PATHOGENETIC MECHANISMS OF THE PYREXIAL REACTION
TO STREPTOCOCCAL ANTIGENS

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Translated from Byulleten' Éxperimental'noi Biologii i Meditsiny, Vol. 55, No. 5,
pp. 69-73, May, 1963
Original article submitted October 31, 1961

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 anti-
pyrogenic 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 antipyro-
genic 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 SF928. 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 ½ h. The injections were then given, and the temper-
ature 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 mil-
lion 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 be-
gan 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 anti-
pyrogenic 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.

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.

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~22~ in order to make certain that the loss of the antipyrogenic action of cortisone was in fact due to changes in the properties of the streptococcal culture. For this purpose, strain SF~22~ 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.