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Research Article

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Hemolytic Complement in Synovial Fluid *

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The binding of complement by antigen-antibody reactions, which is the basis for the very useful complement fixation test, has been extensively studied *in vitro*. Support for the concept of *in vivo* binding of complement is derived from animal studies that have shown a close relationship between the disappearance of circulating antigen, the appearance of circulating antibody, and a fall in serum complement activity (1–4). Lesions in the tissues of the test animal, particularly in blood vessels, myocardium, and the kidney occur simultaneously with these events (2, 4). Similar lesions can be produced by the intravenous injection of soluble antigen-antibody complexes (4, 5); the introduction of these complexes results also in a significant decrease in serum complement activity (4, 6). Immunofluorescent studies have shown antibody globulin localized at the sites of the experimentally produced lesions (3).

Somewhat analogous findings have been obtained in certain human diseases. By immunofluorescent techniques, bound gamma globulin can be identified in the renal lesions of systemic lupus erythematosus (SLE) and glomerulonephritis (7, 8). Complement or complement components have likewise been shown to be present in these areas (9, 10). Klein and Burkholder demonstrated that both gamma globulin and complement are present in the renal lesions of experimental glomerulonephritis (11); similar results were obtained by Freedman and Markowitz in a study of the kidney in SLE (9). By using fluorescein-labeled rheumatoid factor as an indicator for antigen-antibody complexes or aggregated gamma globulin and a fluorescent specific antibody to the $beta_{1C}$ globulin component of complement, Lachmann, Müller-Eberhard, Kunkel, and Paronetto demonstrated that aggregated gamma globulin or antigen-antibody complexes and complement, or all, were present at the sites of the glomerular lesions in SLE and human glomerulonephritis (10). Investigations of serum complement levels in patients with SLE and acute glomerulonephritis have shown decreases in serum complement that parallel the activity of these diseases (12–15). These observations of binding of complement *in vivo* and depression of circulating complement activity have been used to support the role of immunologic phenomena in the pathogenesis of certain diseases of man. Conflicting evidence comes from studies of serum complement in other diseases that have been included in the group of autoimmune disorders, particularly rheumatic fever and rheumatoid arthritis. Several studies have shown that in rheumatoid arthritis the serum complement activity is normal or increased, rather than depressed (15–18). Similar results have been obtained in rheumatic fever (16, 19). The elevation of complement levels in these diseases would seem to be an expression of a nonspecific inflammatory process rather than the result of immunologic phenomena. Our studies were therefore initiated to ascertain whether complement activity in synovial fluid would reflect more closely the disease process in the articular cavity than do the serum complement levels. De Gara showed that complement is present in synovial fluid (20); he was concerned with the *in vitro* antibacterial properties of synovial fluid and did not attempt to correlate the amount of complement found with the disease state that resulted in the effusion. No other investigations of synovial fluid complement have been reported.

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Materials and Methods

Serum and synovial fluid were obtained from normal control subjects and from patients with rheumatoid arthritis, gout, osteoarthritis, and Reiter's syndrome. The 6 normal volunteers were males without historical or clinical evidence of joint abnormality. All patients with rheumatoid arthritis met the American Rheumatism Association's criteria for definite or classical rheumatoid arthritis (21). The rheumatoid patients represented all degrees of disease activity and had received many different therapeutic agents, including salicylates, antimalarials, gold salts, corticosteroids, and nitrogen mustard. The patients with gout had a history of episodic acute inflammatory attacks of arthritis responsive to colchicine, elevated serum uric acid levels, and the presence of sodium urate crystals in the synovial fluid (22). Reiter's syndrome was manifested by concurrent conjunctivitis, nonspecific urethritis, acute inflammatory arthritis of one or more large joints, and either keratodermia or balanitis circinata. Patients with osteoarthritis all had a characteristic history of noninflammatory arthritis and typical radiologic and synovial fluid findings.

The diluent employed in all complement titrations was

TABLE I

*General data**

Identification			Synovial fluid†					Serum	
Patient	Age	Sex	Leukocytes × 100	TP	γ-Globulin	BFT	CH_{50}	CH_{50}	BFT
				g/100 ml	*g/100 ml*				
A. Normal subjects									
TM	35	M		0.5			16		
SC	40	M		0.7			17		
JS	47	M		1.0			19		
CO	42	M		1.8			20		
JA	37	M		1.4			22		
AS	32	M		1.6			25		
B. Osteoarthritis									
MC	55	F	1.0			0	18	190	0
FN	51	M	0.5				22	240	
BR	59	F	1.5	5.1	1.5		25	200	
SH	60	F	4.5	2.2		0	25	294	0
FB	62	F	2.5	1.4			30	250	
FK	60	F	1.0	2.6	0.62	0	40	187	0
FP	40	M	2.0	1.8			40		
JP	57	M	1.0	2.1	0.52		47	171	
LE	70	F	1.5	2.6	0.65		60	215	
MP	43	F	2.5	0.5		0	60	190	0
EC	71	M	4.5	3.1			64	240	
ET	50	F	4.5	3.4		0	70	290	0
MC	48	F	2.5	2.4	0.37	0	71	215	0
CP	45	F	0.5			0	80	245	0
AM	62	F	2.0	5.0			86	255	
SH	50	F	4.5	3.1	0.76	0	120	300	0
C. Gouty arthritis									
HS	70	M	10	3.6	0.93	0	5	186	0
HS	54	M	130	5.3	1.79	0	60	200	0
OW	37	M	11	5.7	2.23		95	260	
LV	45	M	277	5.1		0	100	250	0
AR	53	F	59	5.0	2.08	0	100	220	0
GN	59	M	135	5.0	1.71	0	110	430	0
JF	63	F	50	4.5		0	111		0
SR	45	M	60	5.3	1.42	0	111		0
TH	50	M	200	4.7	1.47	0	115		0
HP	54	M	1.5	4.8	0.90		125	272	
SW	57	M	170	4.4	1.23	0	125	300	0
CR	62	M	346	6.1	1.79	0	130	330	0
RC	47	M	196	5.0		0	140	270	0
LD	49	M	147	7.4	2.52	0	155	330	0
D. Reiter's syndrome									
PB	26	M	400	5.1	2.21	0	149	343	0
JW	40	M	123	5.3	1.32	0	160	310	0
SW	35	M	176	5.8	2.18	0	164	355	0

TABLE I—*Continued*

Identification			Synovial fluid†					Serum	
Patient	Age	Sex	Leukocytes × 100	TP	γ-Globulin	BFT	CH_{50}	CH_{50}	BFT
				g/100 ml	*g/100 ml*				
E. Rheumatoid arthritis									
CA	63	M	19	3.3	1.04	32	0	132	128
EL	52	F	600	4.4		4,096	0	180	4,096
GJ	41	F	42	5.0	2.33		5	250	64
HW	49	M	157	6.2	1.98	2,048	5	220	512
BM	46	F	280	6.7	2.44	1,024	5	235	128
CK	51	M	178	5.6	1.46	156	7	240	256
AS	71	F	110	3.7	1.44	4,096	10	286	256
RS	52	F	58	3.8			12	215	128
VA	59	F	230	4.7		128	14	150	256
AS	40	F	27	2.7	0.75	0	17	227	0
JM	51	M	117	4.3	1.46	128	18	237	256
BB	34	F	245	4.3	1.25	512	18	230	256
GH	58	M	35	5.7	1.94	64	20	290	64
MM	68	F	347	4.5		4,096	21		2,048
FM	59	F	78	5.0			25	217	4,096
AH	39	F	86	4.4			26	208	4
JB	60	F	177	3.7	1.05	64	29	242	4,096
AC	61	F	235	5.1	1.91	64	39	200	256
JM	47	M	51	5.4			39	266	64
LS	55	F	275	4.1		0	39	210	0
KP	43	F	37	3.7	0.74	512	39	245	128
AE	41	F	156	4.2	1.1	128	40	180	128
SD	50	F	210	4.4	2.52	512	41	271	256
GJ	43	M	150	5.4	1.78	32	50	250	
MV	56	F	5				50	200	512
AM	62	F	42	3.5		256	60	235	4,096
GM	68	M	147	4.4	1.18	256	65	234	4,096
JS	38	F	142	5.3		0	86	188	16
JG	47	M	266	5.7	1.50	64	90	275	2,048
RT	73	M	390	4.3	1.18	1,024	104	255	2,048
AM	57	F	213	5.0	1.90	4,096	140	270	512

* Each value represents an individual determination or the average of several determinations on the same subject.
† TP = total protein; BFT = the reciprocal of the bentonite flocculation test titer; CH_{50} = complement activity in 50% U of activity per ml.

triethanolamine (TBS) buffered saline, pH 7.3, μ 0.15, containing 1.5×10^{-4} M Ca^{++} and 5.0×10^{-4} M Mg^{++}. Sheep erythrocytes were collected in modified Alsever's solution, washed with TBS, and standardized spectrophotometrically to a cell concentration of 5×10^{8} cells per ml. Rabbit hemolysin was obtained from commercial sources.

Synovial fluid was obtained by aseptic aspiration of the suprapatellar pouch, immediately placed in ice, and then centrifuged at 5° C until the supernatant liquid was cell free. The fluid was kept in ice if the complement titration was to be performed the same day or at −20° C if done later (in no case later than 4 days from the time of collection). Blood was drawn at the same time as was the synovial fluid and allowed to clot in the cold. The serum was separated by centrifugation in the cold and handled in the same fashion as the synovial fluid.

The method used for C′ determination is a modification of that described by Kent and Fife (23). The serum and synovial fluid samples were the source of complement. The method was evaluated for reproducibility as follows: Serum was obtained from five normal subjects and complement activity measured in each. Each serum sample was separated into portions and frozen. The C′ activity of separate portions was measured at three- to five-day intervals for a month. The C′ values ranged from 150 to 194 U CH_{50} (the complement activity in 50% U of activity per ml), with one standard deviation of from 7.0 to 9.7 CH_{50} over the month interval.

Additionally, fresh serum was obtained from the same subjects at weekly intervals for 4 weeks, and C′ activity was measured. The widest variation noted was ±20%, and two were less than ±10%.

Serial volumes of the diluted serum or synovial fluid sample were added to 0.6 ml of sensitized sheep cells, and TBS was added to give a total reaction volume of 1.5 ml. The mixtures, in standardized 12- × 75-mm tubes, were incubated at 37° C; after 30 minutes 0.5 ml of cold TBS was added to each tube. The tubes were centrifuged, and the optical density of the supernatant fluid was read directly in a Coleman Junior spectrophotometer at 550 mμ. Control tubes containing no complement and tubes giving 100% hemolysis were run simultaneously. The percentage of hemolysis was transformed into probits, and the probits were plotted against the loga-

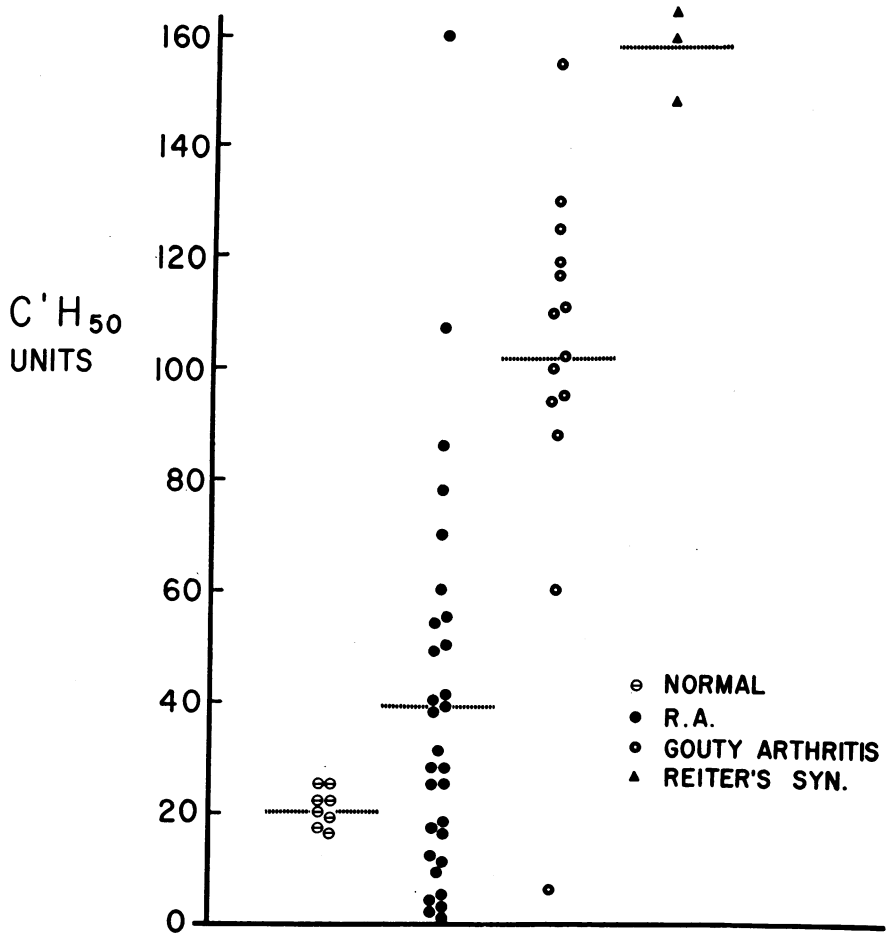

FIG. 1. SYNOVIAL FLUID COMPLEMENT ACTIVITY. Each symbol represents in all figures an individual determination or the average of several determinations on the same subject. The horizontal bars indicate the median value for each group. RA = rheumatoid arthritis.

rithm of the volume of diluted complement. The volume of diluted complement required for 50% hemolysis was determined by means of the log probit regression line. The complement activity is expressed throughout in 50% U, one 50% U ($C'H_{50}$) of complement activity being the amount of complement required to lyse 7.5×10^7 sensitized sheep cells under the stated conditions.

Synovial fluid leukocyte counts and mucin clot were done as described by Ropes and Bauer (24). Total protein was measured by the biuret method (25). Undialyzed samples of synovial fluid were subjected to electrophoresis at room temperature on 3-cm wide paper strips in barbital buffer of ionic strength 0.075 at pH 8.6 for 16 hours at a constant current of 0.6 ma per strip. The Spinco model R paper electrophoresis apparatus was used in this study. The paper strips were oven dried at 110° C for 15 minutes and the proteins stained with bromphenol blue. The dyed strips were analyzed in a Spinco model R densitometer. Before electrophoresis the synovial fluids had been incubated at 37° C for 60 minutes with 150 turbidity reducing units of hyaluronidase[1] per ml of fluid. This treatment was found sufficient to decrease the viscosity of synovial fluid, which normally distorts electrophoretic patterns.

Rheumatoid factor was determined by the bentonite flocculation test (26).

Synovial fluid was tested for anticomplementary activity by adding an equal amount of fluid that had been inactivated at 56° for 45 minutes to a human serum of known C′ activity and titrating the resultant mixture for C′ activity. Similarly, the effect of rheumatoid factor on synovial fluid C′ activity was evaluated by the addition of an equal amount of heat-inactivated sera with high titers of rheumatoid factor to synovial fluid of known C′ activity and titration of the mixture for C′ activity (Table II).

[1] Wydase, Wyeth Laboratories, Philadelphia, Pa.

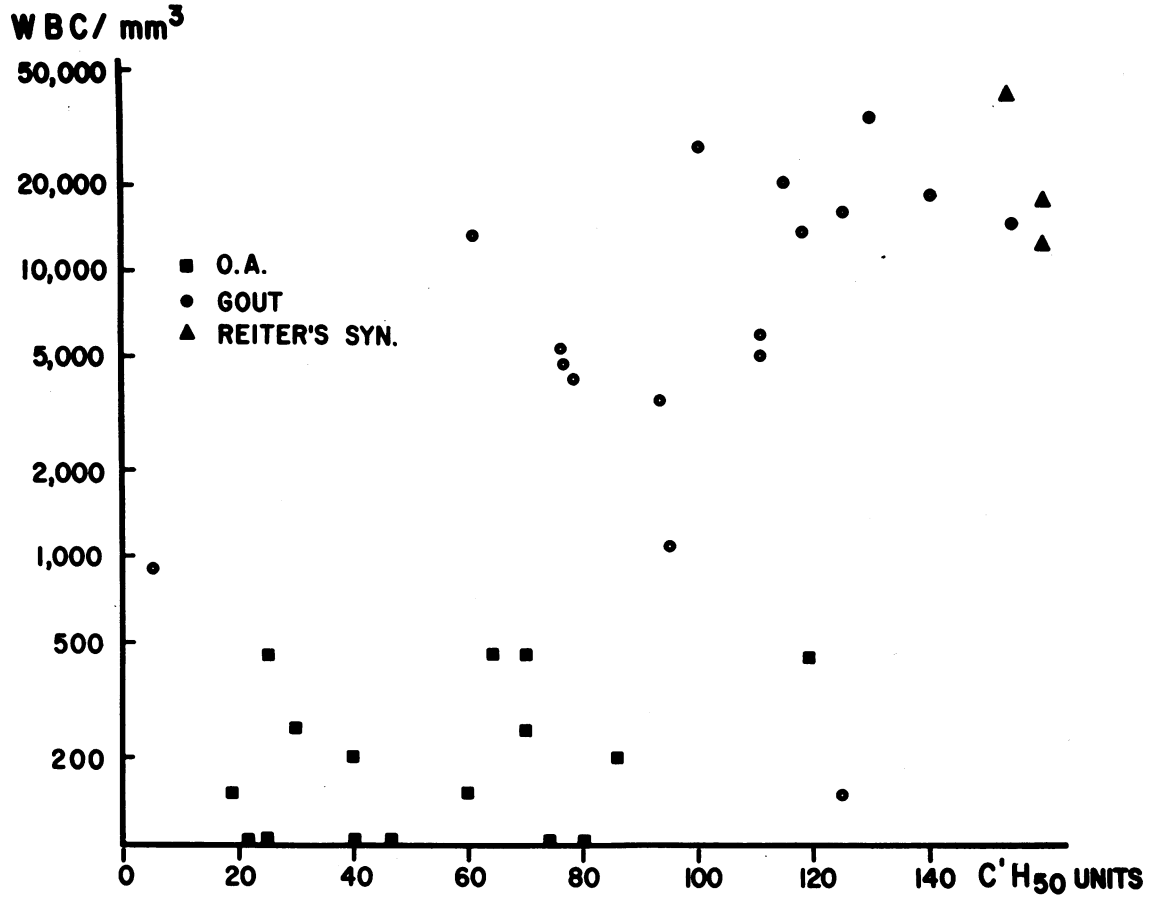

FIG. 2. THE RELATIONSHIP OF SYNOVIAL FLUID LEUKOCYTE COUNT AND COMPLEMENT ACTIVITY IN DISEASE STATES OTHER THAN RHEUMATOID ARTHRITIS. The leukocyte count is on a logarithmic scale. OA = osteoarthritis; $C'H_{50}$ = amount of complement required to lyse 7.5×10^7 sensitized sheep cells under the conditions stated in Methods.

Results

The diagnosis of joint disease, synovial fluid leukocyte count, total protein and gamma globulin concentration, titer of rheumatoid factor, and hemolytic complement activity are shown in Table I, along with serum complement activity and rheumatoid factor.

Serum and synovial fluid C′ values. The serum C′ activity of 8 normal control subjects ranged from 155 to 270 U ($C'H_{50}$). Repeated determinations on successive serum samples drawn over periods of weeks and months were similar. Thirty-one patients with rheumatoid arthritis were studied. Serum C′ values of all but 4 were within the normal range; these 4 were elevated, not depressed. Similarly, the majority of serum C′ values of the 14 patients with gout and 13 of the patients with osteoarthritis were within this normal range; values for the exceptions, 4 and 3 in the two groups, respectively, were elevated. The initial serum values of 3 patients with Reiter's syndrome were all in excess of 300 U.

Synovial fluid complement activity is shown in Figure 1. The complement values in 6 normal controls were uniformly low and closely grouped with a median value of 20 U. The synovial fluid C′ activity of the patients with gout had a median value of 102 U; those with Reiter's syndrome, a median value of 158 U. Seventy-eight synovial fluid C′ measurements in 31 patients with rheumatoid arthritis revealed a significantly lower median value of 43 U; in one-third of the determinations the C′ activity was less than the values in normal synovial fluid.

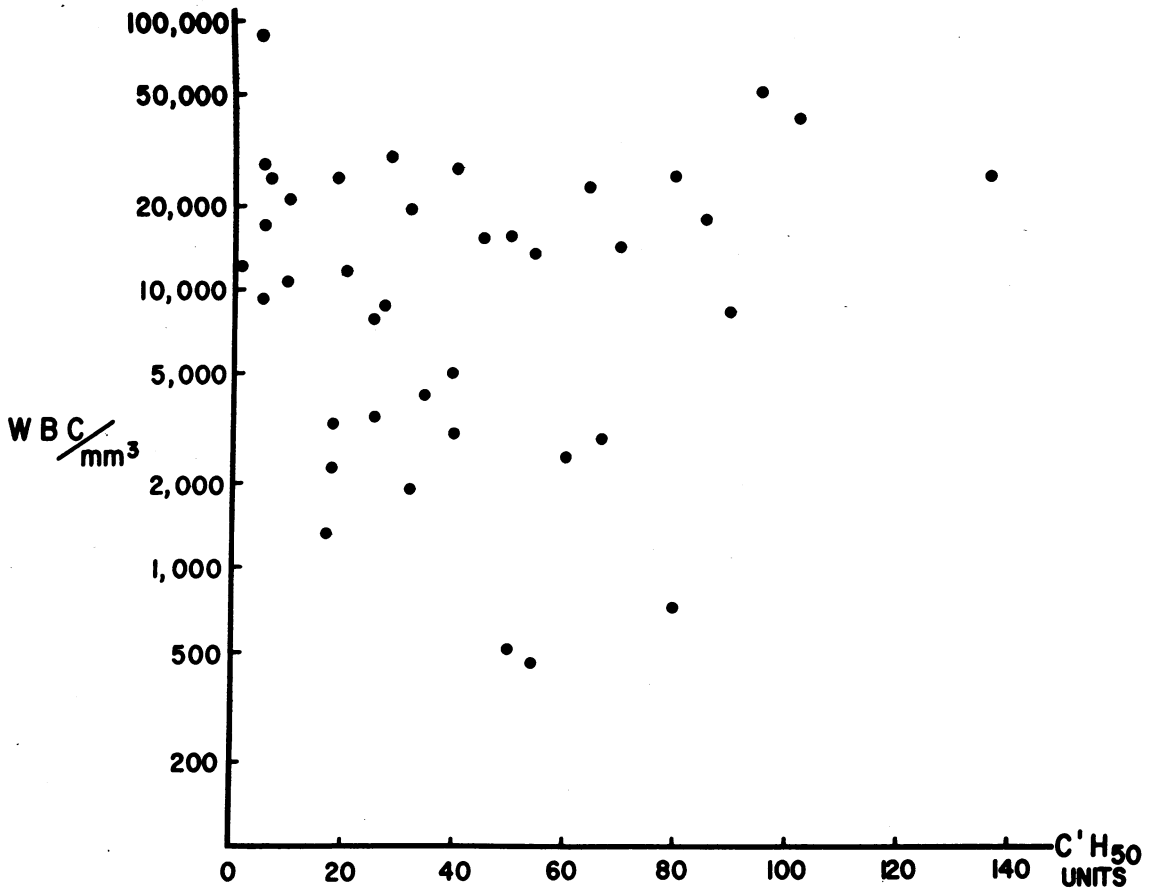

FIG. 3. THE RELATIONSHIP OF SYNOVIAL FLUID LEUKOCYTE COUNT AND COMPLEMENT ACTIVITY IN RHEUMATOID ARTHRITIS. Same scale as Figure 2.

Relationship of synovial fluid inflammatory indexes and C′ activity. The relationship of nonrheumatoid synovial fluid leukocyte count to C′ activity is illustrated in Figure 2. The synovial fluid leukocyte count is usually below 1,000 in osteoarthritis, from 1,000 to 20,000 in gout, and over 10,000 in Reiter's syndrome. In these nonrheumatoid conditions, synovial fluid C′ levels increase with increasing leukocyte count, and the C′ value usually exceeds 70 $C'H_{50}$ U when the leukocyte count is greater than 10,000 per mm^3. In contrast, Figure 3 (on an identical scale) depicts the relationship of rheumatoid synovial fluid leukocyte count to C′ activity. Although the fluid leukocyte counts are elevated over a range comparable to those of gout and Reiter's syndrome, most of the C′ values are low, and few exceed the value of 70 $C'H_{50}$ U.

Figure 4 reveals the relationship of nonrheumatoid synovial fluid protein concentration to C′ activity. Normal fluid is characterized by a protein concentration of less than 2 g per 100 ml and low C′ activity. Most of the protein values in synovial fluid of osteoarthritis are less than 3.5 g per 100 ml, and the C′ values are intermediate. In gout and Reiter's syndrome, the degree of inflammation is reflected in the synovial fluid protein concentration, which approaches that of serum, and C′ activity is high. Figure 5 (identical scale) presents the protein concentration and C′ activity of the synovial fluid of patients with rheumatoid arthritis. Although the protein concentration is elevated over a range similar to that of gout and Reiter's syndrome, the synovial fluid C′ values are low and not related to the amount of protein present in the fluid.

Gamma globulin and synovial fluid C′ activity. Protein electrophoresis of synovial fluid demon-

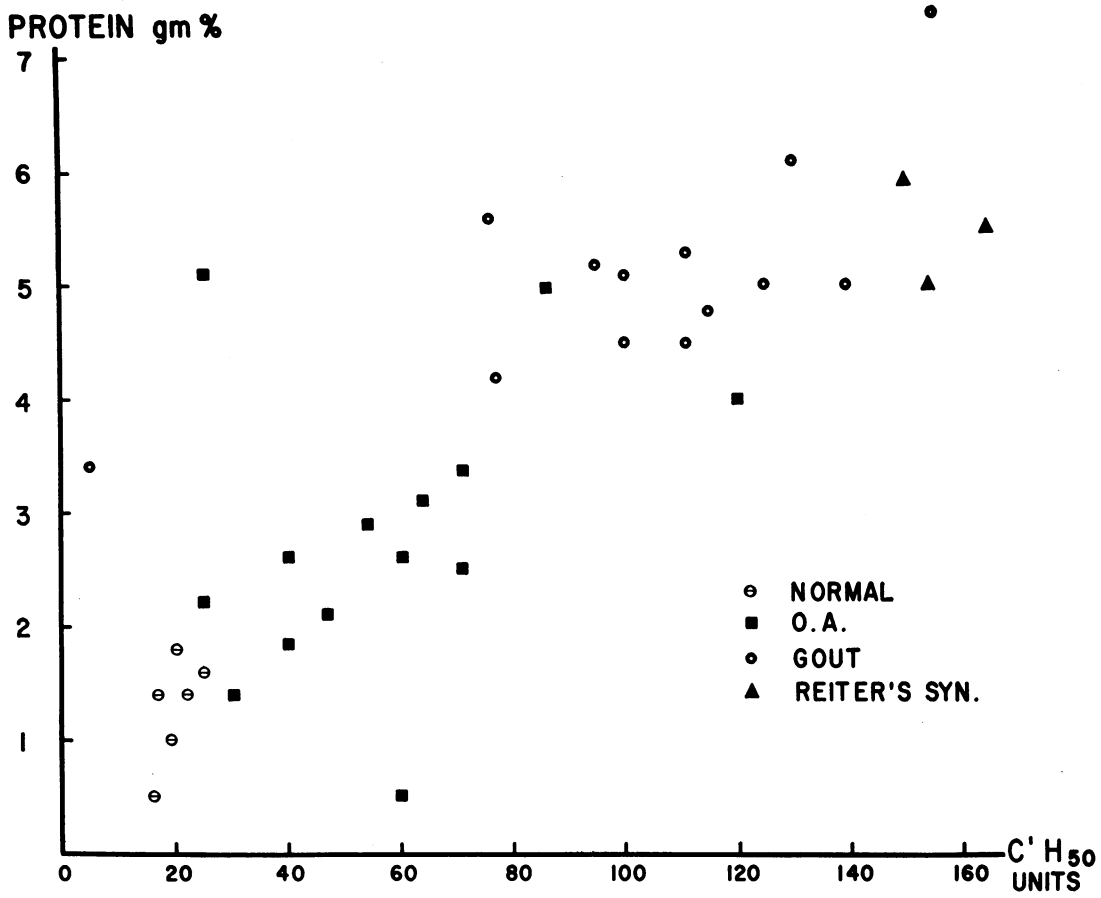

FIG. 4. THE RELATIONSHIP OF SYNOVIAL FLUID TOTAL PROTEIN CONCENTRATION AND COMPLEMENT ACTIVITY IN CONDITIONS OTHER THAN RHEUMATOID ARTHRITIS.

strated that gamma globulin concentration increased with increasing joint inflammation. No distinguishing features were observed in the patterns of the various inflammatory conditions (Table I). The gamma globulin concentrations of the synovial fluids from gout, Reiter's syndrome, and rheumatoid arthritis were elevated to a similar degree and did not explain the observed differences in the synovial fluid C′ activity in these diseases.

In rheumatoid arthritis, rheumatoid factor was invariably present in the synovial fluid when present in the serum. There was no constant relation between the titer of synovial fluid rheumatoid factor and the synovial fluid C′ activity (Table I). Moreover, the addition of several heat-inactivated sera with high titers of rheumatoid factor (greater than 1,028) to synovial fluids of gout and Reiter's syndrome did not lower the C′ levels beyond that which could be accounted for by dilution alone. Rheumatoid synovial fluids with low C′ activity showed no anticomplementary activity when added to human sera of known complement values, nor was anticomplementary activity demonstrable by the addition of rheumatoid synovial fluid with high titers of rheumatoid factor to human sera of known complement activity (Table II).

Changes in synovial fluid inflammation indexes and C′ activity. Serial analysis of synovial fluids from patients with gout and Reiter's syndrome showed that as disease activity subsided, all indexes of inflammation (e.g., volume of fluid, leukocyte count, total protein concentration) were reduced, and C′ activity fell toward the normal range. Two patients with Reiter's syndrome

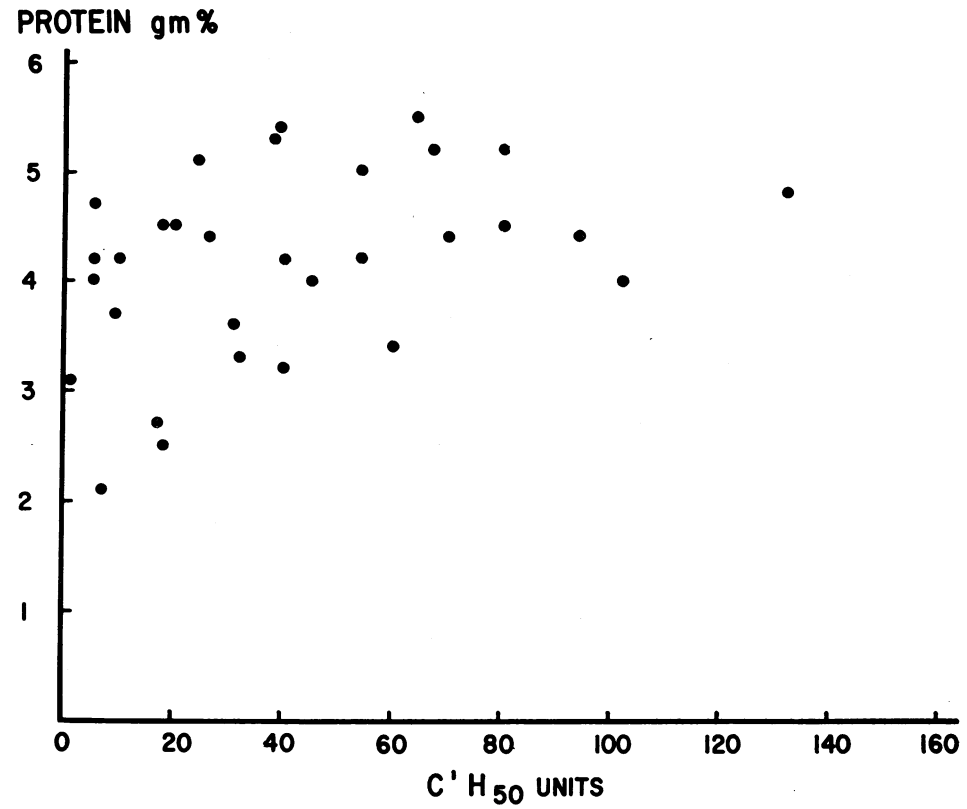

FIG. 5. THE RELATIONSHIP OF SYNOVIAL FLUID TOTAL PROTEIN CONCENTRATION AND COMPLEMENT ACTIVITY IN RHEUMATOID ARTHRITIS.

maintained effusions for several months. The synovial fluid C′ titer was directly related to the activity of inflammation. In the absence of change in inflammatory activity, neither the passage of time nor the duration of the effusion influenced the C′ titer. In several patients with rheumatoid arthritis studied early in the course of the disease, initial synovial fluid C′ levels were increased in proportion to the degree of inflammation, although not so high as those of gout and Reiter's syndrome. With the passage of time and continued disease activity, serial synovial fluid studies demonstrated continued inflammation but a progressive decrease in C′ activity. However, other studies of similar short duration showed very low titers, and two other patients had titers greater than 50 CH_{50} despite long-continued disease activity and duration of effusion. Here too, we were unable to demonstrate that passage of time or duration of effusion was influencing synovial fluid C′ activity. Several patients with chronic rheumatoid arthritis and persistent effusions were followed over periods of time, and successive synovial fluid samples were obtained. Synovial fluid leukocytes, protein concentrations, and C′ values were remarkably stable over periods of time and in both knee joints in those cases in which there was no appreciable change in disease activity. In addition, no correlation of synovial fluid C′ activity was noted with any of the therapeutic measures employed, i.e., salicylate, corticosteroids, gold, chloroquine, or nitrogen mustard.

Discussion

The purposes of these studies were to confirm the presence of complement in synovial fluids, to quantitate the amount of complement in the joint space, and to investigate the local and systemic influences that determine the final concentration of complement in joint effusions.

A substance (or substances) necessary for the hemolysis of sensitized sheep erythrocytes is

TABLE II

Determination of anticomplementary activity of synovial fluids of varying C′ and rheumatoid factor titers when added to an equal volume of normal serum

Synovial fluid		Fluid and serum Resultant
CH_{50}	BFT*	CH_{50}†
Osteoarthritis		
17	0	88
30	0	88
35	0	92
63	0	92
63	0	86
73	0	92
88	0	81
Reiter's syndrome		
149	0	77
160	0	83
Rheumatoid arthritis		
5	0	86
5	0	79
10	2,048	92
15	256	81
15	512	87
20	4,096	83
28	128	91
140	512	83

* BFT = the reciprocal of the bentonite flocculation test titer.

† Normal serum with a C′ titer of 194 was used as C′ source. To this was added an equal volume of synovial fluid inactivated at 56° C for 45 minutes. The resultant mixture was titrated for C′ activity.

normally present in synovial fluid. This activity is lost when synovial fluid is heated to 56° C or after zymosan adsorption. These are features characterizing complement.

The amount of complement present in the joint fluid of 6 normal volunteer subjects was approximately 10% of the serum complement levels. In all of the joint diseases studied, with the exception of rheumatoid arthritis, the greater the inflammatory change in the synovial membrane, the greater was the amount of complement activity present in the synovial fluid.

Previous studies have shown that the severity of inflammation of the synovial membrane is, in general, paralleled by the elevation of the synovial fluid leukocyte count and protein concentration (24). Thus, noninflamed synovial membranes allow the passage of small molecules such as urea, glucose, and uric acid into synovial fluid to concentrations approximately those of serum. Larger molecules, particularly proteins, are found in joint fluid in far lesser amounts. The concentration of albumin is normally about 1 to 2 g per 100 ml and of globulin even less (less than 100 mg) (24). Serum antibodies and blood clotting factors are either absent or present only in small concentrations in normal synovial fluid (27). Minor degrees of inflammation, as in osteoarthritis or traumatic arthritis, change this selective permeability (28–30). The protein concentration rises, and greater amounts of globulin can be found in synovial fluid. The finding that the level of synovial fluid complement increases proportionally with the leukocyte count (Figure 2) and the total protein concentration (Figure 4) is consistent with the notion that complement too enters the joint in proportion to the degree of inflammation present. Osteoarthritis and traumatic arthritis, diseases associated with moderate degrees of inflammation, show mild elevation of complement levels (median value of 54). Gout and Reiter's syndrome, diseases with greater inflammation, have higher complement concentration (median values of 102 and 158 U, respectively). The only exception to this pattern is rheumatoid arthritis. The levels in this condition are only slightly higher than normal (median value, 43 U) and considerably less than the other disease states studied. This finding requires comment.

Several explanations are possible. *1*) The low synovial fluid complement activity could be the result of lesser amounts of complement entering the joint. This might be the case if the serum levels of complement were low in rheumatoid arthritis. The serum levels in the patients studied, however, were normal or elevated. The presence of large amounts of serum proteins in the synovial fluid makes it seem unlikely that complement could not enter the joint cavity. Also, occasional patients with rheumatoid arthritis, particularly those with recent effusions, had elevated synovial fluid complement levels. *2*) The low levels could be the result of increased rate of removal of complement from the joint. Yet protein concentrations were found to be stable over periods of time during continued disease activity. *3*) The low synovial fluid complement levels could be the result of anticomplementary substances in the synovial fluid of patients with rheumatoid arthritis. One substance unique to rheumatoid fluids is

rheumatoid factor. The studies of Mellors, Heimer, Corcos, and Korngold have shown that one site of elaboration of rheumatoid factor is the plasma cells in the rheumatoid synovial membrane (31). Several experiments were performed to exclude the possibility that rheumatoid factor was the cause of the low complement activity noted in the majority of the rheumatoid fluids studied. The levels of rheumatoid factor present were similar to those in the serum; the serum complement levels were normal or elevated, and the fluid levels were low. The addition of sera containing high titers of rheumatoid factor to the synovial fluids from patients with gout and Reiter's disease did not depress the complement activity of these fluids more than could be accounted for by dilution alone. There was no consistent relationship between the titer of rheumatoid factor and the complement level in the synovial fluid. Approximately 15% of the rheumatoid fluids examined had no demonstrable rheumatoid factor present; some of these had high complement levels; others, intermediate or low levels.

The anticomplementary properties of gamma globulin have been recognized for many years (32). Recent studies have demonstrated that this property is the result of aggregation of gamma globulin molecules (33, 34). Several workers have suggested that the proteins of synovial fluid are derived from serum and are identical to the serum proteins when studied by immunoelectrophoresis (35, 36). The gamma globulin concentrations in the synovial fluids from gout, Reiter's disease, and rheumatoid arthritis were similar and did not account for the difference in complement titers in these diseases. No anticomplementary qualities could be demonstrated by the addition of heat-inactivated rheumatoid synovial fluid to human serum of known complement activity.

No attempt was made in this study to evaluate the usefulness of synovial fluid complement determinations as a diagnostic procedure, but several conclusions appear justified. Elevated leukocyte counts, greater than 2,000 cells per mm^3, and a synovial fluid complement level less than 40 U were seen only in patients with rheumatoid arthritis. The association of high cell counts and synovial fluid complement activity greater than 150 U, particularly in the absence of sodium urate crystals, is highly suggestive of Reiter's disease.

Summary

These studies demonstrate the presence of complement in synovial fluid. The level of complement activity parallels the degree of inflammation as reflected in leukocyte count and protein concentration in the disease states studied, with the exception of rheumatoid arthritis. In rheumatoid arthritis, despite inflammation comparable to that of gout and Reiter's syndrome, the synovial fluid complement level is low rather than high. We suggest that this is evidence for a local antigen-antibody reaction utilizing complement in rheumatoid arthritis.

Addendum

Since completion of this work, we have investigated the role of the complement components, C'_1, C'_2, C'_3, and C'_4, in an attempt to further delineate this observation. Results show that C'_1 and C'_4 are disproportionately low in rheumatoid arthritis synovial fluid (37).

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