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Studies on the Etiology of Rheumatoid Arthritis. II. Agglutination Reactions with Hemolytic Streptococci in Rheumatoid Arthritis.

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The present authors reported[1] bacteriological investigations on blood, synovial fluid and subcutaneous nodules in rheumatoid arthritis, which entirely failed to confirm the results of Cecil, Nicholls and Stainsby. Cecil, Nicholls and Stainsby[2] further stated that the sera of patients suffering from rheumatoid arthritis possessed the property of agglutinating their *"typical strains"* to a remarkably high titre.

Through the courtesy of Dr. Cecil several *"typical strains"* were made available. Specimens of serum were obtained from a large number of patients suffering from rheumatoid arthritis and agglutination tests were done using these strains as agglutinogens. For control purposes a large number of other organisms, obtained from a variety of sources, was similarly employed against the sera of patients with rheumatoid arthritis. The study was further controlled by utilizing a large number of specimens of serum obtained from patients suffering from both related and unrelated diseases.

In addition to the "typical strains" of Cecil, Nicholls, and Stainsby, which, in the authors' experience, showed varying degrees of hemolytic properties, cultures of the following organisms were employed in the agglutination tests: (1) *Streptococcus hemolyticus,* 4 strains; these included strains obtained from scarlet fever, erysipelas and from the throat of a patient with rheumatic fever; (2) *Streptococcus viridans,* 7 strains; (3) *Streptococcus anhemolyticus,* 12 strains; (4) green diplococci (exact nature undetermined) 3 strains; (5) *Staphylococci,* 5 strains.

Specimens of sera obtained from 66 patients suffering from typical rheumatoid arthritis were employed during the course of this study. Control sera were obtained from 50 cases of both related and unrelated diseases. These diseases included the following:

[1] Dawson, M. H., Olmstead, Miriam, and Boots, R. H., PROC. SOC. EXP. BIOL. AND MED., 1930, **28**, 419.

[2] Cecil, R. L., Nicholls, E. E., and Stainsby, W. J., Scientific Proc., 30th Annual Meeting Am. Assn. Path. and Bact., New York, April, 1930; Rep. of 45th Annual Meeting, Assn. Am. Physicians, Atlantic City, May, 1930; *Am. J. Med. Sci.*, 1931, **181**, 12.

osteo-arthritis, 18 cases; gonococcal arthritis, 4 cases; spondylitis, 8 cases; intermittent hydrarthrosis, 1 case; subacute rheumatic fever, 6 cases; non-articular rheumatism, 4 cases; other diseases—chronic nephritis, thromboangiitis obliterans, gastric ulcer, lung abscess, pulmonary tuberculosis, pneumonia, sacro-iliac strain, neurosis, tuberculous peritonitis—9 cases.

The results of over 1000 agglutination tests, using 37 different cultures as agglutinogens on 66 cases of rheumatoid arthritis and 50 control cases have led to the following conclusions: (1) In the great majority of cases sera of patients with rheumatoid arthritis possess the property of agglutinating hemolytic streptococci to an extraordinarily high titre. (2) Strains of *Streptococcus hemolyticus* obtained from scarlet fever, erysipelas, and from the throat of a patient with rheumatic fever were agglutinated by these sera to as high a titre as were the "typical strains" of Cecil, Nicholls and Stainsby. (3) Absorption tests carried out with *Streptococcus hemolyticus* from scarlet fever, erysipelas and the "typical strains" of Cecil, Nicholls and Stainsby failed to show any evidence of specificity of the agglutination reaction for the various strains of *Streptococcus hemolyticus* examined. (4) Of the 50 control sera only 2 showed evidence of agglutinins for the strains of *Streptococcus hemolyticus* employed. In these 2 instances the agglutination was of a very low titre and of doubtful significance. (5) Of 31 strains of other organisms used none was agglutinated by the sera of patients with rheumatoid arthritis to any significant titre.

The present study supports the following hypothesis: Rheumatoid arthritis, in the majority of instances, results from infection with *Streptococcus hemolyticus*. The evidence so far accumulated indicates that no specific strain of *Streptococcus hemolyticus* can be considered as the sole etiological agent but this phase of the problem is being further investigated. No evidence has been obtained that the organisms gain access to the circulation or the joint tissues. The suggestion is therefore advanced that the majority of cases of this disease represent the response of the affected tissues to products of *Streptococcus hemolyticus* absorbed from a distant focus.