THE RELATION OF THE CARDIAC LESIONS OF RHEUMATOID ARTHRITIS TO THOSE OF RHEUMATIC FEVER

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The use of the term "rheumatoid" to designate one of the types of chronic arthritis reflects the persistent suspicion that this disease is somehow related to rheumatic fever. Synovitis and subcutaneous nodules occur in both rheumatoid arthritis and rheumatic fever, but we are dealing herein with the less obvious common ground of cardiac damage.

Definition for Present Discussion

For the purposes of the present discussion, the rheumatoid arthritis of childhood (Still's disease) is included, but the ankylosing spondylitis (rheumatoid spondylitis) of Marie-Strümpell is not, except when it occurs as a complication of frank rheumatoid arthritis. Also excluded are degenerative (hypertrophic or osteo-) arthritis, arthritis secondary to focal infection, and, of course, chronic specific infectious arthritis such as that due to tuberculosis. Likewise excluded for the sake of clarity are the numerous early or doubtful cases of rheumatoid arthritis, leaving only the frank, severe, late cases of this disease, whose diagnosis (based on the prominent characteristics of chronicity, tendency to symmetrical involvement, particularly of the proximal interphalangeal finger joints, and tendency to deforming contractures) is obvious and unquestionable.

Cardiac Lesions and Anaphylaxis

Baggenstoss and Rosenberg (1941) have reported from the Mayo Clinic that patients answering this description have at autopsy an abnormally high incidence of cardiac lesions which are identical with those of rheumatic heart disease. Their criteria for recognition of both rheumatoid arthritis and rheumatic heart lesions were carefully defined. This discovery has been confirmed by Bayles (1943), Fingerman and Andrus (1943), and Young and Schwedel (1944), but its interpretation has remained obscure. In discussing possible explanations, Rosenberg and others (1944) have raised the question whether rheumatoid arthritis is responsible for a form of heart disease which is indistinguishable from

rheumatic heart disease, and the question whether rheumatoid arthritis and rheumatic fever are related.

A clue to this mystery may be found in the work of Rich and Gregory (1943, 1944), who were able to produce in experimental animals a carditis which closely resembled that of human rheumatic heart disease. This was accomplished simply by rendering rabbits "hypersensitive" by intravenous administration of horse serum, and the carditis was regarded as a sensitivity phenomenon analogous to anaphylaxis. Rich and Gregory (1943) inclined to the view that an anaphylactic type of mechanism is responsible for the lesions of rheumatic heart disease.

According to the generally accepted theory (cf. Boyd, 1943), the following sequence of events takes place in an anaphylactic reaction: (1) production of antibodies in response to the presence of an antigen; (2) fixation of some antibodies on or in tissue cells (sessile antibody); (3) union of sessile antibody and homologous antigen; (4) tissue response to this union, the nature of the response varying with the tissue and the animal species involved.

Antigens

While in classical rheumatic fever the antigen is probably derived from haemolytic streptococci, Rich and Gregory (1944) have suggested that *other* antigens could well give rise to lesions in man identical with those of classical rheumatic heart disease. It is the purpose of the present communication to propose that such is actually the case in rheumatoid arthritis, that is, that in rheumatoid arthritis, cardiac lesions indistinguishable from those of rheumatic fever are produced by tissue response to the union of sessile antibody and fresh antigen, the latter being necessarily homologous to the sessile antibody but presumably *different* from the

antigen in rheumatic fever. In other words, the mechanism of production of cardiac lesions is the same in the two diseases but the antigens are different. In each case, the specificity of antibody for antigen is unquestioned. Granted the entrance of fresh antigen into the circulation in suitable amounts and at appropriate intervals, the nature of the antigen is immaterial to the theory that the response of heart tissue to the union of antigen and its homologous sessile antibody represents a final common pathway of a non-specific nature.

It is obviously essential to our argument to demonstrate that the cause of rheumatoid arthritis is not the same as that of rheumatic fever. While in both diseases this awaits elucidation, enough is now known to indicate that in all probability the haemolytic streptococcus is a causative factor in rheumatic fever but not in rheumatoid arthritis. The relation of scarlet fever and haemolytic streptococcus sore throat to acute rheumatic fever and the prophylaxis of acute rheumatic fever by sulphonamides are well established. The serologic evidence has been summarized by Rantz and others (1945) with the statement that "high titres of various antistreptococcus antibodies and cutaneous hypersensitivity to products and fractions of haemolytic streptococci are usually demonstrable in persons suffering from acute rheumatic fever or from recurrences of this disease". On the other hand, the extraordinary prolongation of the active stage of the joint lesions of rheumatoid arthritis, their tendency to symmetry, and their indifference to sulphanilamide and penicillin may be cited as evidence against a streptococcal aetiology for this kind of arthritis. The high titre of streptococcal agglutinins in rheumatoid arthritis sera has been the bulwark of the streptococcus theory of aetiology of this disease. However, the apparent strength of these agglutinins has recently been accounted for (Wallis, 1947) as being due to a non-specific enhancement of the action of normally present agglutinins. Whatever the substance eventually to be found serving as antigen in rheumatoid arthritis, the evidence at hand indicates that it is not a streptococcal derivative. It is therefore presumably different from the antigen in rheumatic fever.

In the cases reported by Baggenstoss and Rosenberg, rheumatic-type heart disease was found in 16 of 22 autopsies of frank rheumatoid arthritis, an incidence of 72 per cent., as compared with the over-all Mayo Clinic incidence of 5 per cent. In only 2 of these 16 cases had a history of rheumatic fever been obtainable. These observers noted that cardiac damage tends to be less severe (and therefore usually unrecognizable clinically) in rheumatoid arthritis than in classical rheumatic fever, and sug-

gested that this difference might result from the fact that the onset of rheumatoid arthritis is later than the onset of rheumatic fever. They cited the general belief that the heart is more vulnerable to rheumatic infection in younger persons, and quoted evidence that in 90 per cent. of rheumatic fever cases the onset is before the age of 15, whereas in 90 per cent. of rheumatoid arthritis it is after 15. In less than half their cases had heart disease been diagnosed during life. Nevertheless, the cardiac lesions were regarded as an important contributory cause of death in 7 cases: 3 died in congestive failure, and 4 apparently died of an acute "rheumatic" inflammation. None of the latter 4 gave a history of rheumatic fever. Their ages at death and durations of arthritis were: 14 and 2 years; 24 and 2 years; 17 and 6 years; 55 and 7 years.

Young and Schwedel found an even higher incidence (33 of 38 cases, or 86 per cent.) of "rheumatic heart disease" in autopsies of frank rheumatoid arthritis. There was a history of rheumatic fever in 4 and an ante-mortem diagnosis of heart disease in 18. The cardiac lesions were regarded as an important contributory cause of death in 21. For what it is worth: in the great majority of cases in which temporal relationships could be established, the arthritis preceded the discovery of heart disease. If our interpretation is correct, the adage that "nobody dies of rheumatoid arthritis" becomes untenable.

The concept of sensitivity reactions in rheumatoid arthritis also furnishes an explanation of the presence of focal collections of round cells in the peripheral nerves and skeletal muscles in this disease. The existence of lesions of this type in the peripheral nerves was reported by Freund and others (1942). It seems likely that these cell collections have the same origin as the cardiac lesions which are under discussion, namely the result of union of fresh circulating antigen with homologous sessile antibody. This interpretation is supported by the incidence of "rheumatic" heart lesions in the same patients. Freund and his collaborators examined numerous blocks taken at autopsy from the peripheral nerves of each of 5 individuals. The largest number of cell collections in any case was 65, and this subject also had chronic rheumatic heart disease with mitral valvulitis and pericardial adhesions; the next largest number was 22, and this subject also had acute bacterial (haemolytic streptococcus) mitral and aortic valvulitis; the third largest number was 12, accompanied by a thickened mitral valve; while in the remaining 2 cases, with 5- and 2-cell collections respectively, cardiac lesions of the rheumatic type were not found. Furthermore, Freund and others quoted a report by Koeppen, who

described similar cell collections in peripheral nerves during the acute or subacute stages of rheumatic fever but not after these phases had subsided. One gets the impression that fresh antigen enters the circulation more frequently, over a longer period, and probably in smaller amounts in rheumatoid arthritis than in rheumatic fever, and also that the "sensitivity lesions" are more apt to leave permanent recognizable scars in the heart than in the peripheral nerves.

Collections of round cells have been described in the skeletal muscles of persons with rheumatoid arthritis by Steiner and others (1946). These collections were present in muscle from each of the 9 cases examined. Control specimens from 196 individuals who did not have rheumatoid arthritis failed to show these lesions, with one exception, which was from a case of subacute bacterial endocarditis superimposed on old rheumatic heart disease. Steiner and others mentioned reports by Klinge and by Graeff of the presence of cellular infiltrations in the voluntary muscles in rheumatic fever.

Designation of Heart Disease in Rheumatoid Arthritis

It is not easy to find a satisfactory designation for the heart disease which accompanies rheumatoid arthritis. "Rheumatoid arthritis heart disease" is not descriptive of the cardiac lesions. The term "rheumatoid heart disease", used by Rosenberg and others (1944), suggests a relation to classical rheumatic carditis but fails to connote the concept of Rich and Gregory of lesions resulting from antigen-antibody union. We have avoided the word "allergy" because of its elasticity and because we do not believe that "natural hypersensitivity" (as contrasted with acquired or induced hypersensitivity) plays a part in rheumatoid arthritis. "Anaphylaxis" likewise is unsuitable because it means different things to different people, in its narrowest sense signifying a shock-like state artificially produced in some animals. The origin of the cardiac lesions under consideration is for the present probably best indicated by referring to them as the result of "hypersensitivity" or, better still, simply "sensitivity".

Discussion of the present topic is necessarily on a speculative basis inasmuch as means have not been found for the experimental production of either rheumatoid arthritis or rheumatic fever.

Summary

It is proposed that the cardiac damage which accompanies rheumatoid (atrophic) arthritis results from the union of antigen with homologous antibody which has been previously fixed in heart tissues. As

"sensitivity lesions", these changes would be qualitatively indistinguishable from those of classical rheumatic heart disease, although the responsible antigen is apparently not the same in the two diseases. The occurrence of widespread focal microscopic lesions in other structures (peripheral nerve and voluntary muscle) in both rheumatoid arthritis and rheumatic fever is cited in support of this view.

Acceptance of this proposal would mean to the clinician that rheumatoid arthritis is a potentially fatal disease, and to the pathologist that all cardiac lesions resembling those of rheumatic fever have not necessarily the same cause.

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Rapports entre les Lésions Cardiaques de l'Arthrite Rhumatismale et celles du Rhumatisme Articulaire Aigu

RÉSUMÉ

L'auteur suggère que les lésions cardiaques qui accompagnent l'arthrite rhumatismale (atrophique) résultent de l'union d'un antigène avec l'anticorps homologue qui s'est précédemment fixé dans les tissus cardiaques. En tant que "lésions de sensibilité", ces modifications ne se distinguent pas qualitativement de celles qui sont dues au rhumatisme cardiaque classique, bien que l'antigène responsable semble n'être pas le même dans ces deux maladies. La présence de nombreux foyers microscopiques dans d'autres tissus (nerf périphérique et muscle strié) aussi bien dans l'arthrite rhumatismale que dans le rhumatisme articulaire aigu est donnée à l'appui de cette hypothèse.

L'acceptation de cette théorie signifierait pour le clinicien que l'arthrite rhumatismale est une maladie qui peut être fatale, et pour le pathologiste que toutes les lésions cardiaques ressemblant à celles du rhumatisme articulaire aigu n'ont pas nécessairement la même cause.