no skin response to 0.7 mg. of the same protein. The question of the sensitizing capacity of gelatin and split proteins merits further investigation.

Intracutaneous Compared with Intravenous Injections. No essential differences in skin sensitivity and in serum precipitin response were noted following these 2 methods of sensitization (Table II).

TABLE II.
Serum Precipitin and Skin Sensitivity Titers

Rabbit	Method of Injection	Dilutions human serum 1 cc. amounts injected 14 days apart	Response days after 2nd injection 0 days serum p'ptin	14 days skin s'tivity	14 days serum p'ptin
95	Intracut.‡	1:10	100,000	100	1,000,000
161	Intraven.	1:10	10,000	100	1,000,000

‡ The 1 cc. amount was given in fractional doses of 0.2 cc.

This table also shows that high precipitin titers can be obtained with small sensitizing doses of the proteins, contrary to a widely held belief that it is necessary to give multiple injections of comparatively large amounts to produce high titers. It should be emphasized, however, that variation in skin sensitivity and precipitin titers occurs in rabbits even when the sensitizing injections are made under identical conditions.

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Studies on Sensitization. II. Skin Sensitivity and Serum Precipitin Response Following Injections of Unheated and Heated Serum.

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Fresh, unheated human serum is toxic to the rabbit's skin. If 0.1 cc. of such serum is injected intracutaneously, a marked inflammatory response, boil-like in appearance, measuring from 1 to 2 cm. in diameter, follows with subsidence in about 10 days or longer. When human serum is previously heated for 30 minutes at 56°C., however, it has practically no toxic effect on the rabbit's skin. Intracutaneous injection of 0.1 cc. produces a slight transitory thickening of the skin which usually disappears in 24 hours. The question arose, whether the inflammation accompanying the injection of

unheated serum might serve as a stimulus to the skin sensitivity and serum precipitin responses of the rabbit. Accordingly, one group of 8 rabbits was injected with unheated serum and a corresponding group with heated serum. Usually 2 injections were employed, the first one being 1 cc., and the second (10 or 14 days after the first), 0.5 cc. These amounts were given intracutaneously in fractional doses of 0.2 cc. The results as demonstrated in the accompanying table, show but little difference in the skin sensitivity

TABLE I.

Skin Sensitivity and Serum Precipitin Response Following Intracutaneous Injections of Unheated and Heated Serum

Rabbit	Serum	1st injection, 1 cc.; 2nd inj., 10 days later, 0.5 cc.	Skin reactions following inj. given fractionally in 0.2 cc. doses.	Response—days after 1st injection 10		30		45	
				Skin s'tivity	Serum p'pitin	Skin s'tivity	Serum p'pitin	Skin s'tivity	Serum p'pitin
33	Unheated	1st inj.	Boil-like areas 1.5 cm. diam. necrotic centers, subsidence in 10 days						
		2nd "	Large confluent mass, 10 cm. diam. necrotic centers at points of injection, subsidence in 20 days	100	10,000	10,000	100,000	10,000	10,000
35	Heated 30 min. 56°C.	1st "	Slightly thickened pink areas, subsidence in 24 hours						
		2nd "	Raised inflamed areas 1.5 cm. diam., subsidence in 5 days	10	100,000	100	10,000	1,000	10,000

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.

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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[1] 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-

[1] Opie, E. L., *J. Immunol.*, 1929, **17**, 329.