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 demon-
strate 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 haemo-
lytic-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 sum-
murized by Rantz and others (1945) with the state-
ment that "high titres of various antistreptococcus
antibodies and cutaneous hypersensitivity to pro-
ducts 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 sulphanalamide and penicillin may be
cited as evidence against a streptococcal etiology
for this kind of arthritis. The high titre of strepto-
coccal agglutinins in rheumatoid arthritis sera has
been the bulwark of the streptococcus theory of
etiology 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 rheu-
matoïd 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 Rosen-
berg, 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 “rheu-
matic” 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 “rheu-
matic heart disease” in autopsies of frank rheuma-
toid 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 estab-
ilished, 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 anti-
body. 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 periph-
erald 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 rheu-
matic 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 Kline 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.

**REFERENCES**


**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 (atrophiante) 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.
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