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**Intracutaneous Vaccination of Rabbits with Pneumococcus.
II. Resistance to Infection.**

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In the preceding communication it was shown that the antibody response elicited in rabbits vaccinated intracutaneously with specific type strains of Pneumococcus is characterized by the presence in the serum of antiprotein antibodies in excess, together with a corresponding decrease or complete absence of type specific antibodies. That this change in the order of specific antibodies is related to the mode of inoculation was shown by the fact that the same strain (Type I Pneumococcus), when injected intravenously, invariably stimulates the formation of the dominant type-specific antibodies.

The present paper summarizes the results of a study of the occurrence and nature of the active resistance to infection which develops in rabbits vaccinated intracutaneously with R and S forms of Pneumococcus. Briefly, it may be stated that, following repeated skin inoculation of heat-killed suspensions of type-specific pneumococci or of the R variants, rabbits acquire a considerable degree of active immunity against infection with virulent strains of homologous and heterologous types. For example, rabbits, immunized intracutaneously with Type I may survive the intravenous injection of a dose as large as 0.2 cc. of homologous culture, the virulence of which is such that 0.0000001 cc. kills normal control animals. Similarly, rabbits immunized in the same manner to an avirulent strain of Type III may survive an infecting dose of from 0.5 to 1 cc. of a culture of the homologous type which by animal passage has been rendered so virulent that 0.001 cc. to 0.0001 cc. is sufficient to kill normal rabbits. Furthermore, animals inoculated intracutaneously with Type III become as resistant to subsequent infection with Type I as animals similarly immunized with homologous organisms. Even when an R strain of Pneumococcus derived from Type II is used for injection, rabbits acquire a high degree of resistance against infection with virulent Type I organisms. This form of acquired resistance, like that recently reported by Tillett following intravenous immunization with R pneumococci, may occur in the absence of demonstrable type-specific antibodies in the blood.

Although rabbits treated in this manner develop a solid immunity against infection with virulent strains of Pneumococcus, the serum of these animals, in the majority of instances, when used for the

passive transfer of immunity to mice, affords little or no protection whatever even against organisms of the homologous type.

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In the preceding communications, the intracutaneous vaccination of rabbits with Pneumococcus (S forms) has been shown to give rise chiefly to the formation of the antiprotein rather than the type specific antibodies, and to the development of an increased resistance to infection with organisms of homologous and heterologous types. The present paper describes briefly the development of an altered tissue reaction to Pneumococcus and its protein derivatives in rabbits which have been inoculated repeatedly into the skin with heat killed suspensions of R and S pneumococci.

Mackenzie and Woo¹ have shown that guinea pigs, injected intracutaneously with an alkaline extract of Pneumococcus, develop an allergic reaction in the skin to the bacterial protein; Zinsser and Grinnell² have produced allergic sensitization to pneumococcus autolysates in guinea pigs previously injected intradermally or intraperitoneally with the same material. Bull and McKee³ have recently shown that rabbits, after recovery from infection induced by intranasal inoculation of pneumococci, are highly skin-sensitive to pneumococcus autolysate.

The present observations were made in the course of a study of the antibody response and the immunity developed as a result of intracutaneous injection of rabbits. The intracutaneous injection in normal rabbits of 0.2 cc. of a heated vaccine, representing the bacteria from 2 cc. of broth culture, is followed by the appearance locally of a circumscribed slightly raised and indurated nodule, reddish in color, and measuring about 1 cm. in diameter. Upon repeated injection at weekly intervals the reaction changes in character; the size increases, often reaching a maximum of 4 to 6 cm. in diameter, accompanied by a spreading edema and purplish dis-

¹ Mackenzie, G. M., and Woo, S. T., *J. Exp. Med.*, 1925, xli, 65.

² Zinsser, H., and Grinnell, F. B., *J. Bact.*, 1927, xiv, 301.

³ Bull, C. G., and McKee, C. M., *J. Am. Med. Assn.*, 1928, xci, 396.