

hyperergic state. This state is roughly proportional to the size and number of inoculations. It can be increased up to a certain limit if the animal is repeatedly inoculated at intervals of 5 to 10 days. Its induction appears to be due to the presence of one or more lesions some place in the body. It is not specific in the sense of serum immunological specificity, for an animal made hyperergic with one strain of non-hemolytic streptococci is also hyperergic to other strains which show cultural and agglutinative differences. It seems probable, therefore, that a human disease due to a hyperergic state to non-hemolytic streptococci may not be as specific as one due to direct infection with an immunologically specific bacterium.

¹ Derick, C. L., and Andrewes, C. H., *Proc. Soc. Exp. Biol. and Med.*, 1925, **xxii**, 116.

² Andrewes, C. H., Derick, C. L., and Swift, H. F., *J. Exp. Med.*, 1926, **xliv**, 35.

³ Derick, C. L., and Andrewes, C. H., *J. Exp. Med.*, 1926, **xliv**, 55.

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Immune Tissue Response to Non-hemolytic Streptococci.

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We¹ originally reported that if a rabbit had been recently inoculated by any route with streptococci of any type it would fail to show a secondary reaction following intracutaneous inoculation with suitable strains of streptococcus viridans. This might be due to one of two conditions: first a hyperergic, second an immune state. First, if due to a hyperergic state there might be a combination of accelerated hyperergic-secondary-reaction with the primary reaction; hence the initial response to introduction of the same sized inoculum would constantly increase up to a certain point. Second, if an effective immune state had been induced, the local protective mechanism against the inoculum might be so efficient that the sum of the primary and accelerated secondary reactions would be smaller than the initial response of a normal animal.

These two states were easily demonstrated in rabbits, according to the route used for inoculation. When repeated intracutaneous injections were made of 0.1, 0.01 and 0.0001 cc. at the time of each inoculation, the intensity of the local reaction at the site of each injection increased, up to a certain limit. Another group of rab-

bits inoculated intravenously showed very much smaller local reactions at the site of test intracutaneous inoculations. For example, at the site of a 0.0001 cc. inoculation there was only a slight erythema or a hard nodule 3 to 5 mm. in diameter, contrasted with a hard infiltrated papule 12 to 15 mm. in diameter, and 1 to 3 mm. in height in a hyperergic animal. In a highly immune rabbit the local reaction to 0.01 cc. was distinctly less than that of a hyperergic animal to 0.0001 cc. Immune animals have not developed interstitial keratitis following corneal inoculation, nor have they shown the lethal, tuberculin shock-like, reaction following intravenous injection.

The hyperergic state has been maintained or increased to a certain level by repeated intracutaneous inoculations or by the production of a subcutaneous lesion with an infected agar focus. When these hyperergic animals were inoculated intravenously with small doses of streptococci their condition was changed from a hyperergic to an immune state, while controls, not inoculated intravenously, remained hyperergic. In a few instances it was possible to convert an animal from the immune to the hyperergic state by discontinuing intravenous immunization and producing numerous local foci. Intravenous inoculation with strains of streptococci which were culturally and serum immunologically distinct from those used for the production of focal lesions resulted in the alteration from a hyperergic to an immune state in respect of the latter strains.

It appears, therefore, that both hyperergy and active immunity to non-hemolytic streptococci are not as specific as would be expected, *a priori*, from cultural and serum immunological differentiation. The induction of each state depends more upon the mode of inoculation of the animal than upon the specificity of the streptococci.

Our theory at present is as follows: Hyperergy to non-hemolytic streptococci is an early stage of resistance in which there is a maximal response of the tissues to a minimal stimulus; it is the result of the action of the antigen—the streptococci—in a limited area represented by the focus, where tissue destruction occurs. It may, indeed, depend upon substances arising in such a focus. Complete, or efficient immunity, on the other hand, is an optimal response of the tissues to a maximal—within certain limits—stimulus, and is the result of action of the antigen over a wide area without the induction of focal tissue destruction.

¹ Andrewes, C. H., Derick, C. L., and Swift, H. F., *J. Exp. Med.*, 1926, xlv, 35.