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Agglutination and Precipitation Reactions in Rheumatoid Arthritis with Hemolytic Streptococci Groups A to G.

M. H. Dawson and Miriam Olmstead.

From the Department of Medicine, College of Physicians and Surgeons, Columbia University, and the Arthritis Clinic of the Presbyterian Hospital, New York City.

It has been shown[1-4] that, in a significant proportion of cases, rheumatoid arthritis sera agglutinate certain strains of hemolytic streptococci and precipitate group-specific fractions of these organisms. Lancefield's demonstration of distinct serological groups within the hemolytic streptococci[5, 6, 7] has made possible a more detailed study of the nature and significance of these immunological reactions. Agglutination and precipitation tests were carried out with rheumatoid arthritis and control sera using representative strains of Groups A to G as agglutinogens and group-specific extracts as precipitinogens. Similar studies were recently carried out by McEwen, Chasis and Alexander.[8]

Agglutination. Seventy-six rheumatoid arthritis sera were examined for agglutinins against Group A organisms, 60 against group B, 47 against group C, 67 against group D, 15 against group E, 15 against group F, and 14 against group G by the technic previously described.[3] The results were classified as "positive," "doubtful" or "negative". In classifying the reactions both the character of the agglutination and the titer were taken into consideration. Sera agglutinating in a titer of 1:160 or higher were considered "positive" only if they gave a strong reaction in lower dilutions. Sera agglutinating in a titer of 1:160, 1:320 or even higher were considered "doubtful" unless the reactions in the lower dilutions were definitely more marked than in the higher dilutions. Sera were classified as "negative" when agglutination occurred in dilutions of less than 1:40.

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5 Lancefield, R. C., *J. Exp. Med.*, 1933, **57**, 571.

6 Lancefield, R. C., *J. Exp. Med.*, 1934, **59**, 441.

7 Lancefield, R. C., and Hare, R., *J. Exp. Med.*, 1935, **61**, 335.

8 McEwen, C., Chasis, H., and Alexander, R. C., Proc. Soc. Exp. Biol. and Med., 1935, **33**, 133.

The agglutination reactions with Group A organisms were similar to those previously reported.[3] Quite different results, however, were obtained with the other groups. In only 3 instances were definitely "positive" agglutinations observed with organisms *other than those of Group A.* In 2 of these 3 cases the serum also gave a strongly positive agglutination with group A strains. It was further observed that control sera from a variety of diseases agglutinated organisms other than those of group A to approximately the same degree as did rheumatoid arthritis sera. On the other hand, the only control sera which agglutinated group A organisms in a titer comparable with that observed in rheumatoid arthritis were those from proven, severe, hemolytic streptococcal infections. The results therefore indicate that the agglutination reaction in rheumatoid arthritis sera is one which is highly characteristic of group A hemolytic streptococci.

Precipitation. Reactions were carried out with group-specific extracts of groups A to G prepared by Lancefield's method.[5] It is well recognized that extracts prepared in this manner contain other constituents in addition to the C substance upon which group-specificity depends. In the case of group A and group B strains, however, comparatively pure C substance was made available through the kindness of Dr. Heidelberger and Mrs. Lancefield. These purified extracts were employed in a limited number of experiments. The tests were carried out in the same manner as previously described[4] except that smaller quantities of both serum (0.1 cc.) and extracts (0.2 cc. and 0.05) were employed.

Seventy-eight rheumatoid arthritis sera were tested against the crude HCl extracts of groups A and B, 74 against group C, 64 against group D, 36 against group E, 29 against group F and 33 against group G. The results with the group A extract were of the same general order as those previously reported.[4] Strong precipitins were observed only in those sera which gave a strongly positive agglutination reaction. These sera also gave a certain number of cross reactions with extracts of groups other than group A. but in general the precipitation was definitely less marked. Thus, of 8 sera giving +++ or ++++ reactions with group A, one also reacted with group B and 2 with group G. It is believed that these cross reactions can be accounted for by the presence of common antigenic constituents in the crude extracts. The observation that the sera of rabbits receiving large doses of vaccine or many series of small doses are apt to react with the non-specific protein constituents of other groups supports this conclusion.

Thirty-two control sera were tested against group A extract, 30 against group B, 24 against group C, 20 against group D, 11 against groups E, F, and G. Strong precipitation reactions were observed with group A extract in only 2 cases, one a case of hemolytic streptococcus septicemia (group A) and the other a case of nephritis. The serum from the case of hemolytic streptococcus septicemia also gave a strong precipitin reaction with the crude HCl extract of both groups B and G. This result further suggests that the extracts as prepared contained common antigenic constituents.

When purified group-specific carbohydrates of groups A and B were employed as precipitinogens strong reactions were obtained with the group A material only. It should be mentioned, however, that the purified material was prepared by different methods and the results may therefore not be strictly comparable.[6, 9]

These results in general are in accord with those of McEwen, Chasis and Alexander[8] although these workers obtained a greater number of cross reactions. Our findings indicate that such cross reactions can be accounted for by the presence of common antigenic constituents in the various groups and that both the agglutination and precipitation reactions in rheumatoid arthritis sera are characteristic for group A hemolytic streptococci.

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Antistreptolysin Titers in Rheumatoid Arthritis.

M. H. DAWSON AND MIRIAM OLMSTEAD.

From the Department of Medicine, College of Physicians and Surgeons, Columbia University, and the Arthritis Clinic of the Presbyterian Hospital, New York City.

The findings of Todd,[1] Coburn and Pauli,[2] and others indicate that the antistreptolysin test furnishes an accurate method for determining the presence of recent infection with hemolytic streptococci of group A. Coburn and Pauli showed that, following hemolytic streptococcal infections, the antistreptolysin titer of the serum rises rapidly, remains elevated for a variable number of months

[9] Heidelberger, M., personal communication.

[1] Todd, E. W., *Brit. J. Exp. Path.*, 1932, **13**, 248; *J. Path. and Bact.*, 1934, **39**, 299.

[2] Coburn, A. F., and Pauli, R., *J. Exp. Med.*, 1935, **62**, 137; *J. Clin. Invest.*, 1935, **14**, 769.