigation of allergic reactions of delayed type, including allergy induced by streptococci. The impossibility of their passive transmission with the blood serum distinguishes these reactions from those of the immediate type and requires their segregation into a special group of processes whose mechanisms, according to the majority of authors [5-7, 10], differ from those of reactions of the anaphylactic type. At the same time it has to be noted that modern views on the delayed type of allergy are based on the results of immunomorphological studies. Considering the predominant importance of functional changes in reactivity in the development of allergic processes (mainly affecting the cardiovascular and respiratory systems), such an approach to the study of, above all, streptococcal allergy, lying at the basis of rheumatic fever, cannot be regarded as adequate [3, 4, 8].

The object of the present investigation was to study the changes in the cardiovascular system of animals during streptococcal allergy.

## EXPERIMENTAL METHOD

The investigation, conducted on 42 rabbits, consisted of three series of experiments. A heat-killed vaccine of  $\beta$ -hemolytic streptococci, group A, was used in the experiments and was injected subcutaneously on alternate days in doses of 300 million bacterial cells.

The animals of series I were sensitized for a period of 4 weeks after the final sensitizing injection; the same vaccine was injected intravenously in a dose of 1 billion bacterial cells. After each injection of vaccine, and also before the beginning of sensitization, the following indices were analyzed in all the animals: the EKG, the leukocyte count of the blood, and the clotting power of the blood. The reacting injection of vaccine was accompanied by recording of the arterial pressure following administration of mediators (acetylcholine, adrenalin) and stimulation of the nerves to the heart (vagus, depressor nerve).

The clotting power of the blood was determined from the character of the deposition of fibrin after addition of a 0.5% solution of calcium chloride to blood (Good's method).

The EKG was taken in standard lead 2. Particular importance was attached to the results of the test with adrenalin, injected intravenously in a dose of 10  $\mu$ g.

In the experiments of series II and III the degree of sensitization was studied in the isolated heart: in series II—2 weeks after the sixth injection of vaccine and in series III—after 12 sensitizing injections.

## EXPERIMENTAL RESULTS

In the experiments of series I, carried out on 20 animals, the following changes were observed in the indices studied. In the course of development of sensitization, a gradual rise in the blood leukocyte count was observed in

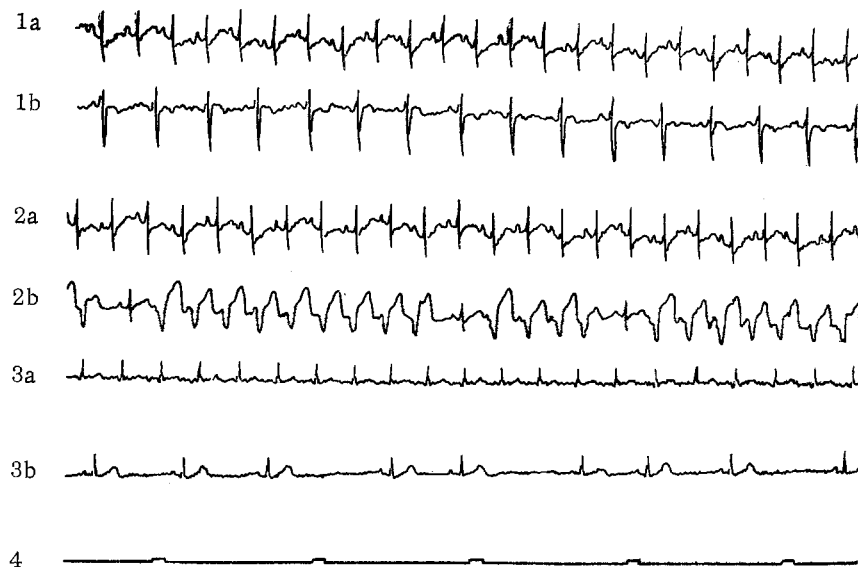


Fig. 1. Changes in EKG after injection of 10  $\mu$ g adrenalin. 1a and 1b) Before beginning of sensitization; 2a and 2b) after the 6th sensitizing injection (multiple ventricular extrasystoles); 3a and 3b) after 12 injections of vaccine (vagus pulse, solitary sinus extrasystoles).

all the rabbits—to 11000-13000, which changed to a marked leukopenia (3000-4000) during the first few hours after the reacting injection of vaccine. In 90% of the animals the clotting power of the blood was increased after the reacting injection of streptococcal vaccine, so that after 1/2 h this index rose from the 3rd-4th degree, corresponding to the normal level, to the 6th-7th degree, and at the same time the bleeding time fell sharply.

The dynamics of the changes in the EKG during application of a functional test in response to adrenalin showed the following special features. In background investigations before the beginning of sensitization adrenalin was injected in a dose of 10  $\mu$ g, which produced transient slowing of the heart rate. In 40% of animals isolated sinus extrasystoles were recorded in individual experiments. After the 5th-6th sensitizing injection of vaccine, in 60% of animals the threshold dose of adrenalin led to the appearance of multiple extrasystoles, mainly ventricular. The phase of slowing of the heart rate was considerably shortened and became less marked than in the background investigations before the beginning of the experiment, which evidently indicated an increase in the excitability of the adrenergic structures of the myocardium.

The concluding sensitizing injections of vaccine were accompanied by a fresh change in the animal's reaction to adrenalin, as determined by the changes in the EKG. In 90-100% of the rabbits, intravenous injection of adrenalin at this stage of sensitization caused the development of a marked bradycardia (vagus pulse), accompanied only occasionally with the appearance of extrasystoles, as a rule single (Fig. 1).

The reacting injection of vaccine, given 2 weeks after the final sensitizing injection and accompanied by recording of the arterial pressure, caused a slight fall of the arterial pressure (on the average by 30%) in 90% of the animals in the course of 1.0-1.5 h; in three rabbits the hypotensive effect was considerable (a decrease of 50% of the initial level).

The tendency towards hypotensive reactions was discovered during the tests in response to adrenalin and acetylcholine and also during stimulation of the nerves to the heart—the vagus and the cardiac depressor nerve. In most animals the administration of a threshold dose of adrenalin was accompanied by biphasic changes in the arterial pressure (a rise and fall to a level below the initial value), such as are observed in normal animals, as a rule, only after administration of doses of the mediator twice or three times as large. The reaction of the arterial pressure to acetylcholine was increased over the normal level on the average by 50%. Meanwhile, in individual experiments a lowering of the threshold of stimulation of the nerves to the heart was observed (Fig. 2).

It could be concluded from these results that the initial stages of streptococcal sensitization are accompanied

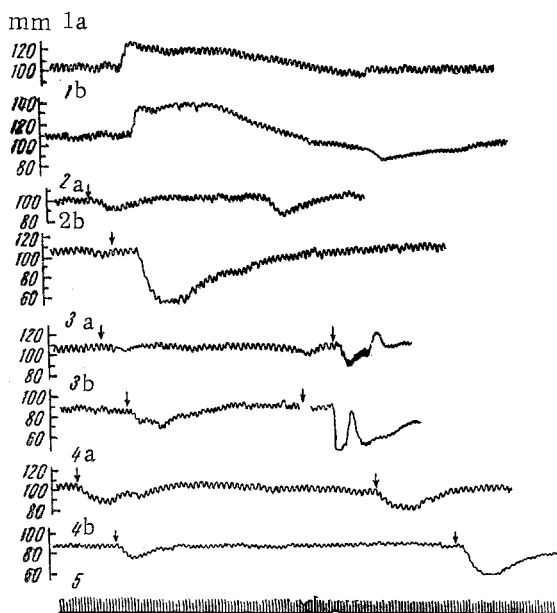


Fig. 2. Reaction of arterial pressure to mediators and to stimulation of nerves to the heart. a) Normal rabbit; b) sensitized rabbit; 1a and 1b) adrenalin  $0.1 \cdot 10^{-4}$ ; 2a and 2b) vagus—2 mA and 3 mA; 4a and 4b) depressor nerve—2 mA and 3 mA; time marked 1 sec.

and a reduction in the leukocyte count of the blood after the reacting injection of vaccine, and a change in the sensitivity of the isolated heart to mediators. However, in contrast to anaphylactic reactions, in streptococcal allergy the dominant features are disturbances of the peripheral, and not the central circulatory mechanisms, and this evidently corresponds to the immunomorphological expression of the delayed type of allergy.

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by corresponding changes in the reactivity of the cardiovascular system in the direction of sympathicotonia, while in the later stages of sensitization parasympathicotonia develops. This conclusion was confirmed in experiments on the isolated heart.

For example, in the experiments of series II, performed on the isolated heart of 12 rabbits sensitized by six injections of vaccine, in 40% of cases a considerable strengthening of the action of adrenalin was observed. A marked positive inotropic and chronotropic effect developed following injection of doses of adrenalin of  $1 \cdot 10^{-11}$ – $1 \cdot 10^{-13}$ , whereas in the isolated heart of a control rabbit stimulation was produced by doses of  $1 \cdot 10^{-6}$ – $1 \cdot 10^{-7}$ . The sensitivity of the heart to acetylcholine remained at the normal level ( $1 \cdot 10^{-6}$ ).

In the experiments of series III, conducted on the isolated heart of 10 rabbits after 12 injections of vaccine, a marked lowering of the threshold dose of acetylcholine was observed, while the reaction to adrenalin was normal. A negative inotropic and chronotropic effect, accompanied by cardiac arrest, was observed when acetylcholine was injected in doses of  $1 \cdot 10^{-11}$ – $1 \cdot 10^{-13}$ .

The results of this investigation showed that the delayed type of allergy, like allergic reactions of the immediate type [1, 2, 19], are characterized by similar changes: a fall in the arterial pressure (as a rule only slight)