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Research Article

FURTHER STUDIES ON THE AGGLUTINATION REACTION IN CHRONIC ARTHRITIS [1]

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The present authors (1), collaborating with Cecil, reported, in 1929, the isolation of streptococci from the blood and joints of patients having rheumatoid arthritis. A large percentage of the organisms thus recovered were culturally and biologically similar, and presented the appearance of hemolytic streptococci on blood agar plates. For convenience, these organisms were designated as "typical strains."

In later communications the authors reported, with Cecil (2), and alone (3, 4), that the serums of a high percentage of patients showing well-developed signs of rheumatoid arthritis gave strong agglutination reactions with "typical strain" streptococci. The same serums gave positive agglutination results with a few hemolytic streptococci from sources other than arthritis, but whenever such reactions took place the organisms were culturally and biologically indistinguishable from "typical strain" streptococci. With other bacterial antigens, however, including indifferent and green-producing streptococci, pneumococci, staphylococci and colon bacilli they gave little or no agglutination. Likewise, negative or insignificant reactions were obtained when the serums of a large number of normal individuals and of patients with other diseases were tested for agglutinations with "typical strain" streptococci. Among these control serums were 79 from rheumatic fever and 16 from osteoarthritis. As a result of this study, the authors concluded that the serums of a high percentage of patients with rheumatoid arthritis gave strong agglutination reactions with a biologically specific type of hemolytic streptococcus. Gray and Gowen (5), and Dawson, Olmstead and Boots (6) have in the main confirmed these observations.

THE PRESENT STUDY

In order to obtain further information concerning this phenomenon, routine agglutination tests were carried out with "typical strain" AB13 on the serums of all patients admitted to the arthritis department of the

[1] This study was carried on with the technical assistance of Edith L. Ross, Edna H. Lindsey, Edith M. Kirkpatrick, and Elnora B. Carmichael.

Cornell Clinic during a two-year period. These tests were repeated, when possible, at intervals throughout the patient's period of observation. The purpose of this paper is to present an analysis of the findings in this study. Unless otherwise stated, all agglutination results reported refer to those at the time of the patient's first visit to the Clinic.

Seven hundred and thirty-three cases are included—a few had to be discarded either because a diagnosis could not be made or because the patients were suffering from diseases other than arthritis. The incidence of each disease is given in Table 1.

TABLE 1

Tabulation of diseases studied

Disease	Number of cases
Rheumatoid arthritis	613
Ostearthritis	44
Monarticular arthritis	41
Rheumatic fever	14
Gonococcus arthritis	16
Gout	4
Intermittent hydrarthrosis	1
Total	733

AGGLUTINATION TECHNIC

The method of performing the agglutination test was similar to that previously described (3) and so need not be explained in detail. No dilutions were made beyond 1 : 5120. Each test was controlled with a serum that was known to possess no streptococcus agglutinins and with a tube containing 0.5 cc. of broth and 0.5 cc. of culture. All agglutinations were heated in a water bath at 56° C. for two hours. The tubes were then placed in a refrigerator and readings were made the following morning. The last dilution in which definite clumping of the bacteria could be detected by the naked eye was recorded as the agglutination titer.

The agglutination tests on each specimen were carried out on two consecutive days and if the readings thus obtained did not correspond, the procedure was repeated until the titer was accurately ascertained.

Occasionally the antigen showed a tendency to become granular. This proclivity was usually overcome by daily transferring the culture to fresh blood broth mediums over a period of several days. Subculturing in broth containing 0.2 per cent disodium hydrogen phosphate, in place of the 1.5 sodium chloride, was also found to encourage diffuse growth of the organisms.

RHEUMATOID ARTHRITIS

Six hundred and thirteen patients were diagnosed as suffering from rheumatoid arthritis—none were included in this group who had symptoms in one joint only.

For convenience, the patients were allotted to one of three groups, according to the degree of joint involvement. The first group includes those who complained of pain in the joints, but failed to show any periarticular swelling; the symptoms were usually migratory in character and tenderness was frequently found. The second group is comprised of those who presented the usual picture of rheumatoid arthritis with characteristic periarticular swelling, generally including fusiform fingers. The third group is similar to the second, but is made up of patients who were in a more advanced stage of the disease—deformities such as ulnar deviation, and partial or complete ankylosis of one or more joints characterize this group. These three groups are indicated by +, ++, and +++, respectively, and the number and percentage of patients in each group are shown in Table 2.

TABLE 2

Tabulation of patients with rheumatoid arthritis

Group	Number of patients	Per cent
+	310	50.6
++	241	39.3
+++	62	10.1
Total	613	100.0

In several tables and figures reference is made to mean agglutination titers. These group averages are computed by multiplying each figure representing a dilution of serum by the number of serums agglutinating at that titer, adding these products and dividing the sum by the total number of serums included in the group.

In order that insignificant information be not included in the tables and figures, titers of 1 : 20 and 1 : 40 have been recorded as negative.

Relation of incidence of disease to age of patient

In Figure 1 the age incidence of patients belonging to each of the three groups (+, ++, +++) is indicated. Only one patient under ten years of age was seen with rheumatoid arthritis, and only seven, in the second decade of life, while there was a sharp falling off after sixty years of age. That rheumatoid arthritis is chiefly a disease of middle life is clearly shown in Figure 1. The small proportion over 60 years of age may be due in part to the failure of patients at this age to seek medical advice, but no such reasoning is applicable to the low incidence in patients of twenty years of age or under. It must, therefore, be concluded that rheumatoid arthritis is a relatively rare disease during the first two decades of life. While the three curves are nearly parallel, there is a distinct tendency in the + group to mark its maximum incidence at an earlier age than do the others.

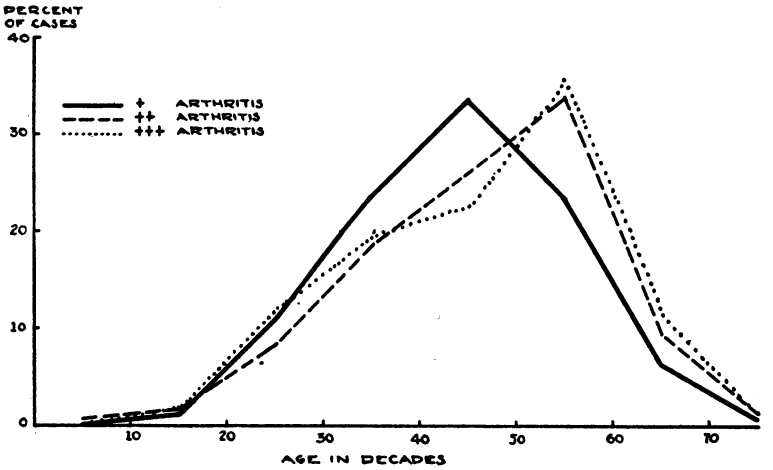

FIG. 1. RELATIONSHIP OF INCIDENCE OF DISEASE TO AGE OF PATIENTS IN RHEUMATOID ARTHRITIS (613 CASES)

Relation of agglutination titer to degree of joint involvement

In a previous study of agglutination reactions with rheumatoid arthritis serums a selection of patients with marked joint involvement was used. Of the 110 serums then examined, 93.6 per cent showed definite agglutination to a titer of 1 : 640 or more (3). In the present study of 613 cases all stages of rheumatoid arthritis are represented. In Figure 2

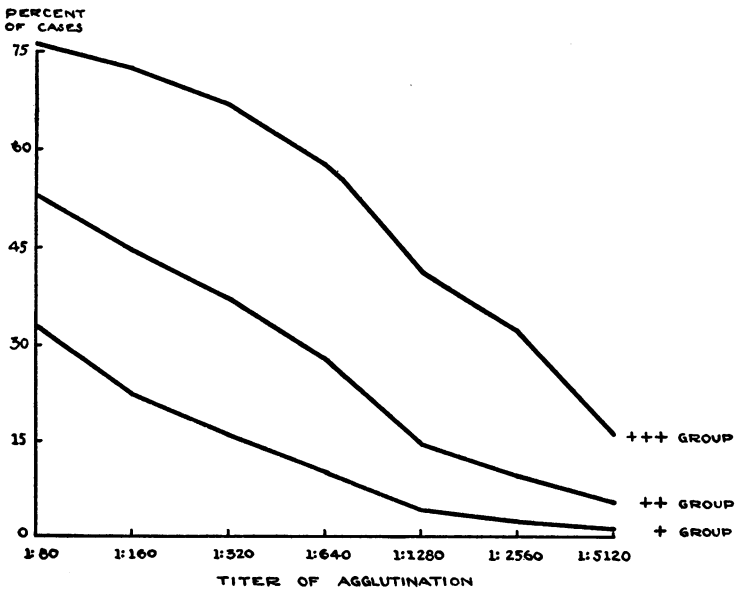

FIG. 2. RELATION OF DEGREE OF JOINT INVOLVEMENT TO TOTAL AGGLUTINATION (613 CASES)

is indicated the total agglutinations for each of the three groups. The highest degree of agglutination was found in the class with advanced rheumatoid arthritis (+++), while a distinctly higher agglutination was found in the moderately advanced group than in the mild cases without swelling (+). From these results it is evident that, on an average, the more advanced the joint involvement, the higher the titer of agglutination.

Relation of agglutination titer to duration of disease

The agglutination titer in rheumatoid arthritis with relation to the duration of the disease is indicated in Table 3 and Figure 3. In 8 cases of disease duration of one month or less there was not the slightest evidence of the presence of agglutinins. In 45 cases of disease duration

TABLE 3

Results of agglutination tests in rheumatoid arthritis in relation to duration of disease

Duration	Cases	Negative	Titer of agglutination							Mean titer
			1:80	1:160	1:320	1:640	1:1280	1:2560	1:5120	
One month or under.....	8	8								0
Over 1 month to 3 months..	45	30	6	5	2	1			1	1:171
Over 3 months to 6 months	66	31	5	6	5	11	3	2	3	1:520
Over 6 months to 1 year....	92	49	14	4	9	8	1	3	4	1:426
Over 1 year to 3 years.....	126	62	10	5	12	16	8	7	6	1:591
Over 3 years to 5 years.....	88	42	11	8	5	9	6	4	3	1:486
Over 5 years.....	188	115	7	13	13	17	7	7	9	1:482

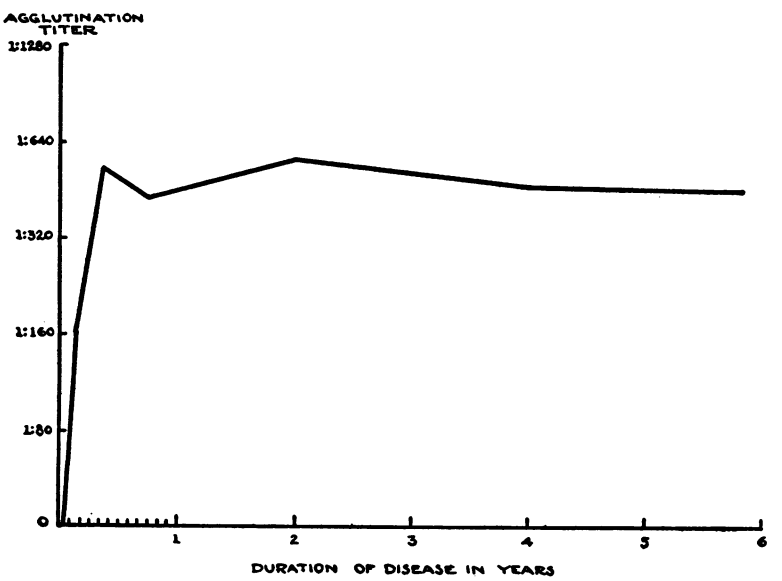

FIG. 3. MEAN AGGLUTINATION TITER IN RHEUMATOID ARTHRITIS IN RELATION TO DURATION OF DISEASE (613 CASES)

from one to three months the highest agglutination titer recorded with one exception was 1 : 640 and the mean was 1 : 171. In the group having the disease from three to six months, 3 showed an agglutination titer of 1 : 5120, while the average was 1 : 520. In the groups covering a disease duration of over six months little variation was noted, the line on the graph closely approaching a straight one. A similar analysis, employing only cases in groups ++ and +++, revealed a curve similar to that when all three groups were used.

From these results it is evident that it takes six months, on the average, for a patient to develop hemolytic streptococcus agglutinins to the maximum titer, but that aside from this initial period the duration of the disease plays no important part in the strength of the agglutination reaction. Dawson, Olmstead and Boots (6), reporting a series of 153 cases, stated that the agglutination titer increased with the duration of the disease. Our findings do not confirm this conclusion.

Relation of agglutination titer to age of patient

In Table 4 and Figure 4 the results of the agglutination tests in rheumatoid arthritis are arranged in relation to the age of the patients. A boy of seven with moderately advanced rheumatoid arthritis was the only patient under 10 years of age seen in the arthritis clinic. His serum

TABLE 4

Results of agglutination tests in rheumatoid arthritis in relation to age of patient

Age	Cases	Negative	Titer of agglutination							Mean titer
			1:80	1:160	1:320	1:640	1:1280	1:2560	1:5120	
years										
Under 10	1					1				
10 to 19	7	4	1			2				1:194
20 to 29	62	34	8	3	4	4	2	2	5	1:616
30 to 39	129	64	18	9	9	9	9	7	4	1:476
40 to 49	184	108	10	12	16	21	3	5	9	1:457
50 to 59	174	94	12	15	13	19	9	6	6	1:444
60 to 69	50	30	4	2	3	5	2	3	1	1:403
70 or over	6	3			1	1	1			

showed an agglutination titer of 1 : 640 with "typical strain" streptococcus AB13. There were but 7 patients between ten and nineteen years of age—serums from 2 of these gave an agglutination titer of 1 : 640, from 1 a titer of 1 : 80, and from 4 there were negative findings, with a mean agglutination titer for the group of 1 : 194. The age period covering the third decade gave, on an average, the highest titer of agglutination, while in the periods following there was a slight gradual drop all the way to the last group which included patients seventy years of age or older.

Dawson, Olmstead and Boots (6) reporting a sharply progressive increase in the median agglutination titers of patients in the third, fourth and fifth decades, concluded that "the property of rheumatoid arthritis serum responsible for the agglutination of hemolytic streptococci is definitely related . . . to the age of the patient." Our results do not agree with their findings. When, however, groups +, ++ and +++ of our series are plotted individually, group +++ tends to show increased titers of agglutination in the fourth, fifth and sixth decades. It seems probable then that the series of cases reported by Dawson, Olmstead and Boots is preponderantly made up of cases corresponding to those in group +++ of the present series. In the opinion of the writers, a more accurate impression of the relation of age to the titer of agglutination can be obtained from the study of the disease as a whole than from an analysis of certain of its phases.

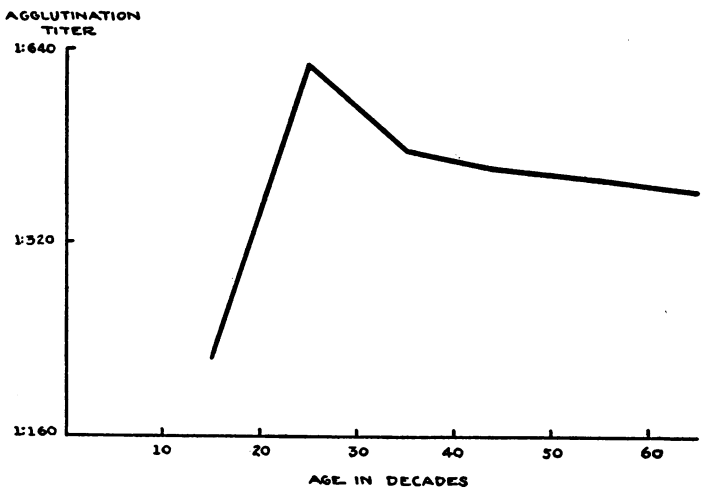

FIG. 4. MEAN AGGLUTINATION TITER IN RHEUMATOID ARTHRITIS IN RELATION TO AGE OF PATIENT (606 CASES BETWEEN THE AGES OF 10 AND 69)

In the present series, the number of patients in the first, second and eighth decades of life is too small to draw any definite conclusions concerning their agglutination reactions with "typical strain" streptococci. It seems probable, however, that in patients under twenty years of age the agglutination titer averages lower than in patients over that age. This impression receives support by the findings in a study of agglutinins in the serums of six patients in Bellevue Hospital suffering from Still's disease, a condition accepted by many as rheumatoid arthritis in early childhood. Although the same technic was carried out, negative results were obtained in each case. It is doubtful if a lower titer in patients under twenty years of age has any significance because during that period rheumatoid ar-

thritis is uncommon and when it does occur it assumes atypical forms, frequently resembling rheumatic fever.

In summing up the relationship of the age of the patient to the agglutination titer, one is led to the conclusion that with the possible exception of the first two decades of life the age of the patient plays no important role in the strength of the agglutination reaction.

Relation of agglutination titer to time of year

Clinically, it is generally recognized that in temperate climates patients with rheumatoid arthritis are usually at their worst in cold weather and at their best in hot weather. In order to ascertain if there is any seasonal variation in the agglutination titers in this disease Table 5 was prepared.

TABLE 5

*Results * of agglutination tests in rheumatoid arthritis in relation to season of year*

Season	Cases	Negative	Titer of agglutination							Mean titer
			1:80	1:160	1:320	1:640	1:1280	1:2560	1:5120	
Winter	98	33	12	8	9	17	8	7	4	1:660
Spring	79	30	3	4	7	16	3	5	11	1:1074
Summer	46	30	3	2	1	4	1	2	3	1:548
Autumn	80	35	4	6	12	7	4	7	5	1:728

* Total of 303 cases—groups ++ and +++ only.

Cases of arthritis in groups ++ and +++ were selected as patients in the more advanced stages appeared to show the greatest seasonal variation. In the table, "Winter" is used to designate the period from January 1 to March 31; "Spring," from April 1 to June 30; "Summer," from July 1 to September 30; and "Autumn," from October 1 to December 31. The findings are interesting. The mean agglutination titer of 79 patients studied in the spring was 1 : 1074, while that of 46 studied in the summer was only 1 : 548. The mean titers during the autumn and winter were 1 : 728 and 1 : 660 respectively. Due to the small number of cases in this series and the distribution of the agglutination titers entering into the means, the degree of probability of chance occurrence of the differences between the means is too high to warrant any definite conclusions. Nevertheless the results are at least suggestive that on the average the agglutination titers are higher in the spring and lower in the summer than at other seasons of the year.

Relation of titer of agglutination to clinical changes

Initial agglutination tests on all patients were repeated at irregular intervals throughout each period of observation. Condensed protocols of those subjected to the test four or more times appear in Table 6. The

TABLE 6

Patients with repeated agglutinations

Patient number	Sex	Age	Duration of disease	Joint involvement	Results of agglutinations												Clinical condition during observation
					Date	Titer	Date	Titer	Date	Titer	Date	Titer	Date	Titer	Date	Titer	
		yrs.															
1	M	47	1 year	+++	12/29/30	1:5120	1/13/31	1:5120	2/9/31	1:5120	2/25/31	1:1280	4/29/31	1:5120	5/19/31	1:5120	Unchanged
2	F	40	3 years	++	4/16/30	1:5120	2/1/31	1:1280	4/15/31	1:2560	4/23/31	1:5120	5/21/31	1:5120	5/23/31	1:5120	Gradually worse
3	F	36	6 months	++	12/26/30	1:640	3/1/31	1:5120	4/22/31	1:1280	7/1/31	1:1280					Unchanged
4	M	53	3 years	++	4/15/31	1:640	6/26/31	1:320	10/9/31	1:640	1/8/32	1:320					Unchanged
5	F	45	6 years	++	1/11/31	1:640	4/29/31	1:320	9/25/31	1:2560	10/16/31	1:640	2/24/32	1:640			Unchanged
6	F	48	6 months	++	1/18/31	1:640	4/13/31	1:5120	6/29/31	1:1280	10/9/31	1:2560					Unchanged
7	F	57	2 months	++	2/7/31	1:160	6/10/31	1:1280	9/30/31	1:320	1/6/32	1:320					Unchanged
8	F	58	15 years	++	9/9/31	1:2560	9/23/31	1:320	3/30/32	1:5120	6/1/32	1:320					Unchanged
9	M	65	5 years	++	1/20/31	1:640	10/7/31	1:80	10/14/31	1:80	12/16/31	1:640	4/13/32	1:320			Possibly slightly worse
10	F	50	2 years	+++	10/28/31	1:320	1/6/32	1:5120	2/4/32	1:2560	4/13/32	1:2560	5/25/32	1:320			Unchanged
11	F	50	3 months	+++	6/3/31	neg.	10/2/31	1:320	10/23/31	1:5120	4/8/32	neg.					Unchanged
12	F	45	6 years	+++	4/17/31	1:640	9/18/31	1:320	11/27/31	1:160	3/4/32	1:160	5/13/32	neg.			Unchanged
13	F	33	4 months	+++	2/15/31	1:2560	6/26/31	1:2560	9/23/31	1:5120	1/22/32	1:640					Gradually worse
14	F	50	1½ years	+++	5/16/31	1:2560	9/23/31	neg.	10/7/31	1:320	3/30/32	1:640					Irregular course. In general worse
15	M	20	2 years	++	1/18/31	neg.	5/1/31	1:320	10/30/31	neg.	11/25/31	neg.	3/16/32	neg.			Irregular course. In general unchanged
16	M	56	4 years	+++	4/22/31	1:5120	8/14/31	1:160	10/16/31	1:640	2/26/32	1:320					Irregular but definite improvement
17	F	51	7 years	++	12/19/31	1:1280	4/1/31	1:5120	6/17/31	neg.	4/13/32	neg.					Slight improvement
18	M	41	3 years	+	12/11/30	1:640	2/1/31	1:320	4/29/31	1:40	9/16/31	1:80	2/5/32	neg.	5/18/32	neg.	Gradually improved
19	M	24	10 weeks	++	12/20/30	neg.	12/29/30	1:640	1/13/31	1:1280	2/7/31	1:80	2/25/31	neg.			Gradually improved. Discharged cured
20	M	9	4 months	++	4/11/30	1:640	11/22/30	1:640	3/1/31	1:160	6/24/31	neg.	6/28/31	neg.	3/11/32	neg.	Gradually improved. Discharged cured
21	F	37	3 months	++	7/10/31	1:160	9/25/31	1:320	11/20/31	neg.	2/5/32	neg.	5/13/32	neg.			Gradually improved
22	F	28	6 months	++	4/8/31	1:2560	4/22/31	1:2560	6/24/31	1:640	10/28/31	1:320	4/15/32	1:640			Gradually improved Cured (4/15/32)
23	F	38	3 years	++	2/11/31	1:80	4/1/31	1:1280	8/9/31	1:320	11/13/31	1:640	2/26/32	1:1280	4/27/32	neg.	Constant improvement beginning spring 1931
24	F	31	4 years	+	1/18/31	1:1280	4/22/31	1:5120	9/16/31	neg.	1/29/32	neg.	5/25/32	neg.			Gradually improved. Discharged cured
25	F	24	3 years	+	7/22/31	1:1280	10/4/31	neg.	10/23/31	neg.	1/4/32	neg.	4/15/32	neg.			Marked improvement beginning spring 1932
26	F	30	1 year	+	12/10/30	1:80	3/1/31	1:640	6/24/31	neg.	9/2/31	1:160	11/25/31	neg.	3/2/32	neg.	Irregular course. Improved last 6 months
27	M	32	2 years	++	9/30/31	1:2560	1/29/32	1:640	3/30/32	1:640	4/29/32	neg.					Gradually improved
28	F	39	2 years	+	1/18/31	1:1280	3/4/31	1:640	5/29/31	1:1280	4/8/32	1:320					Improvement beginning summer 1932
29	F	30	1 year	+	12/10/30	1:80	6/10/31	1:1280	5/16/32	1:80							Severe exacerbations during spring of 1931. 5/16/32 condition about as on admission
30	M	49	4 months	+	1/2/31	1:640	6/3/31	1:5120	9/9/31	1:2560	4/6/32	1:160					Worse during first 6 months. 4/6/32 much improved

findings on one patient who had but three examinations were included because of their special interest.

Patients 1 to 15, inclusive, showed no appreciable change in clinical condition throughout the observation period. In these cases the titers of agglutination evidenced a strong tendency to remain at a constant level.

In contrast to the findings on the fifteen patients mentioned are those of patients 16 to 28 who showed definite clinical improvement, sometimes with complete recovery. In this group the serums tended either to agglutinate at lower levels or else to completely disappear, but generally the strength of the agglutination did not show signs of diminishing until some weeks or months after the patient began to improve clinically. Patient 19 illustrates this proclivity very well. This patient with a history of polyarthritis of only ten weeks standing, whose illness was running a subacute course, presented the typical features of rheumatoid arthritis at the time of his first visit. An agglutination test at that time (December 20, 1930) gave negative results. The patient showed constant improvement dating from the time of his first visit and was entirely free from signs and symptoms on January 13, 1931. In spite of this clinical improvement, the agglutination titer continued to rise for one month and only began to fall after the patient was entirely free from signs and symptoms of the disease.

Patient 23, with a more chronic form of the disease, illustrates the same process. With a history of rheumatoid arthritis of three years duration she showed marked improvement from the Spring of 1931, yet it was several months before the agglutination titer began to diminish and not until one year later that the agglutinins disappeared completely.

Patients 29 and 30 illustrate the tendency of the agglutination titers to rise and fall with changes in the clinical condition. At their first visit both of these patients presented the picture of a very mild and early rheumatoid arthritis. While under treatment their conditions gradually became very much worse, with a definite increase in the agglutinin content of their serums. At a still later period the arthritis showed definite abatement, which condition was followed by a diminution of streptococcus agglutinins in the serums, evidenced by a lower agglutination titer.

In summing up the results of repeated agglutination reactions in rheumatoid arthritis, it is apparent that the agglutinin content in the patient's serum is related to his clinical condition, tending to increase gradually during the development of the disease, and to decrease gradually with the recovery of the patient. There seems also to be considerable individual variation in the time required for clinical change to be manifested in the agglutination reactions.

OTHER FORMS OF ARTHRITIS

The results of agglutination tests in other forms of arthritis seen during the period of this study are presented in Table 7.

TABLE 7

Results of agglutination tests in other forms of arthritis

Disease	Negative	Titer of agglutination							Cases
		1:80	1:160	1:320	1:640	1:1280	1:2560	1:5120	
Ostearthritis	38	6							44
Monarticular arthritis	33	4	1	2	1				41
Rheumatic fever	11	1	1	1					14
Gonococcus arthritis	14	2							16
Gout	4								4
Intermittent hydrarthrosis	1								1

Forty-four patients were diagnosed as suffering from ostearthritis—special care being taken not to confuse true ostearthritis with rheumatoid arthritis showing secondary ostearthritic changes. All of these patients were over forty years of age and not one serum of the 44 gave an agglutination reaction to a titer higher than 1 : 80, while 38 were completely negative.

In the group classified as monarticular arthritis are included, for convenience, cases of spondylitis. Probably some of these 41 cases were of infectious origin, of the rheumatoid arthritis type, but because of the uncertainty of diagnosis they were segregated in this way; 33 gave negative results to agglutination tests, while the highest titer recorded by the remaining 8 was 1 : 640.

Fourteen patients suffered from rheumatic fever. Eleven gave negative agglutinations, while the highest titer recorded was 1 : 320.

Sixteen cases of gonococcus arthritis were seen. A diagnosis made from the history of the association of gonococcus urethritis with the onset of joint symptoms was frequently confirmed by positive findings in a complement fixation test. The highest agglutination recorded for this group was at a titer of 1 : 80.

Four cases of gout and one of intermittent hydrarthrosis gave completely negative reactions.

SUMMARY AND DISCUSSION

Seven hundred and thirty-three patients with chronic arthritis were studied by agglutination tests with "typical strain" streptococcus AB13.

In this aggregation rheumatoid arthritis was the predominating disease, as 613 of the patients were suffering from that affection. The age incidence in this group was an interesting feature. Only one patient under ten years of age was seen and there was a gradual increase up to and including the sixth decade, following which there was a sharp drop. The maximum incidence of patients without joint swelling occurred at a somewhat earlier age than the highest number with joint swelling.

A previous article by the present authors showed that the serums of a high percentage of selected patients with well-developed rheumatoid arthritis gave strong agglutination reactions with a specific type of hemolytic streptococcus. In the present study, all types of rheumatoid arthritis are included and a more detailed analysis of the results has been made.

Apparently, the degree of joint involvement is an important factor in the strength of the agglutination reaction, as the tests proved that the more marked the joint involvement, the higher the agglutination titer. Moreover, as the amount of joint involvement is generally considered to be commensurate with the severity of the disease, it does not seem unfair to assume that as the arthritis increases in severity more evidence is found of streptococcus agglutinins in the serum.

An analysis of the agglutination reaction in relation to the duration of the disease reveals the fact that it takes several weeks following the onset of the disease for the streptococcus agglutinins to become apparent in the serum, and that the maximum titer is not obtained until an average of six months has elapsed. Except in this relation, the duration of the disease appears to play no important role in the agglutination phenomenon.

The age of the patient, likewise, showed little effect on the strength of the agglutination reaction. An exception must be made, however, in the first two decades of life. Although one patient seven years of age gave a definite agglutination to a titer of 1 : 640, the tendency was for the titer in subjects of this age to be weaker and more irregular. As has already been pointed out, little significance can be attached to this observation because such patients seldom manifest the typical clinical picture of rheumatoid arthritis, their signs and symptoms frequently resembling those of rheumatic fever, a disease that does not give positive results in tests with "typical strain" streptococci.

Of particular significance are the findings in patients subjected to repeated agglutination tests extending over a period of months or years. The results of these tests are remarkably consistent as the serums of patients in whom the disease appears to be stationary continue to give similar agglutination titers throughout the period of observation. In patients fortunate enough to show marked improvement or complete recovery, on the other hand, the streptococcus agglutinins either diminish or completely disappear from the blood. Sometimes this is accomplished in a few weeks, sometimes it takes months or even years.

With the information at hand concerning the agglutination reaction in rheumatoid arthritis, it would seem justifiable to consider the nature of this phenomenon. Unfortunately, we do not have a chronic disease that affords a comparison and must, perforce, compare it with an acute disease, such as typhoid fever. In typhoid the Widal reaction is considered to be an immunological one. Following the onset of the disease,

there is a definite interval of several days before a positive typhoid agglutination can be obtained. In the succeeding days or weeks the strength of the reaction tends to increase, while on recovery of the patient it slowly diminishes and in the course of several months or years eventually disappears. In rheumatoid arthritis a similar situation exists. The only essential factor in which it differs from that in typhoid fever is the time element. In typhoid the agglutination changes are apparent after periods of days—in arthritis, after periods of weeks or months. This would seem to be a natural disparity between the processes in an acute and a chronic disease. Although not irrefutably proven, these findings afford strong evidence that the presence of streptococcus agglutinins in such high titers is a true immunological response to a bacterial invader similar in all essential respects to that seen in typhoid fever.

In contrast to the positive results obtained from agglutination tests in rheumatoid arthritis are the negative results in ostearthritis, gonococcus arthritis, rheumatic fever, and gout. A knowledge of this reaction is of practical value in differential diagnosis. A positive reaction at titers of 1 : 320 or higher is indicative of rheumatoid arthritis but the reverse does not hold true because a small percentage of patients even though they present the typical picture of rheumatoid arthritis have serums that give negative agglutination results with "typical strain" streptococci.

CONCLUSIONS

1. A high percentage of patients with rheumatoid arthritis give positive agglutination reactions to a specific type of hemolytic streptococcus.

2. In patients with advanced joint involvement higher average titers are obtained than in those with less involvement.

3. The duration of the disease and the age of the patient play unimportant roles in the strength of the agglutination.

4. Following the onset of the disease, there is a gradual increase in the agglutination titer which reaches its maximum in 6 months, on the average, while following recovery of the patient the agglutinins tend to diminish and eventually to disappear.

5. This reaction of serum in rheumatoid arthritis appears to be a true immunological response.

6. Other forms of arthritis do not give positive results in agglutination tests with typical strain streptococci.

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