small percentage of cases where the injected region is not pinched off and the entire amount of the solute is retained, the fluid in the enlarging vacuole becomes an intense yellow. Such vacuoles progressively become very flaccid. Contact with the least obstacle, or stress exerted by endoplasmic currents easily causes their deformation. Their limp membranes may temporarily infold deeply, and the vacuoles often appear bean-shaped, long ovoid, or pyriform. Systole of these flaccid vacuoles is delayed, and a new vacuolation center appears and functions. In the meantime the original vacuole is carried about, gradually becoming more turgid and uniformly spherical, and finally contracts.

When smaller amounts of picric acid are injected, or when the ameba rids itself of the larger proportion of the solute by pinching off the injected region, the vacuole does not show any evidence of flaccidity but remains spherical and turgid although its contents are appreciably yellow. It increases in size at a rate similar to that subsequent to injections of distilled water,[2] and finally ejects the yellow fluid. After each systole, the collected fluid becomes successively paler until both endoplasm and vacuole have entirely lost the yellow color.

[1] Pollack, H., PROC. SOC. EXP. BIOL. AND MED., 1927, xxv, 145.

[2] Howland, R. B., and Pollack, H., *J. Exp. Zool.*, 1927, xlviii, 441-458.

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Hyperergic Tissue Response to Non-Hemolytic Streptococci.

CLIFFORD L. DERICK AND HOMER F. SWIFT.

From the Hospital of the Rockefeller Institute for Medical Research.

Two years ago in collaboration with Andrewes[1, 2] we described a peculiar response in the skin of rabbits to the inoculation of certain non-hemolytic streptococci. This was termed the secondary reaction because it occurred after the primary reaction to the inoculation had subsided. It was shown[3] not to correspond in its various phases with the Arthus phenomenon which is induced in rabbits by immunization and subsequent skin injection with various coagulable proteins. We, therefore, suggested that if this were an allergic phenomenon it was of the type seen in tuberculosis. Our subsequent investigations have been guided by this hypothesis.

The object of this report is to describe some of the concomitant phenomena of the secondary reaction and suggest their significance.

Eye Reaction: If the locally anesthetized cornea of a rabbit, which has shown a well marked secondary reaction, is lightly scarified and a drop of broth culture sediment of homologous streptococci is instilled into the conjunctival sac, there usually follows a distinct interstitial keratitis, characterized by increasing congestion of the ocular conjunctiva, turbidity of the cornea, and ingrowth of vessels from the sclerocorneal junction; this is followed by a gradual subsidence of signs until only a slight scar remains. The signs usually begin 24 to 48 hours after inoculation and last from 4 to 8 days, sometimes longer. Occasionally the reaction is delayed several days. Normal rabbits and rabbits inoculated intravenously have never shown keratitis following similar eye inoculations.

Skin Reaction: Inoculation of the skin of a rabbit, showing a secondary reaction, with a small dose of culture, *i. e.,* 0.0001 cc. is followed by a local lesion much more intense and of distinctly longer duration than is seen in a normal rabbit. This lesion often has a dull red color comparable with that seen in a nodular syphilide or in lupus nodules. Reinoculation of the skin of a secondary reacting rabbit with larger doses is followed by marked edema and other signs of a more intense reaction than are shown by normal rabbits inoculated with similar amounts. These increasingly severe skin reactions are very comparable with local tuberculin reactions in man, or with the response to cutaneous inoculation with tubercle bacilli in tuberculous animals.

Lethal Reactions: If rabbits shortly after the development of secondary reactions are injected intravenously with doses of homologous streptococcus viridans, which are well tolerated by normal rabbits, they will often die within 24 to 48 hours. They show on autopsy enlarged hemorrhagic lymph nodes, multiple hemorrhages into the bone marrow, a much enlarged thymus filled with petechial hemorrhages and at times hemorrhages into the endocardium and myocardium. Sometimes animals show extreme prostration but recover; if these animals are autopsied shortly after recovery they show similar but less marked lesions. This lethal reaction is similar to that seen in tuberculous animals following intravenous injection of large doses of tubercle bacilli or of tuberculin.

From the foregoing observations it is evident that the secondary reaction is accompanied by a generalized hyper-reactive state of the animal, hence the secondary reaction itself is probably a concomitant phenomenon of this state, and due to the reactivity of the tissues locally to some reaction stimulating substance that has remained at the original site of inoculation. It is true generalized *hyperergy* and for convenience the condition of these animals is designated as the

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.

HOMER F. SWIFT AND CLIFFORD L. DERICK.

From the Hospital of the Rockefeller Institute for Medical Research.

We[1] 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-