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SERUM COMPLEMENT LEVELS IN RHEUMATOID ARTHRITIS

A LONGITUDINAL STUDY OF 43 CASES WITH CORRELATION OF CLINICAL AND SEROLOGICAL DATA INCLUDING RHEUMATOID FACTOR AND THERMOLABILE INHIBITOR OF THE F-II L.P. TEST

BY

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Studies of serum complement levels of patients with rheumatoid arthritis have produced conflicting results (Table I, overleaf). Early investigators, using a 100 per cent. end-point method for the determination of haemolytic activity, reported normal or reduced values (Cadham, 1926; Schnabel, 1933; Rachmilewitz and Silberstein, 1937). With the more refined and dependable technique of the 50 per cent. haemolysis determination of serum complement, raised values were found by Vaughan, Bayles, and Favour (1951), Wedgwood and Janeway (1953), Williams and Law (1958), and Ellis and Felix-Davies (1959). Kellett (1954) concluded that "Isolated readings in the majority of cases of rheumatoid arthritis would lead to results well within the normal range". Similar results were obtained by Laurell and Grubb (1958), Asherson (1960), and Jonsen and Kåss (1961). Recently Perlick (1962) and Geidel, Selle, and Schabinski (1964) recorded predominantly reduced complement levels.

In part, some of these discrepancies may be explained by the use of different techniques of complement assay. The main reason, however, must lie in the small number of cases studied predominantly with a single complement determination. Such cross-sectional studies using a limited sample could produce erratic results if significant fluctuations of serum complement levels occurred during the course of rheumatoid arthritis.

In order to determine whether or not such changes of serum complement levels take place during the course of rheumatoid arthritis, a longitudinal clinical and serological study was conducted at University Hospital and Montebello State Hospital, Baltimore, Maryland. Data were obtained which explain the discrepancy of previous publications, and the results are presented below.

Material

43 patients with classical or definite rheumatoid arthritis (Ropes, Bennett, Cobb, Jacox, and Jessar, 1959) were selected at random for examination at 4- to 8-week intervals in the Arthritis Clinic of University Hospital and on the wards of the Montebello State Hospital, Baltimore, Maryland.

The clinical evaluation and the assessment of disease activity were performed according to a protocol which has already been published in detail (Schubart, Cohen, and Calkins, 1964). Results of every examination were recorded separately for each patient. Disease activity was classified as active or inactive (remission). Active disease was graded as minimal, moderate, or severe. The patients were divided into groups according to the treatment received during the course of observation; 26 patients (Cases 1-26) were treated with salicylates only, and twelve (Cases 29-40) received steroids at some time or another. Steroid treatment consisted of a minimum dose schedule required for partial suppression of disease activity and did not exceed 20 mg. Prednisone per day in any one of the patients. Three patients (Cases 41-43) received gold treatment during the time of observation.

Methods

Serum was obtained at each re-examination. In order to preserve unstable serum constituents, techniques published previously were employed (Schubart, Rothschild, Schroeder, Ewald, and Tuerk, 1963). Sera were stored at $-70°$ C. The following tests were carried out on every serum:

(1) Serum complement levels were determined and expressed in $C'-H_{50}$ haemolytic units following the technique of Mayer (1961). For details see Schubart and others (1963).

TABLE

REVIEW OF SERUM COMPLEMENT LEVELS IN

Author	Year	Number of Patients with Rheumatoid Arthritis			Clinical Classification and Correlation with Disease Activity
		Total	Single Determination	Repeated Determinations	
Cadham	1926	Not stated	—	—	"Chronic arthritis"
Schnabel	1933	4	4	—	"Polyarthritis chronica"
Rachmilewitz and Silberstein	1937	13	11	2	All cases with acute symptoms
Vaughan, Bayles, and Favour	1951	31	25	6	Not reported
Wedgwood and Janeway	1953	11	10	1	Cases with "active disease"
Kellett	1954	79	44	35	Not reported
Williams and Law	1958	48	48	—	13 mild 28 moderate 7 severe
Laurell and Grubb	1958	24	24	—	Not reported
Ellis and Felix-Davies	1959	78	78	Not recorded	Steinbrocker, Traeger, and Batterman, 1949 Stages I to IV
Asherson	1960	13	13	—	Disease activity — | + | ++
Jonsen and Kåss	1961	10	10	—	"Active with severe symptoms" R.A. and ankylosing spondylitis
Perlick	1962	Not stated	—	—	Primär chronische Polyarthritis rheumatica
Geidel and others	1964	Not stated (79 determinations)	Not recorded	Not recorded	Primär chronische Polyarthritis: "schwer, mittel, leicht"

(2) The latex-fixation test for the demonstration of rheumatoid factor was carried out by a modification of the method of Singer and Plotz (1956). For details see Schubart, Cohen, and Calkins (1959).

(3) The thermolabile inhibitor of the rheumatoid factor was determined in the latex-fixation test (see Schubart and others, 1959).

Concentration of rheumatoid factor and thermolabile inhibitor determined with the F-II LP test were expressed in the following manner (see Table II, opposite):

Negative: No agglutination using heat-inactivated serum.

O: Agglutination at a low titre range between 1:10 and 1:160 with the use of heat-inactivated serum. No agglutination with native serum indicating total inhibition; or varying inhibition demonstrated by a prozone.

A: Low titres of rheumatoid factor obtained with heat-inactivated serum ranging between 1:160 and 1:640. Varying thermolabile inhibition with frequent total inhibition.

B: Moderate titres of rheumatoid factor with heat-inactivated serum ranging between 1:640 and 1:5,120. Varying titres of thermolabile inhibition.

C: High titres of rheumatoid factor exceeding 1:5,120 with inactivated serum. Varying thermolabile inhibition.

D: High titres of rheumatoid factor obtained with heat-inactivated serum, exceeding 1:5,120. No thermolabile inhibition.

Age, sex, duration of illness in years, and period of observation in months were recorded for all patients. The clinical evaluation of patients and the serological studies were carried out independently of each other. Clinical and serological data were correlated after conclusion of the study.

I

RHEUMATOID ARTHRITIS REPORTED BY PREVIOUS AUTHORS

Correlation With		Method	Results: Haemolytic Activity		
			Control		Rheumatoid Arthritis
Treatment	Rheumatoid Factor		Total No.	Results	
—	—	100% endpoint	230	0·5-0·8	"Slight loss"
—	—	100% endpoint	29	0·02-0·06	3 normal, 1 reduced
—	—	100% endpoint			All normal
ACTH	—	$C'-H_{50}$ units	35	80-150 units	10 cases >150 units 14 cases >130 units
ACTH	—	$C'-H_{50}$ units	52	Mean 47·7 units	Raised (mean 71 units)
Cortisone ACTH	—	$C'-H_{50}$ units Whole curves	Gastric disorders 38	20-50 units	13 above 40 units 67 normal (20-40 units) 2 below 20 units
2 cases ACTH	—	$C'-H_{50}$ units	123	Mean 44 units	Mean C′ – values Mild 58 U. / Moderate 69 U. / Severe 73 U.
Steroids ACTH mentioned	SCAT	$C'-H_{50}$ units (Pillemer)	9	33-62 units Mean 45	23 normal, 1 reduced
Steroids mentioned	1. Precipitin 2. SCAT	$C'-H_{50}$ units (Walton and Ellis)	143	0·95-2·05 units (Mean units 1·43)	Stage .. I II III IV No. Cases 12 23 24 18 Mean C′ .. 1·9 1·77 1·59 1·70
Cortisone	—	$C'-H_{50}$ units (Walton and Ellis)	40	70-130 units	3 raised 9 normal 1 reduced
—	—	$C'-H_{50}$ units (Jonsen)	None		No controls "Normal in 9 cases" "Reduced in 1 case"
—	—	$C'-E_{50}$	Not recorded	150-250 E	Reduced
Steroids mentioned	—	$C'-H_{50}$ HE	58	20-60 Mean 44 HE	50 per cent. reduced levels Mean 36. 1 HE

TABLE II

KEY TO RECORDING OF TITRE OF RHEUMATOID FACTOR AND THERMOLABILE INHIBITOR IN TABLES III-VIII

Notation	Rheumatoid Factor Titre of F-II L.P. Test with Heat-inactivated Serum	Thermolabile Inhibitor Titre of Prozone in F-II L.P. Test with Native Serum
Negative	No agglutination	—
O	1:10 to 1:160	Varying inhibition (Prozone) Total inhibition prevailing (No agglutination)
A	Low titres 1:160 to 1:640	Varying inhibition (Prozone) Frequent total inhibition (No agglutination)
B	Moderate titres 1:640 to 1:5,120	Varying inhibition (Prozone)
C	High titres >1:5,120	Varying inhibition (Prozone)
D	High titres >1:5,120	None

Results

This study embraced a total of 1,412 patient months for all 43 patients combined. The total duration of observation for each patient ranged between 7 and 81 months (average 33). A total of 925 examinations was performed.

Controls.—Serum complement levels of sixty normal persons serving as controls (single determination only) ranged between 25 and 59·4 C′$-H_{50}$ units (mean of 40·2).

Patients in Permanent Remission.—Two patients with classical rheumatoid arthritis (Cases 27 and 28, Table III) did not require treatment throughout the course of observation of 29 and 26 months respectively. In these patients serum complement levels ranged between 54·5 and 31·2 C′$-H_{50}$ units (mean 42·6). The serological findings in Case 27 are depicted in Fig. 1, which shows a modest fluctuation of serum complement levels well within the range of normal while significant changes in titre of rheumatoid factor ranged between negative and 1:1,280.

Active Rheumatoid Arthritis.—Results in 41 patients are recorded in Tables IV-VIII, in which they are grouped according to the treatment received during the course of observation.

(A) *26 Patients Treated with Salicylates Only* (658 months of observation: Table IV, opposite, and Table V, overleaf):

(1) Seventeen cases exhibiting *constant disease activity* were observed for a total of 353 months (Table IV, opposite). Serum complement levels showed significant fluctuations. Range 81·0 to 26·1 C′$-H_{50}$ units (mean 49·9).

(2) Nine cases observed for a total of 305 months exhibited active disease during 234 months, and they were judged to be in *temporary remission* for a total of 71 months (Table V, overleaf). During the active period serum complement levels ranged between 68·9 and 28·5 C′$-H_{50}$ units (mean 46·5). During remission the range was 77·6 to 28·4 C′$-H_{50}$ units (mean 53·8).

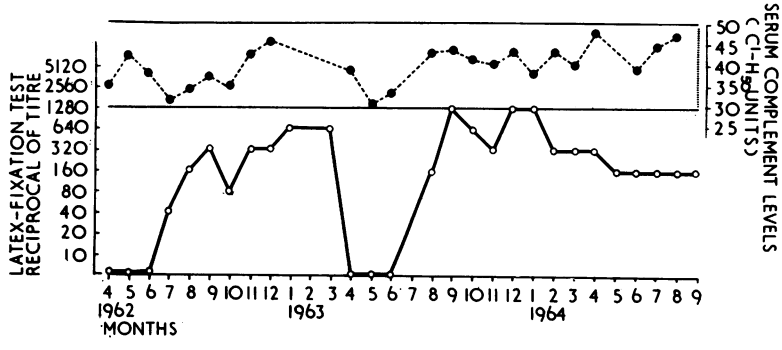

Fig. 1.—Serum complement levels and concentration of rheumatoid factor studied at monthly intervals from April, 1962, to September, 1964, in Case 27, with rheumatoid arthritis in permanent remission.

TABLE III

SEROLOGICAL DATA OF TWO PATIENTS WITH PERMANENT REMISSION OF RHEUMATOID ARTHRITIS, NOT REQUIRING TREATMENT (CASES 27 AND 28)

Case No.	Sex	Age (yrs)	Duration of Illness (yrs)	Period of Observation (mths)	Active Disease (mths)	Remission (mths)	Rheumatoid Factor Serological Picture						Serum C′ – Levels[C′ – H_{50} Units			
							Neg.	O	A	B	C	D	High	Low	Difference between High and Low	Mean
27	F	71	53	29	0	29	+	+	+	+			49·3	31·2	17·9	40·0
28	F	58	9	26	0	26				+	+		54·5	37·2	17·3	45·2
Total	..	..	..	55			1	1	1	2	1	–	51·9	34·2	17·6	42·6

TABLE IV

SEROLOGICAL DATA OF SEVENTEEN PATIENTS WITH CONSTANT DISEASE ACTIVITY OF RHEUMATOID ARTHRITIS, TREATED WITH SALICYLATES ONLY (CASES 1-17)

Case No.	Sex	Age (yrs)	Duration of Illness (yrs)	Period of Observation (mths)	Rheumatoid Factor Serological Picture						Serum C′ – Levels C′ – H_{50} Units			
					Neg.	O	A	B	C	D	High	Low	Difference between High and Low	Mean
1	F	61	2	17				+	+		61·4	43·4	18·0	55·4
2	M	79	8	9					+	+	66·0	26·8	39·2	48·4
3	F	50	13	12						+	51·2	39·6	11·6	45·3
4	M	47	4	27				+	+	+	72·1	30·9	41·2	51·0
5	F	41	6	49				+	+		60·7	35·5	25·2	51·8
6	F	77	3	9						+	61·0	30·6	30·4	45·0
7	F	40	3½	32						+	76·5	40·8	35·7	51·8
8	F	66	5	10						+	70·2	43·9	26·3	56·3
9	F	52	2	19					+	+	74·3	40·7	33·6	56·4
10	F	25	1½	13					+	+	68·5	41·4	27·1	47·2
11	F	35	5½	28						+	54·5	34·1	20·4	41·8
12	M	61	3	8						+	57·1	32·8	25·7	47·3
13	M	49	6	38					+	+	81·0	45·2	35·8	60·5
14	F	50	21	9						+	72·0	46·3	25·7	58·8
15	F	50	14	40				+	+	+	52·6	33·3	19·3	42·0
16	M	64	6	20						+	55·3	26·1	29·2	36·1
17	F	50	7	12				+			62·5	35·0	27·5	53·5
Total	..	..	..	..	353	–	–	–	5	8	14	64·5	36·8	27·7	49·9

(B) *Twelve Patients Treated with Steroids* (624 months of observation: Tables VI and VII):

(1) Nine cases exhibiting *constant disease activity* were observed for a total of 386 months (Table VI, overleaf). Serum complement levels ranged between 75·1 and 22·5 C′ – H_{50} units (mean 47·5).

(2) Three cases exhibited *temporary remissions* (Table VII, overleaf). During the active illness serum complement levels ranged between 53·5 and 26·6 C′ – H_{50} units (mean 41·0). During remission (44 months of observation) the serum complement levels were found to be slightly higher, ranging between 60·7 and 33·3 C′ – H_{50} units (mean 43·4).

(C) *Three Patients Showing Constant Disease Activity were Treated with Myocrysine* (75 months of observation: Table VIII, overleaf). The serum complement levels ranged between 71·1 and 40·0 C′ – H_{50} units (mean 50·6).

Correlation of Serum Complement Levels with Rheumatoid Factor and Thermolabile Inhibitor.— The serological picture of every patient was recorded in Tables III to VIII together with the complement values. Furthermore, the serological data of every single examination were analysed for all patients as shown for Case 27 in Fig. 1. A convincing correlation between serum complement levels and concentration of rheumatoid factor and thermolabile inhibitor did not emerge. Significant fluctuations of serum complement including low and markedly raised values were observed in patients with negative latex-fixation tests as well as in patients with high titres of rheumatoid factor. In many instances marked changes in serum complement were accompanied by fixed titres of rheumatoid factor and thermolabile inhibitor. Inversely, serum complement might remain within the normal range while marked changes in rheumatoid factor concentration occurred (As an example, see Fig. 1).

TABLE V

SEROLOGICAL DATA OF NINE PATIENTS WITH TEMPORARY REMISSIONS OF RHEUMATOID ARTHRITIS, TREATED WITH SALICYLATES ONLY (CASES 18-26)

Case No.	Sex	Age (yrs)	Duration of Illness	Period of Observation (mths)	Active Disease (mths)	Remission (mths)	Rheumatoid Factor Serological Picture						Serum C′ – Levels C′ – H_{50} Units			
							Neg.	O	A	B	C	D	High	Low	Difference between High and Low	Mean
18	M	59	6	25	21					+	+	+	61·2	40·9	21·3	50·6
						4				+	+	+	77·6	48·5	29·1	66·6
19	F	58	28	12	10					+	+	+	56·6	41·0	15·6	49·9
						2				+	+	+	73·2	54·9	18·3	67·0
20	M	55	15	21	17		+						42·1	40·8	1·3	41·4
						4	+						33·3	28·4	4·9	30·8
21	F	56	4	21	18		+						65·5	40·8	24·7	52·5
						3	+						51·2	51·2	0·0	51·2
22	F	50	4	42	22		+						Not done			
						20	+						73·6	40·1	33·5	55·7
23	F	52	13	57	38		+						52·1	32·0	20·1	37·2
						19	+						Not done			
24	F	37	4	40	36		+	+	+				68·9	44·5	24·4	55·3
						4	+						52·9	52·9	0·0	52·9
25	M	61	9	80	70		+						46·1	28·5	17·6	39·2
						10	+	+					43·4	40·8	2·6	41·6
26	F	68	13	7	2								Not done			
						5				+	+		70·4	60·5	9·9	64·6
Total	..	..	..	..	305	Active Disease ..	6	1	1	2	2	2	58·4	37·9	20·6	46·5
						Remission ..	6	1	–	3	3	2	67·6	48·9	18·6	53·8

TABLE VI

SEROLOGICAL DATA OF NINE PATIENTS WITH RHEUMATOID ARTHRITIS SHOWING CONSTANT DISEASE ACTIVITY, TREATED WITH STEROIDS (CASES 29-37)

Case No.	Sex	Age (yrs)	Duration of Illness (yrs)	Period of Observation (mths)	Rheumatoid Factor Serological Picture						Serum C′ – Levels C′ – H_{50} Units			
					Neg.	O	A	B	C	D	High	Low	Difference between High and Low	Mean
29	F	34	5½	65	+						68·1	39·2	28·9	52·4
30	M	74	5½	66					+	+	59·4	40·8	18·6	49·9
31	F	60	5½	36					+	+	61·8	38·0	23·8	49·1
32	F	50	9	49				+	+	+	68·1	38·9	29·2	51·9
33	F	50	2½	17						+	60·0	42·3	17·7	51·3
34	M	70	10	74						+	48·8	22·5	26·3	39·8
35	F	50	2½	22	+	+	+	+			75·1	34·0	39·1	45·7
36	F	57	1½	11	+						56·4	37·6	18·8	47·6
37	F	36	15	46	+						54·0	30·8	23·2	40·7
Total	..	..	..	..	386	4	1	1	2	3	5	61·3	36·0	25·0	47·5

TABLE VII

SEROLOGICAL DATA OF THREE PATIENTS WITH RHEUMATOID ARTHRITIS SHOWING A TEMPORARY REMISSION (SIGNIFICANT SUPPRESSION) DURING STEROID TREATMENT (CASES 38-40)

Case No.	Sex	Age (yrs)	Duration of Illness (yrs)	Period of Observation (mths)	Active Disease (mths)	Remission (mths)	Rheumatoid Factor Serological Picture						Serum C′ – Levels C′ – H_{50} Units			
							Neg.	O	A	B	C	D	High	Low	Difference between High and Low	Mean
38	M	61	16	79	52					+	+		44·3	29·2	15·1	38·1
						27				+	+		60·7	36·8	23·9	45·9
39	F	53	12	78	68		+		+	+	+		53·1	37·0	16·1	43·9
						10	Not done								Not done	
40	F	61	18	81	74						+	+	53·5	26·6	26·9	41·2
						7					+	+	48·5	33·3	15·2	40·9
Total		..	..	238	Active Disease ..		1	–	1	2	3	1	50·3	30·9	19·3	41·0
					Remission ..		–	–	–	1	2	1	54·6	35·0	19·5	43·4

TABLE VIII

SEROLOGICAL DATA OF THREE PATIENTS WITH RHEUMATOID ARTHRITIS SHOWING CONSTANT DISEASE ACTIVITY, TREATED WITH MYOCRYSIN (CASES 41-43)

Case No.	Sex	Age (yrs)	Duration of Illness (yrs)	Period of Observation (mths)	Rheumatoid Factor Serological Picture						Serum C′ – Levels C′ – H_{50} Units			
					Neg.	O	A	B	C	D	High	Low	Difference between High and Low	Mean
41	M	60	2	18						+	53·5	40·0	13·5	49·9
42	M	51	2	15					+	+	55·8	40·8	15·0	50·1
43	M	49	5½	42						+	71·1	39·6	31·5	51·9
Total	..	..	..	..	–	–	–	–	1	3	60·1	40·1	20·0	50·6

Correlation of Serum Complement Levels with Disease Activity of Rheumatoid Arthritis.—Clinical data concerning disease activity charted with results of complement determinations were analysed in detail for every patient. High or low complement levels were shown to occur at all stages of disease activity without any correlation. In order to support this impression, the results of 237 complement determinations (selected at random from cases treated with salicylates only) were plotted against the classification of disease activity (Fig. 2). For minimal and moderate disease activity, the distribution of complement values was similar. Disease activity was judged to be severe in seventeen examinations only. Corresponding complement levels did not deviate from those seen with minimal or moderate disease

In the following analysis serum complement changes were grouped according to treatment for

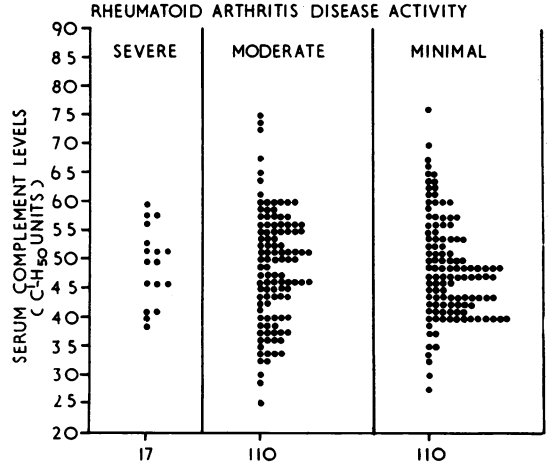

Fig. 2.—Serum complement levels of 237 determinations selected at random from patients with active rheumatoid arthritis (treated with salicylates only) grouped according to clinical assessment of disease activity (severe, moderate, minimal).

correlation with active and inactive disease (Fig. 3). Significant fluctuations of complement levels occurred in active disease regardless of treatment (no significant difference being seen between the steroid and salicylate groups.) Two patients with permanent remission (observed for a total of 55 months) exhibited only minimal variations of complement levels well within the normal range.

Twelve patients (nine treated with salicylates only, three treated with steroids) were found to be in temporary remission at some time or another for a total of 115 months of observation. Significant fluctuation of complement was also seen during remission. The mean complement value obtained during remission was found to be higher than the mean value during the period of active disease in the same group of patients.

Discussion

In rheumatoid arthritis the serum complement system has been studied repeatedly, since it was postulated that an immune mechanism with participation of serum complement might play a role in the pathogenesis of the disease. Early reports indicated that serum complement levels of some patients with rheumatoid arthritis did indeed deviate from normal (Table I). However, conflicting data were presented by various investigators during the following years. Vaughan and others (1951) and Wedgwood and Janeway (1953) reported predominantly raised values, while Kellett (1954) encountered mainly normal levels. Williams and Law (1958) and Ellis and Felix-Davies (1959) attempted a correlation of the severity of rheumatoid arthritis with serum complement levels; raised levels were found in cases with active disease. Laurell and Grubb (1958) reported normal complement values in 23 cases with rheumatoid arthritis; a clinical classification and correlation with disease activity was not mentioned. In recent reports by Perlick (1962) and Geidel and others (1964), the majority of cases had reduced serum complement levels.

The disparity of results found among the investigators mentioned above requires further explanation. The data clearly indicate that serum complement levels may be abnormal in some cases with rheumatoid arthritis. Correlation of complement changes with clinical data is difficult since the natural course of the disease may show a large variety of clinical manifestations. These cannot readily be translated into grades of disease activity or severity (Lansbury, 1963). For this reason, the cases reported in the past may not be comparable. Furthermore, conflicting results can perhaps best be explained by the small number of cases studied in a cross-sectional fashion.

It was, therefore, decided to study patients with rheumatoid arthritis in a longitudinal fashion. Patients were examined at regular intervals (between 4 to 8 weeks) and disease activity was assessed according to a predetermined system. Serum complement levels and concentration of rheumatoid factor and thermolabile inhibitor were determined

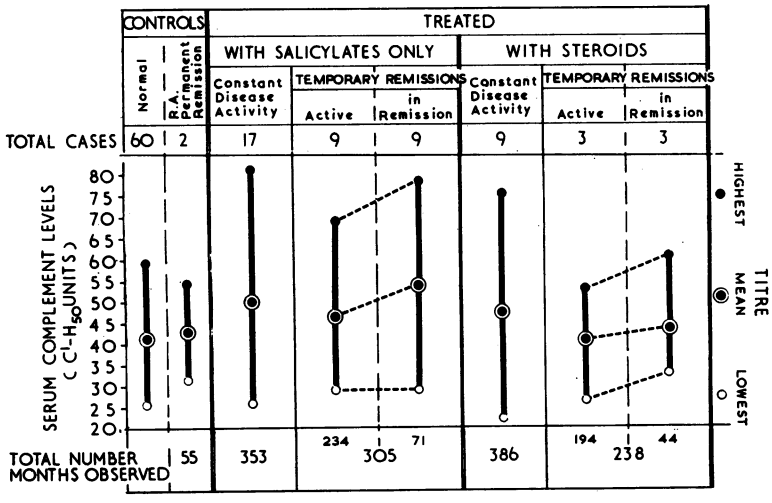

Fig. 3.—Ranges and mean values of serum complement of patients with rheumatoid arthritis grouped according to treatment and activity of disease.

at the same time. After the conclusion of the study, clinical and serological data were correlated in order to determine whether or not changes in severity of the disease are reflected in the serological picture. Active and inactive disease (remission) were clearly defined. An attempt was made to assess disease activity in terms of minimal, moderate, and severe. The limitations of such a classification have previously been discussed (Schubart and others, 1964).

Significant fluctuations in serum complement levels were seen during the course of rheumatoid arthritis. Values ranged between low normal (around 25 $C'-H_{50}$ units) and significantly raised levels. Correlation of these complement changes with disease activity did not reveal a consistent pattern. Low or normal complement titres were found frequently at the time of increased disease activity, while at other times raised complement levels seemed to prevail during a comparable period of the illness.

During permanent remission (two cases observed for 55 months), serum complement levels showed modest fluctuations well withjn the range of normal and not exceeding 55 or 30 $C'-H_{50}$ units; the mean value being comparable to that seen in the control group.

In cases with temporary remissions treated only with salicylates, serum complement levels varied significantly. There was a tendency for complement levels to be higher during temporary remission than during active disease in the same patient (Fig. 3). Sequential changes of complement in relation to disease activity are illustrated in Fig. 4 for Case 18.

Analysis of data of cases treated with steroids indicates that the institution of treatment had no predictable influence on complement levels. Significant fluctuation of complement levels was seen while steroid medication remained unchanged. It is of interest that serum complement levels of patients treated with steroids did not vary significantly from those of patients treated with salicylates while constant disease activity was observed, but in patients treated with steroids who experienced a remission the mean complement values approached normal and fluctuations were less significant even during the active phase of the illness (Fig. 3). The number of these patients was small (three only) though the total time of observation was 238 months. Therefore, it should not be concluded that steroid treatment would be associated with lower complement levels since the complement levels of nine patients with constant disease activity did not differ significantly from those of patients who were treated with salicylates only.

It must be emphasized that the patients in this study received only small doses of steroids (less than 20 mg. Prednisone per day). The effect of larger amounts of steroids or ACTH was not evaluated.

No significant correlation was found when the concentration of rheumatoid factor and thermolabile inhibitor was compared with the serum complement levels. Fluctuations of complement were seen in patients with high titres in the F-II L.P. test and also in patients with negative tests. Furthermore, serum complement levels remained normal in Case 27 (Fig. 1) when the concentration of rheumatoid factor changed from negative to a titre of 1:1,280.

There is no question that the serum complement levels may deviate from normal in rheumatoid arthritis. The changes observed in this study suggest no answer to the question whether or not complement consumption through an immune mechanism is taking place or whether complement

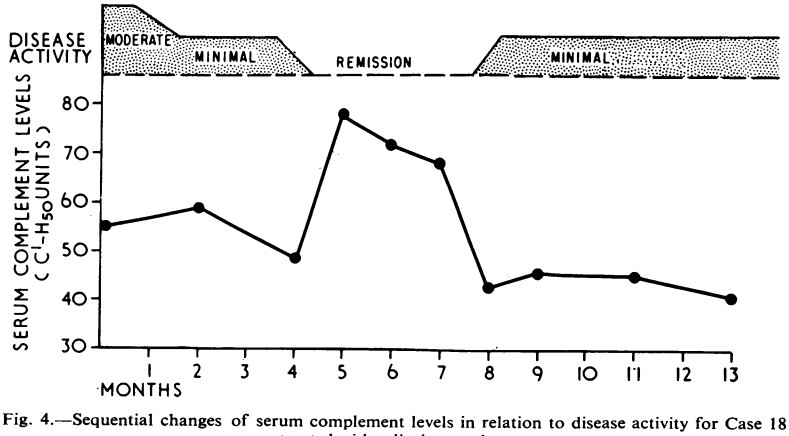

Fig. 4.—Sequential changes of serum complement levels in relation to disease activity for Case 18 treated with salicylates only.

production is at fault when reduced values are encountered. An increase in complement production or release must be postulated whenever raised values are seen. However, the elevation of serum complement levels may be caused in a non-specific way through inflammatory changes, as was shown by Fischel (1953). For this reason, studies such as this are of limited value in solving the problem of specificity or pathogenetic significance of abnormal complement levels. Nevertheless, this correlation of clinical and serological data of 925 examinations of 43 patients with rheumatoid arthritis provided some answers:

(1) Previous studies were confirmed, showing that serum complement levels may exhibit significant fluctuations during active disease.

(2) Abnormal complement levels were found to be predominantly raised. (See high means values in Fig. 3). However, the significant difference between high and low complement values in a given case exceeding the complement fluctuations of normal controls were the characteristic changes of active rheumatoid arthritis (See Tables III to VIII).

(3) There was no apparent relation between serum complement changes and severity of illness.

(4) Serum complement levels remained normal in patients with permanent remission of rheumatoid arthritis.

(5) Changes in concentration of rheumatoid factor and thermolabile inhibitor of the F-II L.P. test showed no significant correlation with changes in serum complement levels.

The careful study of isolated cases may furnish important leads such as were seen in Case 44 (Fig. 5). This patient with classical rheumatoid arthritis and Felty's syndrome (leucopenia, splenomegaly) was found to have reduced complement values when first seen. After a biopsy which was complicated by a staphylococcal infection, the serum complement levels rose to normal. When the patient received blood transfusions in preparation for splenectomy, a precipitate fall in serum complement levels was demonstrated. Simultaneously a slight reduction in the titre of rheumatoid factor was observed in the latex-fixation test. Antinuclear antibodies were demonstrated in the patient's serum using a complement-binding technique. The transfusion was not complicated by any reactions. Careful cross-matching and typing was performed. Following splenectomy the patient's complement returned to normal and has since remained so (Fig. 5).

Pekin and Zvaifler (1962), Zvaifler and Pekin (1963), Hedberg (1963, 1964), and Fostiropoulos, Austen, and Bloch (1964) have recently demonstrated a significant difference between complement levels of synovial fluid and serum complement in patients with rheumatoid arthritis. Complement binding in synovial tissue was suspected. Rodman, Williams, Bilka, and Müller-Eberhard (1964) have demonstrated by immune-fluorescent techniques the presence of bound complement components in synovial tissue. These studies provide evidence for the participation of complement in the disease process of rheumatoid arthritis. The nature and pathogenetic significance of these phenomena remain to be clarified.

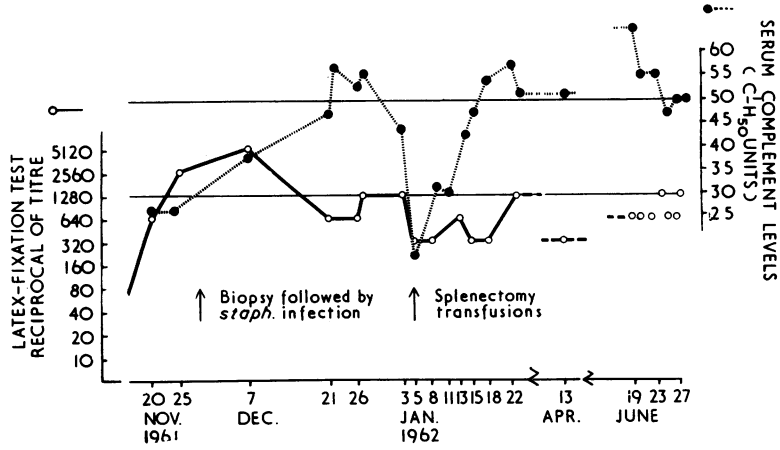

Fig. 5.—Serum complement levels and titre of rheumatoid factor of Case 44, with rheumatoid arthritis with leucopenia and splenomegaly (Felty's syndrome). The relation to infection and blood transfusions is recorded.

Summary

Previous studies of serum complement levels in rheumatoid arthritis having provided conflicting results, 43 patients with rheumatoid arthritis were studied in a longitudinal fashion both clinically and serologically. A total of 925 examinations were performed. The activity of the disease was assessed for correlation with serum complement levels and concentration of rheumatoid factor and thermolabile inhibitor of the F-II L.P. test. The following conclusions were reached:

(1) Previous studies were confirmed, showing that serum complement levels may fluctuate significantly during active rheumatoid arthritis.

(2) Abnormal complement levels were found to be predominantly raised; the significant difference between high and low values in a given case exceeding those in normal controls were the characteristic changes of active rheumatoid arthritis.

(3) There was no apparent relation between serum complement changes and severity of disease.

(4) Serum complement levels remained normal in two patients during permanent remission of rheumatoid arthritis.

(5) Changes in concentration of rheumatoid factor and thermolabile inhibitor of the F-II L.P. test showed no significant correlation with changes in serum complement levels.

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Les taux du complément sérique dans l'arthrite rhumatismale

RÉSUMÉ

En raison des résultats contradictoires des études antérieures des taux du complément sérique dans l'arthrite rhumatismale, on a examiné 43 malades atteints d'arthrite rhumatismale "longitudinalement" du point de vue clinique et sérologique. En tout, on a fait 925 examens. On a déterminé l'activité morbide en corrélation avec les taux du complément sérique, la concentration du facteur rhumatoïde et l'inhibiteur thermolabile du test F-II L.P. On est arrivé aux conclusions suivantes:

(1) On confirme les études précédentes montrant que les taux du complément sérique peuvent fluctuer significativement en cours de l'arthrite rhumatismale évolutive.

(2) Les taux anormaux du complément se trouvent surtout élévés; la différence significative entre les valeurs hautes et basses en un cas donné excédant celles des témoins normaux est une altération caractéristique de l'arthrite rhumatismale évolutive.

(3) Il n'y a pas de rapport apparent entre les altérations du complément sérique et la sévérité de la maladie.

(4) Les taux du complément sérique demeuraient normaux chez deux malades en remission permanente de leur arthrite rhumatismale.

(5) Les altérations dans la concentration du facteur rhumatoïde et de l'inhibiteur thermolabile du test F-II L.P. ne montraient pas de corrélation significative avec les altérations des taux du complément sérique.

Los valores del complemento sérico en la artritis reumatoide

SUMARIO

En vistas de los resultados contradictorios de los estudios anteriores de los valores del complemento sérico en la artritis reumatoide, se ha procedido a una investigación "longitudinal" clínica y serológica de 43 enfermos con artritis reumatoide. Se hizo un total de 925 exámenes. Se determinó la actividad morbosa en correlación con los valores del complemento sérico, la concentración del factor reumatoide y del inhibidor termolábil del test F-II L.P. Se llegó a conclusiones siguientes:

(1) Se confirmaron los estudios precedentes mostrando que los valores del complemento sérico pueden fluctuar significativamente en el curso de la artritis reumatoide evolutiva.

(2) Los valores anormales del complemento fueron predominantemente elevados; la diferencia significativa entre las cifras altas y bajas en un caso dado excediendo las de los testigos normales constituyen una alteración característica de la artritis reumatoide evolutiva.

(3) No hubo relación aparente entre las alteraciones del complemento sérico y la severidad de la enfermedad.

(4) Los valores del complemento sérico permanecieron normales en dos enfermos en remisión permanente de su artritis reumatoide.

(5) Las alteraciones en la concentración del factor reumatoide y del inhibidor termolábil del test F-II L.P. no evidenciaron correlación significativa con las alteraciones de los valores del complemento sérico.