THE NONSPECIFIC CHARACTER OF RESISTANCE ARISING AFTER PARENTERAL INJECTION OF ERYTHROGENIC TOXIN

I.M. Liampert and T.A. Levina

From the Department of Infectious Diseases of Children (Head – the late Prof. P.V. Smirnov) and the Department of Wound Infections (Head – Active Member Acad. Med. Sci. USSR G.V. Vygodchikov) of the N.F. Gamaleia Institute of Microbiology and Epidemiology (Director – Active Member of VASKhNIL S.N. Muromtsev) of the Acad. Med. Sci. USSR, Moscow

(Received May 29, 1957. Submitted by Active Member Acad. Med. Sci. USSR G.V. Vygodchikov)

In a previous report [2] it was shown that the resistance to erythrogenic toxin is increased 24 hours after the injection of 25,000 skin doses intravenously into rabbits reacting to 0.1 skin dose. Animals given a preliminary intravenous injection of 25,000 skin doses of this toxin survived a parenteral injection of a lethal dose whereas injection of such a dose into animals not given a preliminary injection of the toxin caused their death.

The phenomenon of rapid increase in resistance has been produced by a number of workers in animal experiments by bacterial toxins, viruses and bacteria. However, the problem of specificity of the resistance developing after injection of these agents has not yet been solved.

Several workers [1, 3, 6, 9] assert that resistance develops only to the homologous microorganism or toxin, i.e., is strictly specific. However, many other workers have shown that the resistance which develops immediately after injection of bacterial and viral agents is nonspecific in character [4, 5, 7].

It should be mentioned that in order to ascertain the mechanism which is the basis of this rapidly developing resistance it is imperative to explain the specificity of this phenomenon. We put forward the hypothesis [2] that the cause of the rapid increase in resistance after parenteral injection of viruses, bacteria, toxins and bacterial antigens is mobilization of the mechanisms of physiological, natural immunity. However, in such a case the rapid increase of resistance must be nonspecific because the mechanisms of natural immunity are known not to possess specific properties.

In order to ascertain the specificity of this phenomenon we performed cross experiments with erythrogenic and diphtheritic toxins.

EXPERIMENTAL METHOD AND RESULTS

For the experiment 26 rabbits were used which reacted in skin tests to Schick toxin and to 0.1 skin dose of erythrogenic toxin. An injection of 25,000 skin doses of erythrogenic toxin was given to 12 of these animals. Three hours later skin tests were made with 1, 4, 10, 20 and 40 skin doses of the same toxin. After 24 hours it was found that of the 12 rabbits, in seven the reaction was absent in 40 skin doses, one did not react to 20 skin doses and four did not react to 10 skin doses. An intravenous injection of 1 MLD of diphtheria toxin was given to all these animals 24 hours after receiving the 25,000 skin doses of erythrogenic toxin. 1 MLD of diphtheria toxin was also injected into all of the 14 control animals which had not received a preliminary injection of erythrogenic toxin.

Of the 12 animals receiving preliminary erythrogenic toxin, two died within 6 days of the injection of 1 MLD of diphtheria toxin. In the control group 12 animals died within 6 days (Figure 1).

A preliminary injection of erythrogenic toxin was thus shown to have a protective action against diphtheria toxin.

In the next two experiments the protective action of diphtheria toxin against erythrogenic toxin was tested.

Each experiment made use of six rabbits. In addition, there was one control group of four rabbits and another of five rabbits. All the experimental animals received 1/20 MLD of diphtheria toxin, followed 24 hours later by an injection of 1 MLD of erythrogenic toxin. The control animals received 1 MLD of erythrogenic toxin only.

In these experiments the diphtheria toxin showed no protective action against erythrogenic toxin; 9 of the 12 experimental animals died, and 7 out of 9 in the control group died.

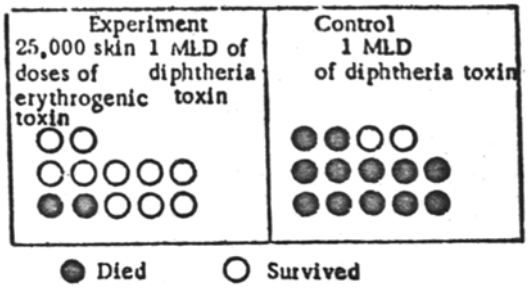

Fig.1. Survival of rabbits after injection of 1 MLD of diphtheria toxin 24 hours after a preliminary injection of 25,000 skin doses of erythrogenic toxin.

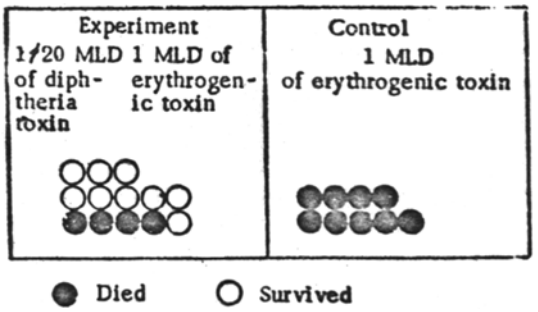

Fig. 2. Survival of rabbits after injection of 1 MLD of erythrogenic toxin 3 days after preliminary injection of 1/20 MLD of diphtheria toxin.

Thus, 24 hours after injection of 1/20 MLD of diphtheria toxin the resistance to erythrogenic toxin was not increased.

In the next series of experiments the resistance of the animals was tested to erythrogenic toxin at a longer interval after injection of diphtheria toxin.

In two experiments 13 animals were injected with 1/20 MLD of diphtheria toxin and, three days later, with 1 MLD. Nine control animals were also injected with 1 MLD of erythrogenic toxin.

Of the 13 animals which were given diphtheria toxin three days before the injection of erythrogenic toxin, four rabbits died. In the control group all nine rabbits died.

Thus three days after injection of 1/20 MLD of diphtheria toxin an increased resistance to erythrogenic toxin was found (Figure 2).

It is interesting to note that the resistance of rabbits to diphtheria toxin was not increased in the case where 1 MLD of this toxin was injected 24 hours after the injection of 1/20 MLD of this same toxin, nor three days after: all the animals – control and experimental – died at the same time. In all probability the preliminary dose of toxin injected was too large.

The possibility is not excluded that the resistance might have been raised if the preliminary dose of toxin injected had been somewhat smaller. This problem calls for special study.

Thus, after injecting rabbits with 25,000 skin doses of erythrogenic toxin their resistance is raised not only to erythrogenic but also to diphtheria toxin. This was shown by testing animals 24 hours after injecting them with the first dose of toxin. Three days after injecting the animals with 1/20 MLD of diphtheria toxin their resistance to erythrogenic toxin was raised. On injection of 1 MLD of diphtheria toxin after 24 hours all the animals died.

Thus, the increase in resistance found during the first few days after parenteral injection of diphtheria and erythrogenic toxins is nonspecific.

The experiments carried out suggest the presence of common mechanisms of natural immunity as playing

a part in toxemias due to both erythrogenic and diphtheria toxins.

Such a mechanism, as was shown in the previous report [2] of a study of erythrogenic toxin, is evidently an increase in the adrenalin content of the blood. Intensification by this means of the reactivity of the sympathetic system prevents a fall in blood pressure and the onset of collapse, as a result of which animals die in toxemia.

The fact that certain workers in some experiments observed cross protection and in others did not, when producing this phenomenon with different viruses, bacteria or toxins, may evidently be explained as follows. In cases where in order to produce this phenomenon agents were used against which there are common mechanisms of physiological immunity, as occurred in our experiments with erythrogenic and diphtheria toxins, cross protection may take place. In those cases where the mechanisms of physiological immunity against the test agents are different, evidently the resistance is increased only to the homologous agent. It is necessary to study this question further in experiments using different infecting microorganisms and toxins.

SUMMARY

It was demonstrated by experiments on rabbits than in 24 hours after the administration of erythrogenic or diphtheric toxin there is an increase of the nonspecific resistance to each of these toxins. Resistance which develops after the administration of erythrogenic toxin is connected with increased reactivity of the sympathetic system. This is shown by the rise of the blood adrenalin level. The latter prevents the development of collapse due to which the animals die during intoxication. This mechanism of physiological immunity is, evidently, the same in development of resistance to both toxins.

LITERATURE CITED

[1] A.Ia. Alymov and D.F. Pletsityi, The Problem of Reactivity in Pathology [in Russian] (Moscow, 1954), pp. 9-18.

[2] I.M. Liampert, Zhur. Mikrobiol., Epidemiol. i Immunobiol. No. 6 (1958).

[3] F.A. Terent'ev and E.P. Stefanova, Zhur. Mikrobiol., Epidemiol. i Immunobiol. No. 2, 20-24 (1954).

[4] G. Dallderf, S.M. Gohen and J.M. Coffey, J. Immunol. 56, 3, 295-300 (1947).

[5] G.B. Edsall, in the book: Annual Review of Microbiology 9 (Stanford, 1955), pp. 347-368.

[6] C.L. Larson, J.F. Bell and C.R. Owen, J. Immunol. 73, 4, 221-225 (1954).

[7] D. Rowley, Lancet 1, 232-234 (1955).

[8] D.R. Wharton and H.J.Creech, J. Immunol. 62, 2, 135-153 (1949).

[9] H.D. Wright, J. Pathol. and Bacteriol. 30, 185-252 (1927).