Diagnostic Concordance of Serological Tests for Antiglobulin Antibodies* **

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Rheumatoid factors are present in a variety of disease states and in normal persons, usually in low titer. High titers of rheumatoid factors are almost exclusively associated with rheumatoid arthritis.

A second group of antiglobulin antibodies, called serum agglutinators, distinct from rheumatoid factors, are anti-Fab IgG antibodies presumably present in the sera of all mammals. High titers of these antibodies are not diagnostic for a specific disease but are closely associated with suppurative infection which is usually due to gram-positive organisms.

Tests for determining the titers of the serum agglutinators are used as diagnostic aids for hidden abscesses. In suppurative infection, and especially in gram-positive septicemia, titers are very high. Elevated titers have aided in differentiating osteomyelitic abscesses from destructive tumor lesions of the bone. The titers of the serum agglutinators will fall when the suppurative lesions resolve; thus, falling titers of these antibodies help in evaluating the resolution of large lesions. In addition, the failure of the patient to respond with a rise in titer in the face of significant or multiple abscesses is usually a warning that the patient is not immunologically competent, such as patients with thymoma, lymphoma or myeloma. Figure 1 demonstrates the method used for studying both of these antiglobulin antibodies.

Rh-positive erythrocytes coated with the incomplete anti-Rh antibody, Ripley, are used to demonstrate the rheumatoid factors. These anti-Rh antibodies, hydrolyzed with various enzymes, are used to demonstrate the different serum agglutinators. Erythrocytes coated with a mixture of intact antibodies and the Fab fragments of antibodies will permit the demonstration of both antibodies.

This prospective study of 1,320 persons, whose sera were examined for the presence of both rheumatoid factors and serum agglutinators, was undertaken to evaluate and compare the effectiveness of the tests for these two distinct antiglobulin antibodies as diagnostic aids in rheumatoid arthritis and suppurative infection, respectively. Three groups of patients were tested:

Group 1 (hospital patients)—Serum specimens from 181 hospital patients were sent to our laboratory primarily to be tested for the presence of serum agglutinators.

Group 2 (ambulatory patients)—Serum specimens from 926 patients attending the connective tissue (rheumatology) clinics were sent to our laboratory to be tested for the presence of rheumatoid factors.

Group 3 ("normal" persons attending the city venereal disease clinic)—Serum specimens were obtained from 213 persons attending the venereal disease clinic. They were primarily young adults,

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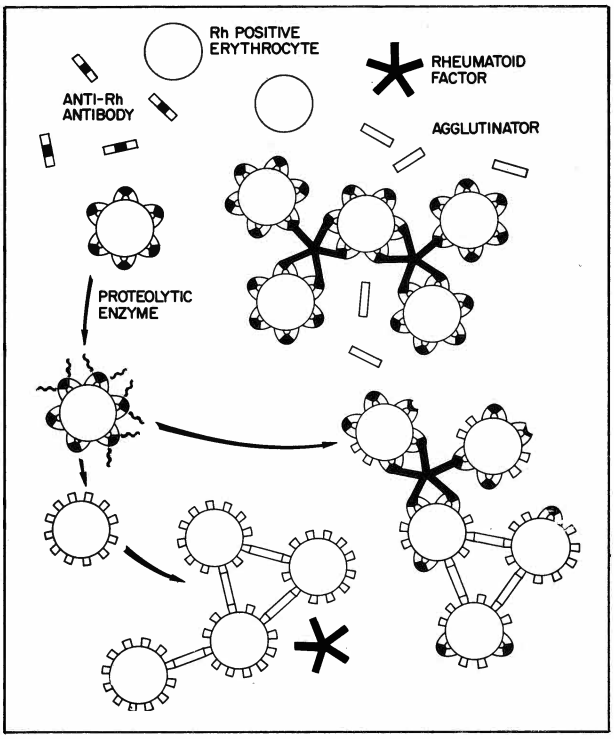

Fig. 1.

some with and some without complaints of urethral or vaginal discharge. Neither antiglobulin test was ordered; these were used as a control group.

For this study, only titers of 160 or above were considered as positive tests. Table 1 shows the results of the tests for rheumatoid factors and serum agglutinators in 1,320 patients. The incidence of positive tests for serum agglutinators was highest in the hospitalized patients (group 1), whereas the incidence of positive tests for rheumatoid factors was highest, understandably, in the patients attending the rheumatology clinic (group 2). In the patients attending the venereal disease clinic (group 3), the incidence for both types of antiglobulin antibodies was only 1–2%.

Table 2 shows the variety of diseases among the 181 hospital patients. The association between positive tests for serum agglutinators and suppurative infection is apparent. In patients with pneumonia, suppuration is variable; in addition, there is natural drainage, and the patients receive early therapy. Thus positive tests are not usual. The incidence of positive tests in patients with localized infections depends upon the severity of the lesion. In neither malignancy nor metabolic disease are

TABLE 1

INCIDENCE OF POSITIVE TESTS FOR ANTIGLOBULIN ANTIBODIES*

Study Group	Total No. Patients	Test for Rheumatoid Factors: No. Positive	Test for Rheumatoid Factors: Percent Postive	Test for Serum Agglutinators: No. Positive	Test for Serum Agglutinators: Percent Positive
1	181	13	7.1	27	14.9
2	926	148	16.0	5	0.5
3	213	3	1.4	4	1.9
Totals	1,320	164	12.4	36	2.7

NOTE. Group 1 = hospital patients. Group 2 = patients attending the rheumatology clinic. Group 3 = patients attending the venereal disease clinic.

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TABLE 2

TESTS FOR SERUM AGGLUTINATORS IN 181 HOSPITAL PATIENTS (GROUP 1) WITH A VARIETY OF DISEASES*

Infection	Patients (no.): Total	Patients (no.): Positive Test
Gram-negative septicemia	2	—
Pyelonephritis	6	1
Pneumonia	11	1
Granulomatous infection	8	2
Subacute bacterial endocarditis	3	3
Large abscesses (empyema, osteomyelitis)	19	12
Infections associated with immunologic deficiency (lymphoma, thymoma, myeloma, transplantation)	5	—
Localized infection (gonorrhea, pyoderma tonsillitis, infectious arthritis, wound infection, decubitus ulcers)	25	4
Malignancy	14	—
Connective tissue diseases (rheumatoid arthritis, lupus, gout)	19	2
Undiagnosed (fever of undetermined origin)	15	1
Metabolic disease (diabetes, nephrosis, toxic drugs, muscular dystrophy, alcoholism, cardiovascular disease)	54	1
Totals	181	27

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these antibodies present in high titer. The exception in this instance was a patient with chronic alcoholic cirrhosis, hematuria and a hemolytic anemia of unknown etiology. Among the patients with connective tissue disease were a two-and-a-half-year-old child with lupus erythematosus and a young boy with juvenile rheumatoid arthritis; both had high titers of serum agglutinators. In neither of these diseases are the tests usually positive. It was the first hospital admission for both children, however, and the possibility that titers may be high in early and explosive disease and then decline in the chronic state cannot be ruled out. Neither child had a positive test for rheumatoid factor or for lupus erythematosus.

Table 3 shows the correlation (or lack of it) between the positive test and the disease for which the test was ordered. The serum agglutinator test was ordered for the hospitalized patients (group 1); the rheumatoid factor test was ordered for the patients attending the rheumatology clinic (group 2); and neither test was ordered for the patients attending the venereal disease clinic (group 3). In 13 of the 181 hospitalized patients, the tests for rheumatoid factors were positive but only six of the 13 had rheumatoid arthritis. Thus, the correlation between positive test and disease state was only 46.2%. Among the same patients, however, 21 of 27 with positive tests for serum agglutinators had suppurative infection.

In the patients attending the rheumatology clinic (group 2), there was a very high correlation between the positive test for rheumatoid factor and the presence of rheumatoid arthritis. Of these 926 patients, five had a positive test for serum agglutinators (0.5%), but none had a suppurative infection.

Of the 213 patients attending the venereal disease clinic (group 3), three had a positive test for rheumatoid factor (1.4%). Only one of these three had gonorrhea. None had rheumatoid arthritis. Of these 213 patients, four had a positive test for serum agglutinators (1.9%). Only one had gonococcal urethritis.

If the results of tests for rheumatoid factors and serum agglutinators, as standardized in this study, are evaluated for correlation of the test with specific disease, the percentages of false-positive tests among the hospitalized patients (group 1) are 3.8% and 3.3%, respectively; among the patients attending the rheumatology clinic (group 2), 0.3% and 0.5%, respectively; and among patients attending the venereal disease clinic (group 3), 1.4% and 1.4%, respectively (Table 4). These percentages of false-positive tests are much higher when titers lower than those used as the standard in this study are accepted as positive tests.

Comments. The requirements for a positive test for rheumatoid factors in this study are more stringent than those used in other studies. Even so, only 46.2% of group 1, with rheumatoid factor titers of 160 or above by the sensitized human cell test, had rheumatoid arthritis. The sensitized sheep cell tests were positive for rheumatoid factor in three

TABLE 3

PRESENCE OF RHEUMATOID ARTHRITIS OR SUPPURATIVE INFECTION IN PATIENTS WITH POSITIVE TESTS FOR RHEUMATOID FACTORS OR SERUM AGGLUTINATORS*

Study Group	Rheumatoid Factor Test Positive	Rheumatoid Arthritis Present	Percent Correlation	Serum Agglutinator Test Positive	Suppurative Infection Present	Percent Correlation
1	13	6	46.2	27	21	77.7
2	148	145	98.0	5	0	None
3	3	0	None	4	1	25.0
Totals	164	151	92.0	36	23	63.0

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TABLE 4

FALSE-POSITIVE TESTS FOR ANTIGLOBULIN ANTIBODIES*

Study Group	Total No. Patients	Rheumatoid Factor Test: No. Positive Without Rheumatoid Arthritis	Rheumatoid Factor Test: Percent False-Positive	Serum Agglutinator Test: No. Positive Without Suppurative Infection	Serum Agglutinator Test: Percent False-Positive
1	181	7	3.8	6	3.3
2	926	3	0.3	5	0.5
3	213	3	1.4	3	1.4
Totals	1,320	13	0.9	14	1.0

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of the hospitalized patients in the absence of rheumatoid arthritis; the diagnoses in these were Wegener's granuloma, chronic heart failure, and sarcoidosis. Thus, it is necessary to conclude that among very sick patients, positive tests for rheumatoid factors only correlate with rheumatoid arthritis about 50% of the time. In patients in whom there is a high degree of suspicion of the disease, however, the correlation is about 98%. It is also obvious that among ambulatory patients attending a clinic for a completely unrelated disease, positive tests for rheumatoid factors are not apt to correlate with rheumatoid arthritis.

Among the 181 hospitalized patients, 27 (15%) had elevated titers of serum agglutinators, which reflects the interest in infection in this group of patients, since the test ordered was for the serum agglutinators. Positive tests for serum agglutinators are unusual in nonhospitalized patients and as a rule, those who do have positive tests do not have severe suppurative infection. In many instances, however, these tests might be helpful in differentiating a hidden abscess from a malignancy. Sometimes, a well-walled-off abscess will cause only modest elevations in the titers of the serum agglutinators, whereas, when the abscess is pierced, its inevitable discharge will stimulate the serum agglutinators and the titers will rise. As resolution of the lesion occurs, the titers will fall.

This study lends credence to the postulate that rheumatoid factors are humoral heterophil antibodies that may be stimulated by a variety of immunologic events. As stated, the correlation of positive tests for these antibodies with rheumatoid arthritis is only about 50% in very sick hospitalized patients.