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Immunological Specificity of Sulfonamide Azoproteins.

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The immunological aspect of the toxic manifestations[1, 2, 3] occurring during the course of sulfonamide therapy has been little studied. There are reports that in guinea pigs there can be obtained cutaneous sensitivity to prontosil,[4] but not to sulfanilamide.[5]

There have been a few instances in which hypersensitive patients have shown positive homologous skin tests.[6–10] The phenomenon of photosensitization[1, 3] is well established and there is evidence[11] for an allergic mechanism. However, usually the patch, scratch, and intradermal tests have been negative.[5, 7, 12–15] Experiments using the serums of hypersensitive patients have been negative no matter whether the antigen was a saline solution of sulfanilamide[5, 10] or the azoprotein.[16]

Methods. The sulfonamide* azoproteins were prepared essentially

1 Long, P. H., and Bliss, E. A., *The Clinical and Experimental Use of Sulfanilamide, Sulfapyridine and Allied Compounds*, Chapter on Clinical Toxic Manifestations, 1st ed. 1939, The Macmillan Company, New York.

2 Keefer, C. S., *Cal. and West. Med.*, 1939, **51**, 143.

3 Mellon, R. R., Gross, P., and Cooper, F. B., *Sulfanilamide Therapy of Bacterial Infections*, 1st ed. 1938, Charles C. Thomas, Springfield and Baltimore.

4 Nitti, F., and Bovet, D., *Bull. Soc. Chim. Biol.*, 1937, **19**, 837; cited by Long and Bliss.[1]

5 Hageman, P. O., and Blake, F. G., *J. A. M. A.*, 1937, **109**, 642.

6 Salvin, M., *J. A. M. A.*, 1937, **109**, 1038.

7 Goodman, M. H., and Levy, C. S., *J. A. M. A.*, 1937, **109**, 1009.

8 Myers, G. B., Vonder Heide, E. C., and Balcerski, M., *J. A. M. A.*, 1937, **109**, 1983.

9 Sézary, A., and Horowitz, A., *Bull. et mém. Soc. Méd. d. hôp. de Paris*, 1936, **52**, 767; cited by Mellon, Gross, and Cooper.[3]

10 Loveman, A. B., and Simon, F. A., *Arch. Dermat. and Syph.*, 1939, **40**, 29.

11 Epstein, S., *J. Invest. Dermatology*, 1939, **2**, 43.

12 Harvey, A. M., and Janeway, C. A., *J. A. M. A.*, 1938, **109**, 12.

13 Beinhauer, L. G.; cited by Mellon, Gross, and Cooper.[3]

14 Steven, R., *Cal. and West. Med.*, 1939, **50**, 419.

15 Erskine, D., *Brit. Med. J.*, 1939, **2**, 104.

16 Schlesinger, E. R., and Mitchell, W. L., *Am. J. Dis. Child.*, 1938, **56**, 1256.

* Sulfanilamide, sulfapyridine, 4-sulfanilamidoaniline, sodium sulfathiazole, sulfanilic acid, sulfanilylhydroxylamine. For the first three compounds I am indebted to the American Cyanamid Company.

according to the method of Landsteiner and van der Scheer.[17] The immunizing antigens were made with sulfonamides coupled to beef serum. Test antigens were made with sulfonamides coupled to human serum or egg albumin. The usual methods were employed with the sulfonamide azoproteins to produce and test cutaneous and anaphylactic sensitivity in guinea pigs and precipitins in rabbits. Precipitin tests were made by the ring contact method. The attempt to secure cutaneous sensitivity to the simple chemicals uncombined with protein, by a series of intradermal injections in guinea pigs, followed the procedure of Golden and Gierson.[18] Other details will be given in a later publication.

Discussion and Summary of Results. 1. In all 3 types of experiment, skin tests, anaphylaxis, and precipitin reactions, the sulfanilamide and sulfapyridine azoproteins produced heterologous antibodies for each other although the homologous reactions were always stronger. The animals injected with sulfapyridine azoprotein were more reactive to sulfanilamide azoprotein than vice versa. Therefore it might be predicted clinically that patients hypersensitive to sulfanilamide could tolerate sulfapyridine better than those patients sensitive to sulfapyridine could tolerate sulfanilamide. 2. Sodium sulfathiazole azoprotein did not form a precipitate with sulfanilamide or sulfapyridine azoprotein antiserums. This suggests the thiazole may be too far removed from the fundamental sulfanilamide structure to participate clinically in heterologous reactions. 3. The highest precipitin titer found was that of sulfanilic acid azoprotein antigen and sulfanilamide azoprotein antiserum. It seems difficult to account for this as a minor group phenomenon. Is it possible that the sulfanilamide *in vivo* is changed to a structure like sulfanilic acid which then acts as a precipitinogen? 4. There was no evidence that the simple chemicals uncombined with protein could serve either as immunizing or testing antigens. However, 2% sodium sulfapyridine inhibited sulfanilamide and sulfapyridine azoprotein precipitins without affecting the precipitins for beef serum.

[17] Landsteiner, K., and van der Scheer, J., *J. Exp. Med.*, 1927, **45**, 1045.

[18] Golden, A., and Gierson, H. W., *J. Immunol.*, 1939, **36**, 277.