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Observations on Streptococcus Toxin-Antitoxin Neutralization as a Basis for Specificity.

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Practically all our experience with the interaction of the toxins and antitoxins of the diphtheria and tetanus bacilli indicates that this reaction is one of the most specific immune reactions, if not the most specific, upon which to base conclusions concerning the difference of species or of subgroups of species. In the study of the hemolytic streptococci, however, two sharply contrasted points of view concerning the specific relation of the toxins and antitoxins to the various disease processes have developed despite extensive research.

Our studies of the streptococci appear to throw additional light on the nature of the toxin-antitoxin reaction and suggest why such divergent conclusions may be reached in the study of these organisms. I am, therefore, presenting these observations from this point of view.

During the past 6 years the toxicity of about 200 strains of hemolytic streptococci from typical cases of scarlet fever and as many more from cases of erysipelas, septic sore throat, and other streptococcus infections has been determined.

Man and goats are the only animals susceptible to the streptococcus toxins, with the possible exception of the rabbit. Different persons and different goats vary in their susceptibility to the toxins of different strains and an individual person or goat does not always react to the same degree to the same toxin. For example, in tests where 2 "scarlet fever" toxins, A and B, and 4 "erysipelas" toxins, C, D, E, and F, were tested on each of 3 individuals, person No. 1 reacted in an equal degree to toxins A, B, D, and E and slightly to toxin F but failed to react to toxin C. Person No. 2 reacted equally to toxins A, B, D, and E but did not react to C or F; while person No. 3 reacted to the 4 erysipelas toxins and to the scarlet fever toxin A but failed to react to the scarlet fever toxin B. Goats susceptible to scarlet fever toxin A in high dilutions were also susceptible to all 4 erysipelas toxins. The scarlet fever toxin B, however, induced reactions only when large doses were given. In another instance 2 toxins of streptococci from cases of epidemic septic sore throat were

tested on each of 2 persons susceptible to the scarlet fever toxin A. Each person reacted to only one of the "septic sore throat" toxins but each to a different one. One of these septic sore throat toxins induced a definite reaction in goats susceptible to toxin A, the other no reaction even in low dilutions.

When repeated tests have been made on the same individual and a period of a month or more has elapsed between tests, variations in susceptibility to the same toxin have been noted. In one person tested repeatedly with 2 scarlet fever toxins, susceptibility to both toxins increased, in 2 others there was a decrease. On the other hand, the reactions induced in 4 persons by one of these toxins became more marked while the reactions induced by the second remained the same. A fifth person became more susceptible to the second toxin and less susceptible to the first.

Although it was apparent that the toxins produced by different strains varied, no significant differences in the toxins of streptococci from different sources have been observed either in potency or in their neutralization by antitoxin. The toxicity of streptococci from all sources varied, some apparently producing no demonstrable toxin; others, toxins of higher or lower potency. Eighty-five per cent of the strains from all sources have produced toxins inducing definite skin reactions in goats.

When varying doses of toxin and serum have been employed, 65 to 70% of all the toxins, irrespective of the source of the strain, have been neutralized by one monovalent antistreptococcus goat serum produced by a representative strain selected as a standard for purposes of comparison. This strain, the Dochez N. Y. 5 strain, was isolated from a typical case of scarlet fever and has been the incitant of 2 typical cases of this disease in members of the laboratory staff. About 35% of scarlet fever toxins and practically the same proportion of toxins of streptococci from other infections have not been neutralized by this serum even when large doses have been employed.

Tests with standardized toxins and antitoxins when only one or 2 skin test doses of toxin have been used and corresponding doses of a monovalent serum, have also given evidence of the similarity of toxins of streptococci from different infections. Under these conditions erysipelas toxins have been neutralized by monovalent scarlet fever antistreptococcus sera, and scarlet fever toxins by monovalent erysipelas antistreptococcus sera.

Differences in the toxins and sera not apparent in the usual toxin-antitoxin neutralization test were brought out when the combining

power of sera for homologous and heterologous toxins was determined. Apparently neutral mixtures of serum and various heterologous toxins were found in some instances to have no neutralizing activity for the homologous toxin; in others, the neutral mixtures possessed an activity only slightly less than that of the same dose of serum alone.

Carefully controlled titration tests of sera against homologous and heterologous toxins have shown marked differences in the neutralizing activity of monovalent sera produced with different streptococci, doubtless corresponding, in some degree at least, to the variations in the action of the toxins which give rise to them. Sera produced by certain strains have been found to be broadly valent and capable of neutralizing toxins from various sources. Other monovalent sera have been found to be of limited valency and to have little demonstrable activity for heterologous toxins, even those of streptococci from the same type of infectious process.

The serum of horses immunized with the Dochez N. Y. 5 strain had an equal neutralizing activity for the homologous toxin and for the toxins of the Dick II strain and for those of certain erysipelas strains, while 2 monovalent goat sera produced against different erysipelas strains neutralized erysipelas toxins and also the N. Y. 5 toxin.

On the other hand, the serum from a horse immunized with the Dick II strain has been found, when tested on some individuals, to have an equal neutralizing activity for both the Dick II and the Dochez N. Y. 5 toxins. When tested on other individuals, however, this serum neutralized in high dilutions its homologous toxin, but had little or no apparent activity for the N. Y. 5 toxin.

Monovalent sera produced in animals of different species with the same strain have also been found to vary in their neutralizing ability for different toxins. Toxins which have not been neutralized by an antistreptococcus goat serum produced by the N. Y. 5 toxin have been neutralized by an antistreptococcus horse serum produced by this same strain.

Animals immunized with other toxic strains of streptococci have shown little or no response even though the immunization has been continued over a long period.

Further evidence that certain strains of streptococcus may be broadly valent in their antigenic activity was apparent from the reactions induced by different toxins in persons before and after immunization with the toxin of one strain.

Children susceptible to both erysipelas and scarlet fever toxins,

after immunization with the scarlet fever toxin, reacted less strongly or not at all to twice the amount of the toxins used in the first test

Summary and Conclusions. Thus from the variations observed in the reactions induced in different persons and different animals of the same species by the various toxins studied and by mixtures of these toxins with different antistreptococcus sera, it would appear that both the streptococcus toxins and antitoxins are quite complex. It would also appear that the action of these toxins in the animal body and their neutralization by antitoxin depend upon particular phases of tissue susceptibility which may be present in one individual and not in another.

Toxins produced by streptococci from various sources appear to be quite similar when tested with a monovalent serum of broad valency. On the other hand, toxins neutralized with such a serum may be found to be quite dissimilar when tested with another serum produced by a different strain or in an animal of a different species or even in different persons or animals. These differences, however, do not appear to be related in any way to the type of infection from which the streptococcus was isolated.

Hence, if toxins of limited activity and antitoxins of narrow range are used and a small number of strains of streptococci are tested, it is quite conceivable that the results would suggest the possibility of dividing the streptococci into apparently specific groups. On the other hand, if representative strains of broad antigenic activity and antitoxins of wide valency are selected and a large number of representative strains from different types of streptococcus infections are studied, it is evident that so many strains would coincide in their reactions, that it is impossible, in the light of our present knowledge, to define the specificity of streptococci in relation to a particular type of infection.