

PATHOGENETIC MECHANISMS OF THE PYREXIAL REACTION TO STREPTOCOCCAL ANTIGENS

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It is generally considered that the development of the pyrexial reaction is associated with excitation of the thermoregulatory centers [1, 2, 6]. We have found that a depressing action on these centers is involved in the antipyrogenic action of cortisone [4]. When cortisone was injected into rabbits the development of pyrexia following administration of a streptococcal vaccine was inhibited, and occasionally a hypothermic reaction developed [3]. This indicated that the streptococcal pyrexia developed by a route common to many forms of fever, the central link in which was excitation of the thermoregulatory centers.

However, when we repeated these experiments after a time we found that cortisone no longer had an antipyrogenic action on the fever due to the vaccine prepared from the same strain of streptococcus. We have attempted to discover the reasons for this phenomenon.

EXPERIMENTAL METHOD

Experiments were carried out on male rabbits. As pyrogenic agents we used heated vaccines from a β -hemolytic streptococcus - strains S-84 and SF₂₂t₂. The concentration of bacterial cells in 1 ml ranged from 500 million to 2000 million in the different series of experiments. The cortisone used was manufactured by the firm of Roussel (25 mg/ml).

The temperature of the animals was measured by means of a maximum thermometer. The base temperature was taken to be the mean of two measurements at an interval of $\frac{1}{2}$ h. The injections were then given, and the temperature was taken hourly for 6 h. To compare the temperature reactions the pyrexial index was determined [4].

EXPERIMENTAL RESULTS

In the first series of experiments, four rabbits were injected simultaneously every day for 18-25 days with standard doses of cortisone (25 mg per rabbit intramuscularly) followed by vaccine (strain S-84 in a dose of 2000 million bacterial cells intravenously). The vaccine was prepared from a strain previously kept in blood broth. On the first day of the experiment vaccine alone was injected. All four rabbits developed a marked febrile reaction with a pyrexial index of between +495 and +550 units. Cortisone was given on and after the second day, and for 7-10 days it prevented the development of pyrexia in every case. Subsequently the antipyrogenic action of cortisone began to diminish, and in response to each injection of vaccine an appreciable pyrexial reaction developed, becoming more marked every day. In all the rabbits an increase in the dose of cortisone (to 37.5 mg) completely suppressed the pyrexial reaction, while a decrease to the original dose once again led to the appearance of fever (Fig. 1).

After a few months the second series of experiments was carried out on six rabbits using a vaccine prepared from the same strain, seeded for a long time previously from broth to broth. The dose of vaccine only was reduced. The results of these experiments differed significantly from those obtained before. In 3 rabbits there was hardly any antipyrogenic effect, and a marked pyrexial reaction appeared after nearly every injection of vaccine. In the other three animals a slight decrease in the temperature reaction was observed between the 5th and 11th days of the experiment.

When the dose of cortisone was increased to 37.5 mg (9 experiments), the results were opposite to those obtained in the preceding series of experiments. In four cases the pyrexial reaction remained the same, while in five cases it was actually increased. The results of one experiment are shown in Fig. 2.

We considered that the conflicting results of the experiments, carried out by the same method but at different

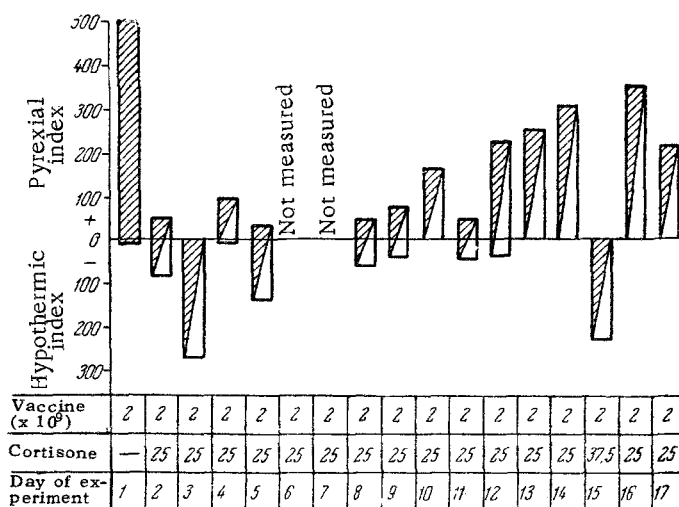


Fig. 1. Temperature reactions of an experimental rabbit after injection of cortisone and vaccine. On the first day of the experiment there is a marked pyrexial reaction to injection of vaccine alone. During the period from the 2nd to the 9th day the pyrexia is suppressed by cortisone. After the 10th day the antipyrogenic properties of cortisone are diminished. An increase in the dose of cortisone on the 15th day of the experiment suppressed the development of the pyrexial reaction.

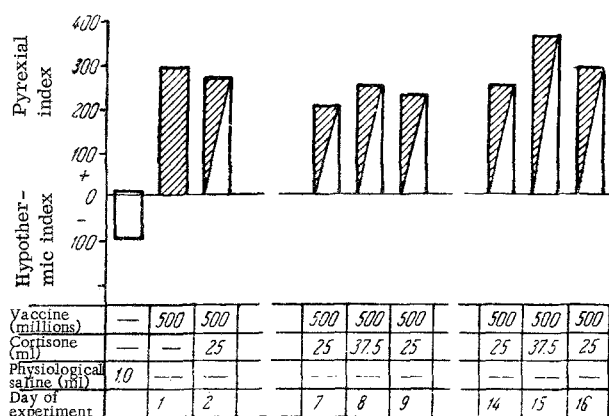


Fig. 2. Effect of an increase in the dose of cortisone on the development of the pyrexial reaction in a rabbit.

the streptococcal culture. For this purpose, strain SF_{22t2} was seeded daily for one month from broth to broth. A vaccine was then prepared by the same technique.

Experiments were conducted on eight rabbits, four of which received vaccine alone and the other four cortisone and vaccine. All the rabbits developed a pyrexial reaction (see table), and the arithmetical mean pyrexial index in the rabbits receiving cortisone was actually greater than that in the rabbits receiving vaccine alone (see Fig. 3), although the statistical significance of the difference between the arithmetical mean values was not confirmed.

times, were due to changes in the biological properties of the streptococcal strain, following its prolonged and almost daily seeding from broth to broth. To test this hypothesis, in a third series of experiments we studied the effect of cortisone on the pyrexia caused by the vaccine. The vaccine in this series was prepared from a fresh strain of streptococcus SF_{22t2}, seeded to "scarlatina" broth from a freeze-dried culture. Experiments were carried out on 16 rabbits, divided into four groups: the first received cortisone and vaccine (strain SF_{22t2}), the second, a control for the first — vaccine only (strain SF_{22t2}), the third — cortisone and vaccine of the old strain (S-84), and the fourth, a control for the third — vaccine only (strain S-84).

It is clear from Fig. 3 that cortisone completely suppressed the development of the pyrexial reaction to vaccine from the fresh strain, but had absolutely no antipyrogenic action on a more moderate degree of fever caused by vaccine from the old strain.

In a fourth series of experiments we attempted to modify the properties of the new strain SF_{22t2} in order to make certain that the loss of the antipyrogenic action of cortisone was in fact due to changes in the properties of

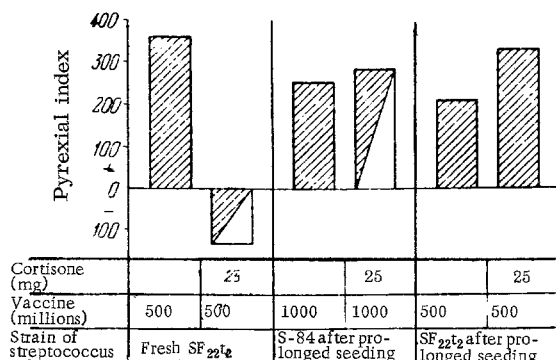


Fig. 3. Effect of cortisone on the development of the pyrexial reaction to vaccine prepared from a fresh strain of streptococcus and on the reaction to vaccine from the same strains after prolonged seeding from broth to broth.

Pyrexial Index in Rabbits Receiving Vaccine from Streptococcal Strain SF_{22t2}, Seeded Daily from Broth to Broth, alone or together with Cortisone

Vaccine	Vaccine and cortisone
+186	+272
+391	+378
+126	+457
+160	+224
<i>M</i> = +215	<i>M</i> = +333

We may ask why cortisone suppresses the pyrexia caused by vaccines from fresh strains of streptococci, yet has absolutely no inhibitory effect on the pyrexia caused by vaccines from the same strains if previously seeded from broth to broth for a long period. This is evidently due neither to the quality of the cortisone, which was the same in each case, nor to differences in the reactivity of the animals, for in all the rabbits receiving vaccine from the fresh streptococcal strains cortisone suppressed the development of pyrexia, while in all the rabbits receiving vaccine from strains undergoing prolonged seeding it had no antipyrogenic action. The cause was evidently the different properties of the vaccines prepared from strains cultivated in different conditions. The fact that cortisone depresses fever in animals receiving one vaccine, yet has no such effect in animals receiving the other vaccine, indicates that the mechanisms of development of pyrexia are different in the two cases, and that streptococci may possess at least two pyrogenic substances. With a change in the conditions of cultivation of the streptococcus these factors may cumulate or disappear. This hypothesis is confirmed by the literature. For instance, Cremer and Watson [5] isolated two pyrogenic factors from group A hemolytic streptococci which did not exhibit complete crossed tolerance. These findings indicate that different mechanisms may take part in the development of the febrile reaction caused by each of these pyrogens.

Our results confirmed the presence of two different mechanisms of the pyrexial reactions caused by vaccines from normally cultivated strains S-84 and SF_{22t2} and from vaccines of the same strains of streptococci previously subjected to prolonged seeding from broth to broth.

Attention should also be paid to the results showing that after injection of vaccines from strains cultivated for long periods in broth, not only is the pyrexia not diminished, but in some cases, particularly if the dose of cortisone is increased, it may actually be increased. This phenomenon was not specially investigated. It may be suggested, however, that it has something in common with the action of cortisone on the dinitrophenol hyperthermia of thyroidectomized rabbits, which also is increased after administration of cortisone [3]. This analogy in the present case suggests that pyrexia may develop as a result of stimulation of exothermic metabolic processes in the tissues themselves, but this hypothesis requires careful examination.

SUMMARY

Cortisone given to rabbits in a dose of 25 mg depressed the development of pyrexial reactions caused by the intravenous injection of warmed streptococcus vaccine. However, when these experiments were repeated a few months later it appeared that cortisone did not produce its usual antipyrogenic effect on fever induced by the vaccine prepared from the same streptococcus strain. This was connected with the changes in biological properties of the streptococcus culture. To confirm this statement the author prepared a vaccine from a new streptococcus strain (SF_{22t2}), formerly stored in the form of lyophilized culture. Cortisone inhibited the development of fever, provoked by this vaccine. To change the biological properties of this strain, streptococcus culture was subjected to daily transfers from broth to medium (scarlet fever) for one month. After such treatment the vaccine was prepared again and the antipyrogenic action of cortisone was tested once more. In all the cases cortisone had no depressive effect on fever, which by its intensity even exceeded that in control animals.

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All abbreviations of periodicals in the above bibliography are letter-by-letter transliterations of the abbreviations as given in the original Russian journal. *Some or all of this periodical literature may well be available in English translation.* A complete list of the cover-to-cover English translations appears at the back of this issue.