

and serum precipitin titers following the injection of these 2 types of serum.

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### Studies on Sensitization. III. Skin Sensitivity in the Absence of Serum Precipitins.

R. L. KAHN.

*From the Department of Bacteriology, University of Michigan.*

It is generally assumed that the tissue hypersensitiveness which follows repeated injections in rabbits of substances protein in nature, is accompanied by the presence of serum precipitins in these animals. Opie<sup>1</sup> claims that the local inflammatory response in sensitized animals is due to the meeting of the serum precipitin with the antigen in the tissues. In our studies, we have constantly found serum precipitins to accompany skin sensitivity in the early weeks of sensitization. But with time, especially after a lapse of several months following the initial sensitization of the rabbits, skin sensitivity is frequently present in the total absence of serum precipitins. The accompanying table gives an illustration of such findings.

TABLE I.  
Skin Sensitivity and Serum Precipitins Following a Prolonged Period after Discontinuance of Sensitizing Injections.

Rabbit	Weeks after Sensitizing Injections	Skin Sensitivity	Serum Precipitin
176	14	10,000	—
198	11	1,000	—
209	8	10,000	und.*
211	8	100,000	—
212	8	100,000	—
215	8	10	—

\* Precipitation obtained with undiluted serum only.

Studies now in progress indicate that sensitization following injection of protein, frequently precedes by a few days the appearance of serum precipitins. Soon, the latter reach a high level—even up to 1:1,000,000 dilution, or higher—the skin sensitivity titer usually lagging. Shortly the serum precipitin titer begins to drop, gradually becoming negative. The skin sensitivity titer, however, remains at a fairly high level for many months. No data are available at pres-

<sup>1</sup> Opie, E. L., *J. Immunol.*, 1929, **17**, 329.

ent as to the length of time a rabbit will remain sensitized after the protein injections have been discontinued.

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Studies on Sensitization. IV. Antitoxin Immunity Contrasted with Tissue Hypersensitiveness.

R. L. KAHN.

*From the Department of Bacteriology, University of Michigan.*

In connection with our studies of tissue hypersensitiveness following repeated injections of protein in rabbits, it seemed of interest to obtain a picture of antitoxin immunity in the same animal that is sensitized to some protein. A quantitative method for measuring skin immunity to diphtheria toxin, based on the Schick test, and for measuring the amount of antitoxin present in the serum of the immune animal, following intracutaneous injections of toxoid has been described.<sup>1</sup> Briefly, the least quantity of diphtheria toxin, in a 0.1 cc. volume, that is capable of producing an erythematous response following an intracutaneous injection in a normal rabbit is determined. This quantity usually ranges from 0.000003 MLD to 0.0000003 MLD. A given amount, such as 0.5 cc. of toxoid is then injected intracutaneously in fractional doses of 0.25 cc. in the same rabbit. After about 3 weeks, it will be found that the least quantity of diphtheria toxin that will produce erythema following intracutaneous injections of 0.1 cc. amounts, is considerably higher than 0.000003 MLD. With an additional injection of toxoid, the amount of toxin necessary to produce an erythematous response might be 0.1 or 1 MLD. With continued injections of toxoid, a skin response may not be obtained until 5 or 10 MLD of toxin are injected intracutaneously.

Parallel with this picture of the development of skin immunity to the toxin is the increase of antitoxin in the blood serum of the immunized animal, also measured by intracutaneous means, and determined as follows: A small dose of diphtheria toxin is chosen that invariably produces a definite inflammatory response in the skin of a normal rabbit when given intracutaneously in a 0.1 cc. amount. This dose, 0.0003 MLD, is mixed in series with varying dilutions

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<sup>1</sup> Kahn, R. L., *J. Bact.*, 1933, **25**, 81.