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Superinoculation experiments with Treponema pallidum.

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The majority of investigators have interpreted the results of superinoculation experiments with *Treponema pallidum* as showing that one infection affords protection against another. The chief criterion for determining results has been the production of a characteristic lesion containing spirochetes, it being virtually assumed that if no lesion occurred no infection had taken place. When it is recalled that the lesion produced at the portal of entry in a first infection may be very slight or entirely absent[1] and that organisms may multiply in the body for months or even years without giving rise to any external manifestation of disease, it is obvious that such a standard of measurement is of more value as an index of the ability to produce a manifestation of disease than of infection, and that infection cannot be excluded upon this basis. It would appear, therefore, that before the results of superinoculation experiments can be made clear, the subject must be approached from a broader point of view and that evidence must be adduced which will enable one to see beyond the reaction at the site of inoculation.

With this idea in view, a large series of superinoculation experiments was carried out on rabbits with five strains of *Treponema pallidum* representing organisms of a wide range of virulence for these animals. These strains included the highly virulent ones of Nichols and of Zinsser and Hopkins, isolated in 1912 and 1913, and three less virulent strains, isolated during the fall of 1919. In general, the animals were first inoculated in one or both testicles while the second inoculation was made intracutaneously on the sheath or at the base of one ear using equivalent doses of a testicular emulsion. The reaction to superinoculation was studied from the period of early primary infection to that of latency following spontaneous healing of primary or generalized lesions in-

[1] Brown, W. H., and Pearce, L., PROC. SOC. EXPER. BIOL. AND MED., 1921, xviii, 200.

cluding both the local reaction and the subsequent course of the disease. Especial attention was given to conditions which appeared to influence either of these reactions and the results were controlled by parallel observations on the reaction produced by the infection of normal animals.

While all of the details of the experiments are not as yet available, certain definite results may be recorded in so far as the local reaction is concerned. Briefly, four general types of reaction were observed:

1. The first reaction consisted of a mild, acute inflammatory process which was followed by a papular infiltration in the skin associated with more or less enlargement and induration of the regional lymph nodes. In its typical form, this reaction began within 24 hours and reached its height within 5 to 7 days after inoculation; it then subsided very rapidly, disappearing completely within 9 to 14 days after inoculation.

2. A second form of reaction differed from that described above in only one respect. With the fading of the cutaneous lesions, there was only a partial resolution of the lymphadenitis followed almost immediately by a progressive enlargement and induration which resembled the satellite adenitis of a primary infection in all essential respects. This condition persisted for weeks or even months.

3. With a third group of animals, an additional feature was introduced in the form of a diffuse or papular infiltration of the skin at the site of inoculation. These lesions presented the appearance of early primary infiltrations or of the slight cutaneous lesions frequently observed in primary infections and contained actively motile spirochetes in abundance. The reaction was usually manifest within 7 to 14 days; while the regional lymph nodes exhibited a progressive and persistent enlargement and induration, the cutaneous lesion was transient and usually disappeared within 2 to 3 weeks.

4. The fourth type of reaction was characterized by the development of persistent cutaneous lesions associated with a pronounced lymphadenitis. The cutaneous lesions assumed the form of flattened or elevated papules varying from a few millimeters to a centimeter in cross diameter or developed into large, well

indurated lesions which were difficult to distinguish from primary lesions produced by this mode of inoculation. The differences noted were a more rapid growth and a tendency to early and widespread necrosis with central softening—reactions which in the rabbit are indicative of a malignant turn of the infection.

The gradations in the reactions described (omitting Type 1) may all be observed with a first infection in any considerable series of animals inoculated with well adapted strains of *Treponema pallidum* and the more characteristic ones furnish conclusive evidence that a local infection together with the usual manifestations of disease may be produced by the reinoculation of animals already infected. Further than this, it is by no means certain that infection may not occur also in instances where no lesion is produced at the site of inoculation since the immediate production of a lesion cannot be regarded as an essential criterion of infection.

The character of the results obtained could be definitely related to a number of factors, among which may be mentioned the relative virulence of the organisms used for the primary and for the secondary inoculation, the progress of the original infection (acquired resistance), the presence of actively developing lesions (inhibition), and individual animal variation (native resistance). Finally, reactions of Type 4 which include all of the essential features of the local reaction to a primary infection were obtained with ease in certain animals by the superinoculation of the two older strains of *Treponema pallidum* upon the more recently isolated ones, even after the original lesions had practically resolved. It is thus clear that in given instances, the resistance acquired as a result of infection with an organism of low virulence may never reach the point of an effectual protection against one of high virulence. However, the crucial test of the possibilities presented by the problem of superinfection rests more upon the demonstration of a definite influence upon the course of the disease than upon any form of local reaction which may be produced. This phase of the subject is reserved for a separate communication.