

Tests of Possible Antagonism of Gold for Histamine Toxicity and Certain Allergic Reactions.*

WILLIAM C. KUZELL AND ROBERT H. DREISBACH.

From the Department of Pharmacology and Therapeutics, Stanford University School of Medicine, San Francisco, Calif.

There has been considerable discussion about the possible allergic nature of rheumatoid arthritis as a disease process. The supporting evidence has been both clinical and experimental. According to Hench,¹ "no one has been able to set up any one particular syndrome as allergic arthritis or to prove that any of the arthritides are chiefly or solely the results of bacterial or food allergy." However, many attempts have been made to determine the possible role of bacterial allergy in the production of rheumatoid arthritis.² Klinge has reported the production of an arthritis in rabbits sensitized to horse serum by subsequently injecting horse serum into the joints.³ More recently Rich and Gregory have suggested that the characteristics of rheumatic carditis develop as a result of anaphylactic hypersensitivity.⁴

At the same time, increasing evidence has accumulated that gold salts favorably influence the clinical course of rheumatoid arthritis.^{5,6,7} In rats and mice the experimental arthritis produced by the pleuropneumonia-like organisms is prevented by the use of gold

salts and the disease once begun is arrested by their use.^{8,9}

In view of the favorable claims for an allergic factor in rheumatoid arthritis and because gold salts seem to alter favorably the course of the disease in some unknown way it was thought desirable to determine whether the gold ion could prevent histamine toxicity and anaphylactic shock and beneficially effect the Arthus phenomenon in animals. If it could be demonstrated that the gold ion altered beneficially experimental allergic reactions, the mode of beneficial action of gold in rheumatoid arthritis would be indicated, and conversely, if such experimental responses were not altered, this would suggest that gold acted in some other manner.

Anti-Anaphylactic Effect. Ten guinea pigs (weighing from 210 to 375 g) were each given 0.1 cc of horse serum hypodermically, and on the same day and every 3 days thereafter for 7 doses the guinea pigs were given 10 mg per kg of gold sodium thiosulfate intramuscularly. Twenty-eight days after the initial injection of the horse serum the animals were given 0.5 cc of horse serum intravenously and 11 of the 12 animals died in 5 to 15 minutes. Twelve control animals were given similar doses of horse serum without gold sodium thiosulfate, and only 1 animal survived in this group.

Acute Histamine Toxicity. Ten guinea pigs (weighing from 210 to 375 g) were given 10 mg per kg of gold sodium thiosulfate intramuscularly for 5 doses in a 7-day period and 4 of the animals died during the week. At the end of the week the 6 remaining animals, which had received gold were given 1 mg per kg of histamine phosphate intravenously, and they all died in 1 to 5

* This work was done under contract with the Office of Naval Research.

¹ Hench, P. S., Bauer, W., Ghrist, D., Hall, F., Holbrook, W. P., Key, J. A., and Slocumb, C. H., *Ann. Int. Med.*, 1938, **11**, 1089.

² Cecil, R. L., *Proc. Mayo Clinic*, 1940, **15**, 556.

³ Klinge, F., *Beitr. z. path. Anat., v. z. all. Path.*, 1929, **83**, 185.

⁴ Rich, A. R., and Gregory, J. E., *Bull. Johns Hopkins Hosp.*, 1943, **72**, 65; *ibid.*, 1943, **73**, 239.

⁵ Freyberg, R. H., Block, Walter D., and Wells, G. S., *Clinics*, 1942, **1**, 537.

⁶ Ragan, Charles, and Tyson, T. L., *Am. J. Med.*, 1946, **1**, 252.

⁷ Freyberg, R. H., *Proc. Staff Meet. Mayo Clinic*, 1942, **17**, 534.

⁸ Sabin, A. B., and Warren, J., *J. Bact.*, 1940, **40**, 823.

⁹ Tripi, H. B., and Kuzell, W. C., *Stanford Med. Bull.*, 1947, **5**, 98.

minutes. Nine guinea pigs in the same weight range were taken as controls and given only the histamine phosphate in the same dosage, and they all died in 1 to 5 minutes after the injection.

Arthus Phenomenon. Rabbits were used to determine the possible ameliorating effects of gold sodium thiosulfate on the Arthus phenomenon. The method was as follows: 10 rabbits were sensitized by weekly subcutaneous injections of 1 cc of a 1 to 10 dilution of horse serum in physiological saline solution, according to the method previously used in this department.¹⁰ After sensitization was established, as shown by swelling at the site of injection, the rabbits were divided into 2 groups of 5 each. One group was given weekly intravenous injections of gold sodium thiosulfate beginning at 10 mg per kg and increasing to 30 mg per kg. The total dosage was 100 mg per kg in 6 weeks. The other group of 5 rabbits were kept as a control. The day following the intravenous injections of gold sodium thiosulfate, all 10 animals were given a subcutaneous injection of 1.0 cc of a 1 to 10 dilution of horse serum in physiological saline. The diameters of the resulting swellings were recorded at the end of 24 hours. The average diameters of the swellings in the control group ranged from 2.5 to 4.0 cm and in the gold treated group from 2.4 to 4.6 cm. Thus there was no demonstrable difference between the treated and untreated animals in the size of the

wheals resulting from the horse serum.

Gold was given intravenously to these rabbits as a matter of convenience and because this method is also used clinically.

Discussion. Evidently gold sodium thiosulfate given intramuscularly to guinea pigs offers no protection against anaphylactic shock, or the acute toxicity of histamine. Further, gold sodium thiosulfate does not affect the development of the characteristic wheal in the Arthus phenomenon; although, it should be stated that the antihistamine agents, pyribenzamine and benadryl, likewise fail to inhibit the development of this phenomenon.¹¹ However, Kyser, McCarter, and Stengle have recently reported that antihistamine drugs impede the development of myocardial lesions in rabbits injected with horse serum.¹² Since gold sodium thiosulfate does not appear to alter these manifestations of experimental sensitivity, it seems reasonable to assume that the beneficial action of gold therapeutically also does not rest on inhibition or suppression of allergic responses.

Conclusions. (1) Gold sodium thiosulfate failed to protect guinea pigs against lethal doses of histamine and anaphylactic shock, and did not demonstrably alter the magnitude of the Arthus phenomenon in rabbits. (2) These negative results suggest that the gold ion mediates its beneficial effects in rheumatoid arthritis in ways other than by amelioration of objective allergic manifestations.

¹⁰ Chu, W. C., and Cutting, W. C., *Proc. Soc. Exp. Biol. and Med.*, 1946, **63**, 347.

¹¹ Dreisbach, R. H., *J. Allergy*, 1947, in press.

¹² Kyser, F. A., McCarter, J. C., and Stengle, J., *J. Lab. and Clin. Med.*, 1947, **32**, 379.