

EVALUATION OF HAEMAGGLUTINATION TESTS IN THE DIAGNOSIS OF RHEUMATOID ARTHRITIS

I. THE S.S.C., F.II S.C., AND F.II L.P. SYSTEMS*

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Objective

Since the reports of Meyer (1922) and Waaler (1940) demonstrating that sera from patients with rheumatoid arthritis potentiated the agglutination of sensitized sheep erythrocytes, many investigators have modified the observed phenomenon in order to devise through it a test which might be diagnostic of this disease. Many modifications have been used in order to make the test more specific and less complicated. The Fourth Division Arthritis Laboratory of New York University-Bellevue Medical Centre, as part of its programme to carry out diagnostic laboratory tests on the various rheumatic diseases (Hartung and Mahood, 1955), has sought to standardize and compare these tests to make them more practical for routine use, and we have also attempted to evaluate their diagnostic accuracy.

Tests Used

Three haemagglutination tests for rheumatoid arthritis were performed:

- (1) The Heller I modification of the Rose test, formerly designated as the SEA or SCA test (Heller, Jacobson, and Kolodny, 1949) and now as the S.S.C.† test;
- (2) The Fraction II or gamma globulin modification of Heller, Jacobson, Kolodny, and Kammerer (1954), now referred to as the F. II S.C.† test;
- (3) The Latex Fixation or F.II L.P.† test (Singer and Plotz, 1956).

More sensitive methods utilizing the agglutinating and inhibiting factors of the euglobulin fraction of rheumatoid serum isolated by various techniques (Svartz and Schlossmann, 1953; Ziff, Brown, Badin, and McEwen, 1954) are not at this time suitable for routine diagnostic tests because of their length and complexity.

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† A meeting sponsored by the Arthritis and Rheumatism Foundation was held in the early part of 1957. The topics were Haemagglutination Tests in Rheumatoid Arthritis and the factors involved. It was attended by various workers in this field and because of the confusion of nomenclature these abbreviations were agreed upon.

(1) The S.S.C. test consists essentially of inactivating complement in the patient's serum, absorbing the naturally occurring sheep erythrocyte agglutinin (Forssman antibody) in the test serum, and finally preparing serial dilutions of the latter to which sheep erythrocytes sensitized by anti-sheep erythrocyte rabbit serum are added. These agglutinate in the presence of the rheumatoid factor. The final reading is made after incubation at 37° C. for 1 hr and refrigeration overnight. Heller reported that this test was positive at titres of 1 : 28 and higher.

(2) In a later study, Heller examined the inhibitory effect of Human Plasma Fraction II (gamma globulin) on the S.S.C. test. He also modified the latter, using Fraction II instead of anti-sheep erythrocyte rabbit serum to sensitize the sheep cells. This technique does not eliminate any of the other steps in the S.S.C. test. In addition the sheep cells must be treated with tannic acid before adding the sensitizing amount of F. II globulin. In each of the steps described, the pH of the media must always be adjusted to 8. In the final test, the serum is set up in dilutions of 1 : 28 to 1 : 56,000. For controls, unsensitized sheep cells are added to the test serum. Each time a test is performed, concurrent tests are done with positive and negative reference sera. The test is observed after refrigeration overnight and is positive if agglutination occurs in the test sera of 1 : 56 or higher and the controls check out properly. This test, although of value in diagnosis, is not of practical use in a diagnostic laboratory when simpler tests are available, and was devised by Heller as a research tool by which he was able to show that the reactants in the S.S.C. and F. II S.C. tests were heterogenetically related.

(3) The latex fixation test of Singer and Plotz used latex particles of uniform size instead of sheep erythrocytes. Thus absorption of Forssman antibody from the test serum and also inactivation of complement in the test serum is unnecessary. The latex suspension is sensitized with a specific amount

of F. II fraction of human plasma. The diluent in all steps and to the latex gamma globulin mixture is a glycine-buffer solution of pH 8.2. The final dilution of the test serum is 1 : 20-1 : 5120 and a diluent control is also set up. The tubes are placed in a water bath at 56° C. for 1½ hrs and then centrifuged at 2,300 r.p.m. for 3 minutes. Agglutination of 1 : 20 or greater is considered a positive test. Although not necessary, refrigeration overnight after being in the water bath may help to give better readings.

In the evaluation of the tests described, the diagnostic value of each was weighed in relation to the simplicity of performance. The simplicity of a test such as the F. II L.P. method would not be an advantage if it were not of equal or better diagnostic value. When concurrent tests were performed, it appeared that "positive values" in some of them would have to be changed from the accepted standards by one or more dilutions as many sera from non-rheumatoid patients gave positive tests in lower titre dilutions. Thus, in the S.S.C. test, 1 : 56 was considered positive instead of 1 : 28, and in the F. II L.P. test, 1 : 160 instead of 1 : 20. Singer and Plotz (1957) also believe this latter correction to be justified.

Material

The three techniques described were used concurrently to test the sera of 239 patients. The sera were obtained from the University Hospital and Bellevue Hospital, Fourth Division, and from about half of the 43 arthritis clinics in Greater New York.

As part of the service offered by the New York Chapter of the Arthritis and Rheumatism Foundation, our laboratory, since its formation in 1955, has performed approximately 3,800 haemagglutination tests on patients with an established or tentative diagnosis of one of the rheumatic disorders. In 202 of these patients, in whom all three concurrent tests mentioned above were performed, a presumptive diagnosis by the referring physician accompanied the serum sample. The diagnosis of rheumatoid arthritis was made in 147 cases. Of these 134 were classified, according to criteria set up by the American Rheumatism Association (Ropes, Bennett, Cobb, Jacox, and Jessar, 1956), as follows:

- Classical or Definite Rheumatoid Arthritis, 83;
- Probable Rheumatoid Arthritis, 24;
- Possible Rheumatoid Arthritis, 27;

The other thirteen patients had other diagnoses:

- Gout and/or Rheumatoid Arthritis, 6;
- Psoriatic Arthritis, 3;
- Rheumatoid Spondylitis, 4.

The remaining 55 cases were divided as follows:

- Gout, 4;

- Osteo-Arthritis, 15;
- Fibrositis, Synovitis, and Periarthritis, 10;
- Collagen Disease, 2 (one of the latter was diagnosed as Disseminated Lupus);
- Polyserositis, 5 (some if not all of these might have been grouped under Collagen Disease);
- Palindromic Rheumatism, 1;
- Rheumatic Fever and Rheumatic Heart Disease, 4;
- Non-Arthritic, Non-Collagen Disease, 14 (these included Diabetes Mellitus, Asthma, Rhinitis, and one case of Multiple Myeloma).

No normal controls were sought since these tests were to help differentiate rheumatoid arthritis from other cases appearing in an arthritis clinic.

Also included in this report is an analysis of the tests of the sera of 274 patients (Table IV) on whom only concurrent S.S.C. and F. II S.C. procedures were performed during the period before the F. II Latex technique was begun in this laboratory.

Results

The results are presented in the accompanying Tables. Table I demonstrates the overall comparison of these three tests in 239 patients with all diagnoses. It shows that in 74 cases all three tests were positive and in 124 all three tests were negative. The overall percentage of agreement was 83 per cent. When the results were further resolved the S.S.C. and F. II L.P. tests agreed in 92.2 per cent. and disagreed in 7.8 per cent., the latter including 4.1 per cent. F. II L.P. positive and S.S.C. negative, and 3.7 per cent. S.S.C. positive and F. II L.P. negative. The F. II S.C. and F. II L.P. tests agreed in 89.2 per cent., the disagreement comprised a higher percentage of F. II S.C. positive with F. II L.P. negative (10.4 per cent.). The S.S.C. and F. II S.C. tests agreed in 84.7 per cent., but disagreed in that here even a higher percentage were

TABLE I
ANALYSIS OF CONCURRENT S.S.C.(S), F. II S.C.(F),
F. II L.P.(L) TESTS IN 239 PATIENTS (ALL DIAGNOSES)

Tests	No. of Patients	Percentage of Total
S+ F+ L+	74	31.0
S- F- L-	124	52.0
S+ F- L-	6	2.5
S- F+ L+	9	3.7
S+ F+ L-	22	9.3
S+ F- L-	3	1.2
S- F+ L+	1	0.4

SUMMARY OF THE THREE SYSTEMS

Tests	Percentage Agreed	Percentage Disagreed
S.S.C., F. II S.C. F. II L.P. ...	83.0	17.0
S.S.C. and F. II L.P. ...	92.2	7.8
F. II S.C. and F. II L.P. ...	89.1	10.9
S.S.C. and F. II S.C. ...	84.7	15.3

F. II S.C. positive, with S.S.C. negative (12·9 per cent.). Correlation of these figures shows a higher agreement between the S.S.C. and F. II L.P. tests.

Table II breaks down the results of the three concurrent tests in the diagnosed cases and Table III summarizes the positive tests by diagnosis.

In 75 cases of classical rheumatoid arthritis, all three tests agreed positive in 62·8 per cent. and agreed negative in 25·4 per cent. Further analysis of these results shows that the S.S.C. test was positive in 66·3 per cent., the F. II L.P. in 68·2 per cent., and the F. II S.C. test in 72·2 per cent.

In probable rheumatoid arthritis, the S.S.C. test was positive in 13·6 per cent., F. II L.P. in 9·1 per cent., and F. II S.C. in 27·2 per cent.

In possible rheumatoid arthritis the S.S.C. test was positive in 20·8 per cent., the F. II L.P. in 29·2 per cent., and the F. II S.C. in 37·4 per cent.

It appears that the F. II S.C. test gives more positive results than the others, but it would be superficial to call it more sensitive. This is brought out by analysing the results in 46 cases of non-collagen disease, where the percentage of positive tests was S.S.C. 8·6 per cent., F. II L.P. 4·3 per cent., and F. II S.C. 15·2 per cent. It was noted that where the F. II S.C. was positive and the other two tests negative, the former was usually positive in the lower titres between 1 : 56 to 1 : 448 and rarely in the strong titres of 1 : 3584 or 1 : 7168.

In a previous study, S.S.C. and F. II S.C. tests

TABLE II
ANALYSIS OF CONCURRENT S.S.C.(S), F. II S.C.(F), F. II L.P. (L) TESTS IN 202 DIAGNOSED CASES

Diagnosis	No. of Cases	S+F+ L+		S-F- L-		S+F- L-		S-F+ L+		S+F+ L-		S-F+ L-		S-F- L+		S+L+		S-L-		S-L+		
		No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	
		Rheumatoid Arthritis	Classical ..	83	47	56·8	19	22·9	2	2·4	4	4·7	1	1·2	2	2·4	—	—	3	3·6	3	3·6
	Probable ..	24	2	8·3	16	66·7	—	—	—	—	1	4·2	3	12·5	—	—	—	—	2	8·3	—	—
	Possible ..	27	4	14·7	14	52·0	1	3·7	3	11·1	—	—	2	7·4	—	—	—	—	2	7·4	1	3·7
Psoriatic Arthritis	..	3			3																	
Rheumatoid Spondylitis	..	4	1		2														1			
Gout and/or Rheumatoid Arthritis	..	6	4		1									1								
Gout	..	4			2		1												1			
Osteo-Arthritis	..	15			14					1												
Fibrositis, Synovitis, Periarthritis	..	10	1		8							1										
Palindromic Rheumatism	..	1			1																	
Collagen Disease	..	1			1																	
Disseminated Lupus Erythematosus	..	1			1																	
Polyserositis	..	5			2		1						1						1			
Rheumatic Fever	..	4			2								2									
Other Diseases, Diabetes Mellitus, etc.	..	14	1		11								1						1			

TABLE III
POSITIVE RESULTS IN CONCURRENT S.S.C., F. II S.C., AND F. II L.P. TESTS

Diagnosis	No. of Patients	S.S.C.		F. II S.C.		F. II L.P.		
		No.	per cent.	No.	per cent.	No.	per cent.	
Rheumatoid Arthritis	Classical ..	75	50	66·3	54	72·2	51	68·2
	Probable ..	22	3	13·6	6	27·2	2	9·1
	Possible ..	24	5	20·8	9	27·4	7	29·2
Non-Rheumatoid Arthritis Diseases (excluding Collagen Diseases, but not Rheumatic Fever)	..	46	4	8·6	7	15·2	2	4·3

were done with 274 cases. Analysis of these results also showed a much higher percentage of positives with the F. II S.C. than with the S.S.C. technique (Table IV). In 108 cases of classical rheumatoid arthritis these tests agree in 76 per cent., but the S.S.C. was positive and the F. II S.C. negative in 6.5 per cent., and the F. II S.C. positive and the S.S.C. negative in 16.7 per cent.

In 58 cases of probable rheumatoid arthritis, the tests agreed in 77.6 per cent., but the S.S.C. was positive and F. II S.C. negative in 5.2 per cent., and the F. II S.C. positive and S.S.C. negative in 17.2 per cent.

In 94 cases of possible rheumatoid arthritis the tests agreed in 71 per cent., but the S.S.C. was positive and the F. II S.C. negative in 5.6 per cent., and the F. II S.C. positive, and S.S.C. negative in 23.4 per cent.

This question was studied further; eighteen patients of the above group in which the S.S.C. and F. II S.C. tests did not agree were retested 3 to 9 months later with new serum samples and repeated diagnoses were made at the time the blood was taken (Table V, opposite). Where an F. II S.C. titre is positive in the lower range, even up to 1 : 448, it may at times revert to a negative test, but that the higher titres rarely fail to remain so. It is rare to see a positive S.S.C. titre become normal without therapy and here again it is in the low titre of 1 : 56 that may become 1 : 28.

In concluding this section dealing with observations, in all three techniques a one-tube difference in titre may occur when the same serum sample is re-tested.

Discussion

Evaluating these three haemagglutination tests for rheumatoid arthritis shows that, with the exception of the F. II S.C. test, they are about equal in sensitivity.

In classical rheumatoid arthritis, the S.S.C. was positive in 66.3 per cent., the F. II L.P. in 68.2 per cent., and the F. II S.C. in 72.2 per cent.

Also in probable and possible rheumatoid arthritis these tests gave higher positive results than for non-rheumatoid and non-collagen diseases. In the latter group, which in this investigation served as controls, the S.S.C. was positive in 8.6 per cent., the F. II L.P. in 4.3 per cent., and the F. II S.C. in 15.2 per cent. It follows that the lowest titre now accepted as positive in the F. II S.C. test, namely 1 : 56, should be increased to a titre of 1 : 448 or 1 : 896. Informal talks with workers in the field and experience with repeat serums in low-positive titres (Table V), show that such a change will make the test more diagnostic and eliminate false positives.

It can be observed here that more than one rheumatoid factor may be involved in these tests, depending on whether anti-sheep erythrocyte rabbit serum or Human F. II globulin is the sensitizing agent, since a substantial number of patients with classical rheumatoid arthritis will give positive S.S.C. and negative F. II S.C. tests and *vice versa*. Hellebrandt was the first to show this by means of absorption studies of rheumatoid arthritis sera with the S.S.C. and F. II S.C. methods. He found that, while in the majority of the sera cross-reactions occurred, in some after completion of the S.S.C. test the

TABLE IV
ANALYSIS OF CONCURRENT S.S.C. AND F. II S.C. TESTS

Clinical Diagnosis		Total No. of Tests	Agree Negative		Agree Positive		S.S.C. Positive F. II S.C. Negative		F. II S.C. Positive S.S.C. Negative	
			No.	per cent.	No.	per cent.	No.	per cent.	No.	per cent.
Rheumatoid Arthritis	Possible ..	94	51	54.0	16	17.0	5	5.6	22	23.4
	Probable ..	58	25	43.2	20	34.4	3	5.2	10	17.2
	Classical ..	108	31	28.6	52	48.2	7	6.5	18	16.7
Classical Rheumatoid Arthritis and Psoriasis	3	2	66.7					1	33.3	
Rheumatoid Series	263	109	41.7	88	33.4	15	5.6	51	19.3	
Osteo-Arthritis	4	3	75.0	1	25.0					
Fibrositis	1	1								
Lupus Erythematosus	3	2	66.7			1	33.3			
Psychogenic Rheumatism	1	1								
Bursitis	2	1						1		
Total	274									

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TABLE V

(a) DIAGNOSIS AND CONCURRENT S.S.C., F. II S.C. TESTS IN EIGHTEEN PATIENTS

(b) REPETITION OF THESE TESTS WITH NEW SERUM SAMPLES AND DIAGNOSES 3 TO 9 MONTHS LATER

Patient and Diagnosis		S.S.C. Titre	F. II S.C. Titre
1	a	112	28
	b	56	28
2	a	28	3,584
	b	112	28
3	a	112	28
	b	56	1,792
4	a	14	112
	b	14	28
5	a	28	15,000
	b	56	15,000
6	a	112	28
	b	56	28
7	a	28	224
	b	56	224
8	a	14	112
	b	14	7
9	a	7	224
	b	14	224
10	a	56	28
	b	56	28
11	a	7	224
	b	7	28
12	a	7	112
	b	7	56
13	a	28	3,584
	b	224	3,584
14	a	7	112
	b	7	7
15	a	14	448
	b	14	28
16	a	14	448
	b	14	28
17	a	28	7,168
	b	14	1,792
18	a	56	28
	b	28	28

supernatant sera would react by the F. II S.C. technique and *vice versa*. He concluded that the rheumatoid factors were heterogenetically related (Heller, Kolodny, Lepow, Jacobson, Rivera, and Marks, 1955). Also to be taken into account is the presence of an inhibitory factor and its effect on the activity of the rheumatoid factors.

There was a higher correlation of results between the S.S.C. and the F. II L.P. techniques. Plotz and Singer (1956) reported that their F. II L.P. results were 71.3 per cent. positive, and our figure is 68.2 per cent.

In tests done with control sera (non-rheumatoid,

non-collagen diseases) our results were not so close. In our series, the F. II L.P. test gave positive reactions in 4.3 per cent., while Plotz and Singer reported a similar control series as 2.5 per cent. positive. One reason for the difference in our figures, as far as the lower incidence of positive tests in classical rheumatoid arthritis is concerned, is that we used 1:160 as our lowest positive dilution, whereas in their original report they set the minimum positive as 1:20. They have since said that it is very rare for a positive serum to be positive only in concentrations below 1:160. We have found a good many positives in only the 1:20 to 1:80 range in non-rheumatoid controls which were negative by the other tests.

Summary

(1) Concurrent S.S.C., F. II S.C., and F. II L.P. tests in 239 patients with all diagnoses showed agreement in 83.0 per cent. There was a higher degree of correlation between the S.S.C. and F. II L.P. tests.

(2) In cases of classical or definite rheumatoid arthritis, all three tests agreed positive in 62.8 per cent. The S.S.C. was positive in 66.3 per cent, the F. II L.P. in 68.2 per cent., and the F. II S.C. in 72.2 per cent.

(3) In cases of probable and possible rheumatoid arthritis the three tests consistently gave more positive tests than in the controls.

(4) In the control series (non-rheumatoid and non-collagen disease), the S.S.C. was positive in 8.6 per cent., the F. II L.P. in 4.3 per cent., and the F. II S.C. in 15.2 per cent.

(5) The higher incidence of F. II S.C. positives in all series is due in part to the use of a titre of 1:56 or higher as the positive standard. This value should be changed and the positive titre standardized at 1:896 and higher.

(6) Analysis of concurrent S.S.C. and F. II S.C. tests of 263 rheumatoid sera show that more than one rheumatoid factor may be present in rheumatoid sera. Factors inhibiting the activity of the rheumatoid factors are also recognized as important.

(7) All three tests (with allowances for proper standards of positive titres) are equal in sensitivity for routine diagnostic screening.

(8) The F. II L.P. test is to be preferred to the others because of its simplicity and rapidity, but the lowest titre recognized as positive should be 1:160.

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L'évaluation des réactions d'hémagglutination dans le diagnostic de l'arthrite rhumatismale

I. Systèmes S.S.C., F. II S.C. et F. II L.P.

RÉSUMÉ

Les auteurs décrivent ces trois méthodes: la S.S.C. est une modification de la réaction de Rose; dans la F. II S.C., la Fraction II du plasma humain est employée au lieu du sérum lapin-anti-mouton; dans la méthode F. II L.P., une suspension de particules de latex est substituée aux globules rouges de mouton.

(1) Les réactions S.S.C., F. II S.C., et F. II L.P. chez 239 malades avec tous les diagnostics s'accordaient dans 83% des cas. L'accord était plus prononcé entre la S.S.C. et la F. II L.P.

(2) Dans les cas d'arthrite rhumatismale classique ou définie, le pourcentage des trois réactions simultanément positives était 62,8%. La S.S.C. était positive en 66,3%, la F. II L.P. en 68,2%, et la F. II S.C. en 72,2% des cas.

(3) Dans les cas d'arthrite rhumatismale probable et possible il y avait appréciablement plus de réactions positives, selon les trois méthodes, que chez les témoins.

(4) Chez les témoins (n'atteints pas de maladie rhumatismale ou collagène) la réaction S.S.C. était positive chez 8,6%, la F. II L.P. chez 4,3%, et la F. II S.C. chez 15,2%.

(5) La plus grande fréquence des réactions F. II S.C. positives dans toutes les séries est due au fait qu'on avait accepté un titre minimum de 1 : 56 comme standard de positivité; ce standard devrait être changé à 1 : 896.

(6) L'analyse des réactions S.S.C. et F. II S.C. sur les mêmes 263 sérums rhumatismaux a montré qu'il pourrait y avoir plus qu'un facteur rhumatismal. On

reconnait aussi l'importance des facteurs inhibiteurs de l'activité rhumatismale.

(7) Pour des besoins ordinaires de diagnostic, les trois réactions (tenant compte de standards de positivité des titres) ont une sensibilité égale.

(8) La réaction F. II L.P. est préférable aux deux autres en raison de sa simplicité et rapidité, porvu qu'on accepte un titre minimum de 1 : 160 comme positif.

Valoración de reacciones de hemaglutinación en el diagnóstico de la artritis reumatoide

I. Sistemas S.S.C., F. II S.C., y F. II L.P.

SUMARIO

Los autores describen los tres métodos: la S.S.C. es una modificación de la reacción de Rose; en la F. II S.C., la Fracción II del plasma humano se emplea en lugar del suero conejo-anti-oveja; en la reacción F. II L.P. una suspensión de partículas de latex se ve sustituida a los eritrocitos de oveja.

(1) Las reacciones S.S.C., F. II S.C., y F. II L.P. en 239 enfermos con todos los diagnósticos se acordaron en un 83% de los casos. El acuerdo fué más pronunciado entre la S.S.C. y la F. II L.P.

(2) En la artritis reumatoide clásica o definida, las tres reacciones fueron simultáneamente positivas en un 62,8% de los casos. La S.S.C. fué positiva en un 66,3%, la F. II L.P. en un 68,2%, y la F. II S.C. en un 72,2% de los casos.

(3) En los casos de artritis reumatoide probable y posible hubo apreciadamente más reacciones positivas, según los tres métodos, que en los testigos.

(4) En los testigos (sin enfermedad reumática o colagena) la reacción S.S.C. fué positiva en un 8,6%, la F. II L.P. en un 4,3%, y la F. II S.C. en un 15,2%.

(5) La mayor frecuencia de las reacciones F. II S.C. positivas en todas las series se debe al hecho de haber aceptado un título mínimo de 1 : 56 como norma de positividad. Esta norma se deberá cambiar a 1 : 896.

(6) El análisis concurrente de las reacciones S.S.C. y F. II S.C. sobre 263 sueros reumáticos mostró la posible existencia de más de un factor reumático en estos sueros. Se reconoce también la importancia de factores inhibidores de la actividad reumática.

(7) Para las necesidades ordinarias de diagnóstico, las tres reacciones (tomando en cuenta las normas de positividad de los títulos) tienen una sensibilidad igual.

(8) La reacción F. II L.P. se prefiere a las demás por ser simple y rápida, provisto que se acepte un título mínimo de 1 : 160 como positivo.