SEROLOGICAL STUDIES IN RHEUMATIC FEVER

I. The "Phase" Reaction and the Detection of Autoantibodies in the Rheumatic State

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(Received for publication, March 4, 1949)

It has been suggested that an allergic type of mechanism may be responsible for the rheumatic process. However, it must be recognized that the evidence for this is far from conclusive. The allergic hypothesis of the disease is based chiefly upon certain characteristics of the disease which suggest allergy (5) such as the latent period after infection with *S. hemolyticus* (1–5), the clinical similarity to serum sickness (6), and the morphological analogy between rheumatic lesions and those produced by necrotizing allergic reactions in experimental animals (7–11). It is generally recognized that infection with the hemolytic streptococcus is frequently followed by the appearance of circulating antibodies (12, 13) or skin sensitivity (14–16) to streptococcus products. However, these responses do not appear to differ qualitatively or quantitatively in rheumatic subjects from those of non-rheumatic individuals with streptococcus infections, particularly if the infection is persistent (17–19). Identification of the antigens or antibodies involved in the presumed allergic reaction in rheumatic fever would give experimental support to the allergic hypothesis. There are relatively few reported studies concerned with the demonstration of antibodies in rheumatic patients which are not found in other individuals recovering from streptococcus infections. Thus, the phase reaction reported by Coburn and Pauli (20), and the development of autoantibodies to liver tissue (Brokman, Brill, and Frendzel (28)) and to heart tissue (Cavelti (30)) have been advanced as serological phenomena peculiar to the rheumatic state, and possibly related to the necrotizing allergic reaction presumed to occur. The present study is concerned with an attempt to repeat and, if possible, to extend previous investigations indicating the existence of allergic mechanisms in rheumatic fever.

A. The Phase Reaction

In 1939 Coburn and Pauli (20) reported that a substance called a "precipitinogen" appeared in the serum of a rheumatic subject following a sore throat which precipi-

* This work was done during the tenure of a Life Insurance Medical Research Fellowship. Aided in part by the Masonic Foundation for Medical Research and Human Welfare.

tated when mixed with the serum taken during the subsequent rheumatic attack. Because the reaction occurred with serum obtained during phase I or II (the sore throat and the latent periods), when mixed with serum from phase III (the period of rheumatic activity), it has been called the "phase reaction." If a rheumatic attack did not develop following the sore throat, it was reported that the precipitinogen was not present, and no precipitin developed. When the rheumatic attack ran a polycyclic course, the precipitinogen and the precipitin alternately appeared in the serum. It was suggested that this precipitinogen might represent a "secondary antigen" derived from a combination of streptococcal products and human tissue constituents. Although the phenomenon did not necessarily represent an antigen-antibody reaction, it appeared to be one, and one intimately associated with the occurrence of rheumatic fever.

Despite the apparently fundamental significance of this reaction, there were no further reports concerning it until 1946 when Wedum and Wedum (21) seemed to have confirmed some of the observations of Coburn and Pauli. However, there are certain differences between the two reports which would appear to be incompatible with the hypothesis suggested by both groups of investigators. Wedum and Wedum found that their presumed antigen occurred during the first few days *after* the onset of a rheumatic attack, not preceding it, and again appeared at the end of the attack in contrast to Coburn's observations. Occasionally both substances, *i.e.* precipitinogen and precipitin, were said to coexist in the same serum sample, because a fine precipitate occurred when the unmixed sample of serum was incubated (21). Wedum and Wedum also found that the phenomenon was not peculiar to rheumatic fever. It occurred in uncomplicated nasopharyngitis, in primary atypical pneumonia, and in a few miscellaneous conditions. Unfortunately, much of this work was done with the sera of different individuals; that is, serum from one subject with a sore throat was mixed with that of another subject who had rheumatic fever.

Experimental.—Sera were obtained from patients on the wards and in the Rheumatic Fever Follow-up Clinic of the Presbyterian Hospital, the Babies Hospital, and The Pelham Home for Children. The latter institution, a convalescent home, offered an opportunity to obtain sera from known rheumatic subjects before the onset of a sore throat or of a rheumatic recrudescence. Sera were obtained at weekly intervals, generally more frequently during active illness, and less frequently during late convalescence and quiescent periods. Usually sera taken at different times from the same individual were used for one series of tests. In a number of instances sera from these patients were intermixed with no alteration in results.

The tests were performed using the technique previously described (20). 0.1 ml. of each serum to be tested was mixed with an equal quantity of another sample from the same patient. The mixture was incubated at 37°C. for 2 hours, and put in the ice box overnight. After centrifugation the next morning, tubes were agitated and examined with a lens. Particulate matter, scarcely visible to the unaided eye, was the strongest positive reaction obtained, as in the original work. Readings were graded as ±, +, and ++, and independent readings by each author gave little significant variation. Unlike the previous work, controls of test serum alone, and test serum plus normal serum, were used in addition to the serum plus saline controls. Every serum was cross-tested with every other serum from the same patient.

The sera tested included 221 samples from 38 cases of rheumatic fever (20 cases with only a single serum sample); 16 samples from 7 cases of streptococcus pharyngitis in non-rheumatic individuals; 85 sera from 11 cases of streptococcus pharyngitis in rheumatic subjects who did

not develop demonstrable rheumatic activity; and 21 sera from 4 miscellaneous cases—2 of "idiopathic" myocarditis, 1 of acute gonorrheal arthritis, and 1 of an asymptomatic inactive rheumatic subject.

The results of the tests are shown in Table I. From 18 active rheumatic patients followed for long periods of time (Table I, A), negative, irregularly positive, and uniformly positive precipitin reactions were obtained. When positive precipitin tests were obtained they were obtained with any combination of serum samples irrespective of their relationship to the phase of the disease. Indeed, many of these positively precipitating sera also showed positive reactions when mixed with control non-rheumatic sera. Table I, A illustrates the haphazard relationship of a negative or a positive precipitation test to the periods of sore throat, and to the course of active rheumatic fever. Table I, B and I, C presents the results of the "phase reaction" test in inactive rheumatic subjects and in normal (non-rheumatic) patients with sore throats not followed by attacks of rheumatic fever. Of the inactive rheumatic group (Table I, B) positive precipitation was noted with the sera from four patients, no precipitation occurred with the sera from four other patients; and doubtfully positive precipitation was noted with the sera from the remaining three individuals. There is a preponderance of negative precipitation tests in the non-rheumatic group with sore throats (Table I, C). It should be noted that fewer sera were obtained in these instances. Samples of serum from a case of gonococcal arthritis (Table I, D) were positive throughout. A completely inactive and asymptomatic subject with a history of rheumatic fever 3 years previously gave scattered weakly positive and doubtfully positive precipitation reactions. Therefore, no correlation was found between the occurrence of precipitates and the occurrence of any clinical episode, either sore throat or rheumatic fever. Furthermore, repeated tests failed to give reproducible results.

Further evidence against a possible antigen-antibody reaction occurring in these sera appeared from the following observations:

When one or both sera usually showing precipitates were diluted with an equal amount of saline, and mixed, no precipitation occurred. If either serum contained a true precipitin, and the other an antigen, slight dilution of one or the other of the reagents would not be expected to affect the formation of the precipitate.

Sera, showing precipitate, were mixed in various dilutions in the presence of complement. No fixation of complement occurred if amounts of serum below the anticomplementary concentrations were used. Certain known antigen-antibody systems do not fix complement. Therefore, this observation is only suggestive of the absence of an immune system.

Carmine dye particles (22) and collodion particles (32) were used in an attempt to make a microscopic reaction more visible. No agglutination of the mixtures occurred.

Serum obtained from one patient after a sore throat was injected intracutaneously during his rheumatic attack. No skin reaction occurred, either of the immediate or delayed type. Similarly an attempted Prausnitz-Küstner reaction in a normal individual with the sera containing the "precipitinogen" and "precipitin" gave negative results.

TABLE I

The Results of Precipitin Tests for the "Phase Reaction"

Patient	No. of sera	Periods during which sera were obtained	Results and comments on cross-precipitin tests in relation to course	Precipitin reaction with normal sera of same blood group
		A. Acute Rheumatic Fever		
J. M.	18	(*a*) Initial sore throat. (*b*) Latent period, 1 mo. (*c*) Polycyclic rheumatic fever for 4 mos.	Slight precipitation scattered throughout	+
J. B.	11	(*a*) Early and polycyclic acute rheumatic fever (*b*) Quiescent convalescence over 4 mos.	Precipitation present in all tests	+
F. M.	6	(*a*) Very early acute rheumatic fever for 2 wks. (*b*) Quiescent convalescence for 3 wks.	Two sera at end of period of activity showed weak precipitation with each other and when alone. All others negative	−
A. T.	16	(*a*) Latent period 3 wks. (*b*) Early rheumatic fever. (*c*) Polycyclic course for 4 mos.	Scattered precipitation, particularly with one of latent period sera against all later sera and against controls	+
R. C.	3	(*a*) Acute rheumatic fever becoming normal by all usual criteria in 10 days	Weak precipitation between 1st and 3rd sera	−
B. V.	15	Acute rheumatic fever polycyclic for 3 mos.	All negative	−
A. G.	4	(*a*) Acute rheumatic fever for 1 mo. (*b*) Convalescent 1 mo.	First serum precipitates with remaining three but all four precipitate with control	+
C. D.	3	Acute rheumatic fever, 1 mo. duration	All sera form slight precipitates with each other, by themselves, and with controls	+
G. W.	4	(*a*) Acute rheumatic fever for 1 mo. (*b*) Quiescent for 1 mo.	Scattered precipitates in six of the tests but three are sera alone	+

TABLE I—*Continued*

Patient	No. of sera	Periods during which sera were obtained	Results and comments on cross-precipitin tests in relation to course	Precipitin reaction with normal sera of same blood group
		A. Acute Rheumatic Fever—Continued		
W. H.	3	(*a*) Acute rheumatic fever for 2 wks. (*b*) Quiescent in 3rd wk.	All negative	−
R. A.	6	(*a*) Sore throat (*b*) Latent period for 2 wks. (*c*) Asymptomatic exacerbation for 4 wks. (ESR rising to 80)	All sera precipitate against each other	−
B. D.	19	(*a*) Asymptomatic 2 wks. (*b*) Sore throat 1 wk. (*c*) Latent period 3 wks. (*d*) Exacerbation 5 wks. (*e*) Quiescent 9 wks.	Scattered precipitations unrelated to course	+
H. H.	17	(*a*) Sore throat 1 wk. (*b*) Latent period 2 wks. (*c*) Active rheumatic fever 13 wks. polycyclic (*d*) Quiescent 5 wks.	Scattered weak precipitations—no relation to course	+
M. P.	18	(*a*) Sore throat 1 wk. (*b*) Latent period for 5 wks. (*c*) Acute rheumatic fever for 12 wks. (*d*) Quiescent for 6 wks.	As above	+
A. S.	24	(*a*) Asymptomatic 3 wks. (*b*) Tonsillitis 1 wk. (*c*) Immediate onset acute rheumatic fever which continued polycyclic for 15 wks. (*d*) Quiescent 4 wks. (*e*) ESR rising to 43 for 3 wks., then normal (*f*) 4 samples in next 4 mos.	As above	−
G. K.	13	(*a*) Subsiding acute rheumatic fever (*b*) Quiescent 2 wks. (*c*) Sore throat 1 wk. (*d*) Asymptomatic 3 wks. (*e*) Recurrent activity 3 wks. (*f*) Quiescent for 2 mos.	All tests showed weak precipitates	+

TABLE I—*Continued*

Patient	No. of sera	Periods during which sera were obtained	Results and comments on cross-precipitin tests in relation to course	Precipitin reaction with normal sera of same blood group
A. Acute Rheumatic Fever—Continued				
E. C.	11	(*a*) Subsiding acute rheumatic fever 6 wks. (*b*) Quiescent 14 wks.	As above	+
B. F.	17	(*a*) Rheumatic fever for 3 mos. (*b*) Quiescent for 1 mo. (*c*) Chorea for 1 mo.	Scattered positives with no relation to course	+
6 other cases of acute rheumatic fever—sera obtained at various times during the course—all gave a weak precipitate alone, with one another and with controls				+
B. Inactive Rheumatic Subjects with Sore Throats Not Followed by Recrudescences				
R. B.	7	Sore throat for 4 days. Elevated ESR for 2 wks. Quiescent for 6 wks.	All sera precipitate weakly with each other and with controls	+
I. R.	4	Sore throat	All negative	−
C. V.	3	Sore throat—followed for 2 2 wks. after	All negative	−
A. I.	4	Sore throat 1 mo. thereafter	All negative	±
C. S.	14	Followed 4 mos. at convalescent home, before, during, and after sore throat without rheumatic activity	Scattered precipitates unrelated to any period of observation	Occasionally positive
R. H.	10	5 mos. at convalescent home. One sore throat. No active rheumatic fever	All tests show precipitate formation	+
A. H.	9	As above	Scattered precipitates	+
L. L.	11	As above	All doubtfully positive	±
B. C.	6	As above	All doubtfully positive	+
P. C.	8	As above	All doubtfully positive	+
S. C.	9	As above but with two sore throats	All tests negative	−

TABLE I—*Concluded*

Patient	No. of sera	Periods during which sera were obtained	Results and comments on cross-precipitin tests in relation to course	Precipitin reaction with normal sera of same blood group
C. Non-Rheumatic Subjects with Streptococcus Pharyngitis				
G. D.	2	(*a*) Sore throat (*b*) Quiescent 2 wks. later	Doubtful precipitation	−
G. G.	2	Same but 18 days apart	Negative	−
H. H.	2	Same 12 days apart	Negative	−
B. G.	3	Sore throat, 5 days and 1 mo. later	Negative	−
T. M.	2	2 days apart	Negative	−
M. O'C.	2	13 days apart	Negative	−
R. S.	3	Sore throat, 3 days and 13 days later	Negative	−
D. Miscellaneous Cases				
J. R.	8	Old rheumatic subject. Asymptomatic and quiescent for 3 mos.	Scattered weak and doubtful precipitates	±
R. T.	3	3 wks. of gonorrheal arthritis	All tests precipitate including controls	+
W. M.	5	"Idiopathic" myocarditis 5 wks.	All tests negative	−
B. S.	5	Probable "idiopathic" myocarditis and pulmonary embolism 6 wks.	All tests negative	−

Serum of a patient which did show a tendency to form particulate matter with other sera, including control sera, showed the same tendency, if after incubation by itself, and centrifugation, the supernatant was again incubated and centrifuged. Therefore, the "reagents" could not be absorbed from the sera.

Discussion.—The "phase reaction," a serological phenomenon thought to be specific in rheumatic individuals has been cited as laboratory evidence for the hypothesis that an allergic mechanism is concerned with the development of rheumatic fever. This study has not corroborated previous reports. The inconstant nature of the formation of precipitates on repeating identical tests,

and the lack of visible formation of precipitates on dilution with saline, suggest that the particulate matter formed in these tests is not due to a specific immune reaction. It is perhaps not unlike the non-specific precipitation that occurs in uncontaminated sera which are allowed to stand for a period of time, even in the ice box. Sera cleared of particulate matter after prolonged centrifugation in the cold before the performance of a quantitative precipitin test (23) occasionally develop particulate matter after incubation at 37°C. This may result in a precipitate giving an appreciable amount of nitrogen in the serum control or "blank" tubes. There are a number of poorly understood changes in the sera of patients with rheumatic fever and certain other illnesses which are reflected in phenomena such as the erythrocyte sedimentation rate (25) and the "colloidal" tests (26). In addition, chemical changes are known to occur in active rheumatic sera (24, 27). These abnormalities may or may not be related to the non-specific precipitation that occurs in serum when it stands alone in the ice box or when it is mixed with another serum and incubated.

B. Autoantibodies in Rheumatic Fever

Autoantibodies and isoantibodies occasionally cause severe necrotizing allergic reactions, as in the Donath-Landsteiner reaction, erythroblastosis foetalis and, occasionally, cold hemagglutination. However, such antibodies may exist without obvious widespread tissue damage, as in the case of the Wassermann antibody. Therefore, the demonstration of an autoantibody in rheumatic fever may be of interest but does not *per se* establish the rôle of the tissue reaction in response to the autoantibody in rheumatic fever. The concept of an autoantibody in rheumatic fever was suggested by Brokman, Brill, and Frendzel (28). They found that sera from rheumatic patients fixed complement when mixed with an extract of liver obtained at the autopsy of a rheumatic child. Sera from other diseases did not fix complement with this "antigen." Unfortunately, anticomplementary controls were not reported. It is well known that tissue extracts are frequently anticomplementary, as are, occasionally, rheumatic or other sera in certain concentrations. Furthermore, Eaton and his associates reported that complement fixation occurs when liver tissue is mixed with sera from a variety of illnesses as well as with some normal sera (29).

Experimental.—Tests were made for a reaction similar to that of Brokman, Brill, and Frendzel. In the absence of fresh liver tissue, heart and lung tissue from a rheumatic individual, and placental tissue from a living rheumatic subject were used as "antigens." Eight sera, from active rheumatic subjects of the same blood groups as the individuals from whom the tissues had been obtained were mixed in various dilutions in the presence of 4 hemolytic units of complement. The traditional technique was employed, with 0.2 ml. of diluted "antigen," 0.2 ml. of diluted serum, and 0.2 ml. of complement. After incubation for a half hour, 0.2 ml. of a standardized suspension of sensitized sheep cells was added. No evidence of complement fixation was found in dilutions of serum and of tissue extract which were not anticomplementary alone.

Another autoantibody system was suggested by Cavelti (30). He found that one of four normal (*i.e.*, non-rheumatic) hearts used as antigen reacted strongly with sera from 27 of 36 rheumatics studied. By mixing the antigen with collodion particles, the presumed immune aggregation was made macro-

TABLE II

Results of the Collodion Particle Method for the Detection of "Autoantibodies" in the Sera of Rheumatic and Syphilitic Patients

Patient and serum No.	Antigens																	
	M. (carcinoma)					W. (chronic nephritis)					H. (rheumatic)					(Rheumatic)		
	Heart	Lung	Liver	Spleen	Kidney	Heart	Lung	Liver	Spleen	Kidney	Heart	Lung	Muscle	Spleen	Kidney	G's tonsil	A's tonsil	P's heart
Rheumatic fever																		
Zi. 1	0	+	+	0	0	0	0	0	0	0	0	+	0	0	0	0	0	0
" 2*	0	0	++	++	+	0	0	0	0	0	0	0	0	0	0	0	0	0
Pe. 1	0	0	0	0	0	0	0	0	0	0	0	0	0	++	0	+	0	0
" 2	0	0	0	0	0	0	0	0	0	0	0	0	0	+++	0	+++	0	0
Ki. 1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	+++	++	0
" 2	0	0	0	0	0	0	0	0	0	0	0	0	0	+++	0	0	+	0
Va. 1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
" 2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	±	0	0
Dr. 1	±	0	±	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
" 2	0	0	0	++	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Du.	0	0	0	0	0	0	0	0	0	0	0	+	0	0	0	0	+	0
To.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	++	0	0
We.	0	0	0	0	0	0	0	0	0	0	0	+	0	0	0	0	0	0
Fe.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Mc.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Pi. 1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
" 2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Te. 1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
" 2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
An. 1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
" 2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Wi.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Ma. 1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
" 2	0	0	0	0	0	0	0	+	0	0	0	0	0	0	0	0	0	0
Syphilis																		
A	0	0	0	0	0	0	0	0	0	0	0	0	0	+++	++++	0	0	++
B	0	0	0	0	±	0	0	0	+	0	0	0	0	0	0	0	0	0
C	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	+
D	0	0	0	±	++	0	0	0	+	0	0	0	0	0	0	0	0	0

* Serum 2 is at a later period in the course of the disease.

scopically visible. When the surface of the particles is coated with antigen, the whole particle exhibits many of the properties of its protein covering (31). A reaction of antigen on the particle surface with its antibody results in macroscopic agglutination (32).

Experimental.—Colloidal particles were prepared by the method of Cavelti (33). To tubes containing 0.2 ml. of a mixture of collodion particles and a dilution of a clear saline extract of

the antigen, 0.5 ml. of antiserum in various dilutions was added. After being mixed and standing at room temperature for 2 hours, the mixture was centrifuged, agitated, and the degree of agglutination was observed.

Tests were made to determine the optimal concentration of particles, antigen, and antibody, using two known systems: rat kidney and rabbit anti-rat kidney serum R 673 (obtained from Dr. B. C. Seegal), and the type-specific polysaccharide SS II of the Type II pneumococcus (obtained from Dr. M. Heidelberger) and its homologous rabbit antibody. Although the collodion particle method appeared to give positive results with known antigen-antibody systems, inconstant quantitative relationships were obtained at various times when the same system was repeated. No false positive results were obtained with good preparations of collodion particles.

Five or more tissues were obtained within 12 to 24 hours after the death of three individuals. One case (H.) had inactive rheumatic heart disease and pulmonary edema. The other two cases had carcinoma of the gall bladder (M.) and chronic glomerulonephritis (W.). In addition, heart tissue from one active rheumatic individual, and tonsil specimens from two inactive rheumatic children were also obtained. The tissues were kept in the solid CO_2 storage chest until ready for use. They were then ground with sand and extracted with cold saline to make a 20 per cent mixture by weight. After centrifugation, the clear supernate was separated for use in the tests. In all instances the tissues were from individuals of blood group O. All the tests reported employed group O sera to obviate the possibility of a false positive test due to an incompatible blood group reaction. For control tests, normal sera and uncoated normal particles were used, as well as the variety of tissues and concentrations. In addition, a precaution not previously employed was used. Known positive Wassermann sera from syphilitics served as controls.

Several batches of particles occasionally gave a preponderance of negative or of positive results with the tissue extract-serum systems, although particles from the same lot appeared to be similar to previous batches in their reaction with the known antigen-antibody systems.

A summary of some of the tests employing the collodion particle method is seen in Table II. All the sera listed here are from active rheumatic or syphilitic patients. Normal sera rarely gave a positive reaction with one of the tissue extracts. The sera from ten of the active rheumatic patients gave no reaction, or a rare weakly positive agglutination. Five gave positive reactions, usually against more than one tissue. In other tests, not shown here, these and other sera appeared to cause most marked agglutination with extracts of tonsil, spleen, kidney, and lung. Since streptococci were cultured from the tonsils at operation, antibodies to the streptococci were probably instrumental in causing the marked agglutination of the tonsillar tissue.

Discussion.—The occurrence in rheumatic sera of agglutinins to collodion particles coated with a heart tissue extract was observed infrequently as compared with reactions to particles coated with extracts of other tissues. In addition, sera from syphilitic patients appeared to contain the agglutinins more frequently than did rheumatic sera. Since we performed these tests, Dr. Cavelti has informed us that he has had difficulty repeating his results with antigens other than the extract of the one heart tissue which gave strongly positive reactions. The diminution of his supply of the original antigen precludes any attempt at analysis. The possibility continues that the reaction noted

constitutes (1) a reaction between antibodies and bacterial contaminants of the tissues used, or (2) a modification of the flocculation tests for syphilis, since the Wassermann antigen is a constituent of normal tissues (34, 35). The occurrence of biologically false positive Wassermann reactions in many diseases has been reviewed by Davis (36).

SUMMARY AND CONCLUSIONS

1. An attempt was made to repeat and extend various tests which have been presumed to demonstrate specific antigens and antibodies in rheumatic fever.

2. The "phase reaction" appears to be an inconstant phenomenon probably related to a colloidal abnormality of the serum, rather than to a specific antigen-antibody system.

3. No specific autoantibodies to human tissue extracts were demonstrable by complement fixation or by the collodion particle technique. Variable results were noted with the same test sera on different occasions, and positive reactions with control tissues and control sera were observed.

4. The possibility should be considered that autoantibodies are not necessarily specific for rheumatic fever but may be manifestations of the occurrence of a type of reaction similar to a biologically false positive Wassermann reaction.

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