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# THE ELECTROPHORETIC DISTRIBUTION OF PROTEINS IN PLASMA IN RHEUMATOID ARTHRITIS<sup>1, 2</sup>

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Abnormalities in the electrophoretic patterns of plasma proteins in rheumatoid arthritis have been described by various workers. With few exceptions an increase in the relative concentration of  $\alpha_1$ -,  $\alpha_2$ -, and  $\gamma$ -globulin and of fibrinogen and lowering of the albumin concentration have been observed and have been associated consistently with activity of the disease (1-15). Olhagen (4, 10) and Svartz and Olhagen (8) ascribed a possible prognostic significance to isolated elevation of  $\alpha$ - or  $\gamma$ -globulin. They suggested that an elevation of the  $\alpha$ -globulins without an increase in the  $\gamma$ -fraction, often noted in acute cases, indicated a tendency to more rapid healing, whereas a high  $\gamma$ -globulin with low  $\alpha$ -globulins represented a poor prognosis. Wallis (13) described a "T component" in three patients with active rheumatoid arthritis. A protein with a similar electrophoretic mobility,  $\gamma'$ -globulin, was noted by Paul and Routh (14) in normal sera. These authors observed a small decrease of this fraction in the sera of seven patients with rheumatoid spondylitis but found no change in 27 patients with generalized rheumatoid arthritis. Recently, Laurell (16) and Mehl and Golden (17) have demonstrated the occurrence of small amounts of two proteins with isoelectric pH values lower than that of serum albumin when electrophoresis was performed in acetate buffer of pH 4.5. The concentration of one component, which at pH 8.6 in diethylbarbiturate migrates with a mobility of the  $\alpha_2$ -globulin, was considerably increased in sera from patients with rheumatoid arthritis (17) and disappeared on treatment with cortisone (16).

In the present series the electrophoretic patterns of 88 plasmas from 32 patients with rheumatoid arthritis have been studied. The changes in the protein fractions were correlated with the duration of the disease and with the clinical and laboratory indications of the degree of severity of the arthritis. Classification as to stage of disease and functional ability was made by the criteria approved by the American Rheumatism Association (18).<sup>4</sup> Alterations in the protein fractions have been followed during periods of exacerbations and remissions of activity of the arthritis. Of the 32 patients, 4 had had rheumatoid arthritis for less than one year, 7 for one to two years, 5 for two to five years, 8 for five to ten years, and 8 for over ten years.

## EXPERIMENTAL TECHNIQUES

Blood for analysis was collected in the fasting state with 2 mg. potassium oxalate per ml. as an anticoagulant. After removal of the red cells by centrifugation, the plasma was stored at  $-30^\circ$  C. until analyzed. The Pregl micro-Kjeldahl method was used for the determination of total nitrogen, and of the non-protein nitrogen on a tungstic acid filtrate. Prior to electrophoresis the plasma was diluted with buffer to a nitrogen concentration of 3.0 mg. per ml., corresponding to 1.87 per cent protein, assuming a factor of 6.25 for conversion to weight basis. The solution was then dialyzed at  $5^\circ$  C. for three days with frequent changes against large volumes of the buffer employed in the analysis. In most experiments a 0.1 N sodium diethylbarbiturate buffer of pH 8.6 and 0.1 ionic strength was used, but

<sup>4</sup> The stage of disease is determined by the degree of presumably irreversible involvement rather than activity. Stage I is characterized only by subchondral bone atrophy; Stage II by cartilaginous and cortical destruction; Stage III by deformities such as ulnar deviation and subluxation; Stage IV by fibrous or bony ankylosis. Nodules and significant muscle atrophy must not be present in Stage I. The functional classes are: I. Ability to carry on all usual duties without handicaps; II. Adequate for normal activities despite handicap of discomfort or limited motion in one or more joints; III. Limited only to few or none of the duties of usual occupation or self-care; IV. Incapacitated, largely or wholly; little or no self-care.

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<sup>3</sup> Now at the Rockefeller Institute, New York.

TABLE I  
The average electrophoretic distribution of proteins in six pools of normal human plasma \*

Buffer composition	pH	Concentrations in per cent as					
		Albu- min	Globulins				
			$\alpha_1$	$\alpha_2$	$\beta$	$\phi$	$\gamma$
0.1N NaV-0.02 NHV†	8.6	56.5	4.9	8.3	13.7	5.2	11.4
0.064M $K_2HPO_4^-$ 0.008 $MKH_2PO_4$	7.7	61.4‡	6.4	15.0	5.3	11.9	

\* Protein concentrations: 1.8 per cent.

† V = diethylbarbiturate.

‡ Albumin and  $\alpha_1$ -globulin unresolved in this solvent.

in a few cases the solvent was potassium phosphate of pH 7.7 and 0.2 ionic strength. Electrophoresis was performed at 1.5° C. in the apparatus described by Tiselius (19), equipped with the Schlieren scanning device of Longworth (20).

The concentrations of the electrophoretic components were calculated from planimetric measurements of the enlarged tracings of the diagrams. The method of Tiselius and Kabat (21) was used to allocate the area of each peak. The results are expressed in per cent, *i.e.*, the ratio of the area ascribed to each component to the total area, exclusive of the  $\delta$  and  $\epsilon$  boundaries. Each value is the average obtained from the ascending and the descending pattern.

Blood for the determination of sedimentation rates by the method of Rourke and Ernstone (22) was collected

on the same day as that for electrophoresis, with 1 mg. heparin (Hynson, Wescott, and Dunning) per 4 ml. of blood as anticoagulant.

Fibrinogen was estimated according to the method of Cullen and Van Slyke (23).

## RESULTS

As shown by Svensson (24, 25) and also in this laboratory (26), the relative distribution of electrophoretic components is a function of the protein concentration and the ionic strength. Therefore, the experiments reported here were all carried out with a protein concentration of 1.87 per cent and at constant ionic strength. As a basis for comparison the values obtained from six pools of normal plasma in the two solvents (Table I) were used. The difference in the apparent electrophoretic composition in the two types of buffers is slight, and the results are in close agreement with those of other investigators (27-33).

The influence of fibrinogen on the distribution of the protein fraction is evident from a comparison of the values obtained with serum, defibrinated plasma, and plasma (Table II). The concentration of fibrinogen calculated from the electrophoretic patterns of normal plasma and from those of rheu-

TABLE II  
Electrophoretic distribution of proteins in normal serum, plasma and defibrinated plasma \* †

Case	Material	Total protein Gm./100 cc.	Concentrations in per cent as					
			Albumin	Globulins				
				$\alpha_1$	$\alpha_2$	$\beta$	$\phi$	$\gamma$
1	Serum		61.9	3.8	5.8	14.2		14.3
	Defibrinated plasma		61.3	4.0	5.9	14.8		14.0
	Plasma		58.2	4.1	5.9	14.7	5.9	11.2
2	Serum	7.62	59.6	4.3	9.6	12.1		14.4
	Defibrinated plasma		59.0	4.3	9.9	12.8		14.0
	Plasma	7.05	55.2	4.8	9.7	12.8	5.4	12.1
3	Serum		59.7	3.2	9.0	13.2		14.9
	Defibrinated plasma		59.5	3.3	8.3	14.0		14.9
	Plasma	6.69	57.9	3.4	8.3	12.7	5.6	12.1
4	Serum		57.0	5.3	11.0	13.7		13.0
	Defibrinated plasma		57.2	5.2	10.5	14.0		13.1
	Plasma	6.75	52.5	5.3	10.6	14.3	7.2	10.1
5	Serum	7.75	58.7	4.5	7.6	14.1		15.1
	Defibrinated plasma		58.3	4.2	7.1	14.4		16.0
	Plasma	6.94	56.7	4.1	7.3	12.5	7.4	12.0
6	Serum	6.19	55.6	4.4	11.9	16.3		11.8
	Defibrinated plasma		54.8	4.5	12.3	16.7		11.7
	Plasma	5.80						

\* Protein concentrations: 1.8 per cent.

† In sodium diethylbarbiturate buffer of pH 8.6 and 0.1 ionic strength.

TABLE III

Variations in the electrophoretic distribution of proteins in rheumatoid plasma \* †

Unit No.	Total protein Gm./100 cc.	Concentrations in per cent as					Fibrinogen (chemically) Per cent of total protein	Sedimentation rate mm./min.	
		Albumin	Globulins						
			$\alpha_1$	$\alpha_2$	$\beta$	$\phi$			$\gamma$
Normal	7.00	56.5	4.9	8.3	13.7	5.2	11.4	3.6	0.40
393050	7.07	50.0	8.2	15.1	12.1	6.0	8.6	6.4	1.00
379668	5.19	47.9	6.6	12.6	13.7	10.1	9.1	7.4	1.24
425859	6.81	41.6	6.5	10.4	14.5	15.2	11.8	9.3	1.62
352223	6.87	45.5	6.4	11.9	13.6	9.7	12.9		1.56
631712	7.50	48.6	6.2	10.3	11.6	7.2	16.1		0.73
386915	6.63	48.8	4.3	7.5	14.6	8.0	16.8	4.3	0.60
350995	7.06	47.5	5.8	9.9	11.1	7.4	18.3	5.5	1.19
389427	6.94	45.6	6.1	9.7	11.9	8.5	18.2	6.4	0.69
327699	7.16	36.9	6.9	13.0	12.9	11.2	19.2	8.8	1.66
169863	7.38	42.7	5.4	7.5	12.3	11.8	20.3	4.8	1.44
519333	6.75	37.2	7.0	13.1	12.5	9.8	20.4	7.6	1.52
389209	7.87	30.5	7.2	11.7	10.6	11.5	28.5		1.52

\* Protein concentrations: 1.8 per cent.

† In sodium diethylbarbiturate buffer of pH 8.6 and 0.1 ionic strength.

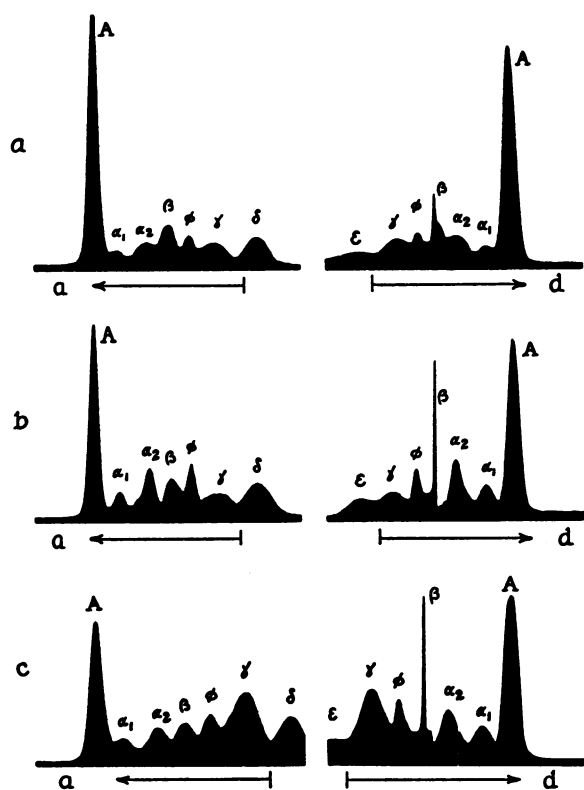


FIG. 1a, b, AND c. ELECTROPHORETIC PATTERNS OF 1.8 PER CENT SOLUTIONS OF PROTEINS OF NORMAL PLASMA (a) AND OF THE PLASMA OF PATIENTS WITH RHEUMATOID ARTHRITIS (b AND c)

Electrophoresis was carried out in sodium diethylbarbiturate buffer of pH 8.6 and  $\Gamma/2$  0.1 for 12,600 seconds at a potential gradient of 5.1 volts per centimeter.

matoid arthritis was always 1.5 to 2-fold higher than the chemically determined value. This may be taken as an indication that the electrophoretic fraction is increased by some non-clottable protein with a mobility similar to that of fibrinogen.

Characteristic plasma electrophoretic patterns in active rheumatoid arthritis are well exemplified in Figure 1, which for comparison also shows that of normal plasma. The extreme variation from high concentrations of  $\alpha_1$ - and  $\alpha_2$ -globulins, associated with normal  $\gamma$ -globulin (Figure 1b) to marked elevation of the  $\gamma$ -fraction in the presence of only a slight abnormality of the  $\alpha$ -globulins (Figure 1c) is demonstrated. Further evidence of the variations in the concentrations of individual fractions which occur in rheumatoid arthritis is provided in Table III. In general, all of the globulins and the fibrinogen are elevated, but in the majority the greatest change is in the  $\gamma$ -globulin fraction, which occasionally rises to 32 per cent. The albumin concentration may decrease to 30 per cent.

Consecutive observations of the electrophoretic distributions of plasma proteins during the course of exacerbations and remissions in rheumatoid arthritis indicate that the protein changes reflect alterations in clinical activity of the disease and correlate, in general, with variations in the sedimentation rate. Elevation of the  $\alpha$ -globulins apparently tends to occur early in the course of increasing activity of the disease and is followed by a predomi-

nance of  $\gamma$ -globulin in later stages. (See Case 1 in 1942 and in 1950, and Case 4, Table IV.) These findings are similar to those described by Olhagen (4, 10) and Dole and Rothbard (9) in rheumatoid arthritis and those noted in the course of other diseases (35-37).

In most cases, however, shifts in the relative concentrations of albumin, globulin, and fibrinogen occur simultaneously and correspond to alterations in the clinical state and sedimentation rate (see Cases 1 through 4, Table IV). Occasionally the

fibrinogen concentration remains unaltered despite a marked reduction in the sedimentation rate (see Cases 5 and 6).

Dissociation of the sedimentation rate from the clinical and electrophoretic manifestations of disease activity was found in Case 7 of Table IV. During a period of several years (from 1943 to 1947) in which the clinical course and the sedimentation rate remained relatively constant, the composition of the electrophoretic pattern did not change. On a subsequent severe exacerbation (in

TABLE IV

*Changes in the electrophoretic distribution of plasma proteins with alterations in activity of rheumatoid arthritis \**

Case	Date	Concentrations in per cent as						Sedimentation rate mm./min.	Stage of disease†	Functional class‡
		Albumin	Globulins							
			$\alpha_1$	$\alpha_2$	$\beta$	$\phi$	$\gamma$			
Normal		56.5	4.9	8.3	13.7	5.2	11.4	0.40		
1 J. A.† 384135	12/17/42	44.5	7.6	15.8	11.5	9.3	11.3	0.94	3	4
	2/16/43	42.1	7.5	12.8	13.1	8.8	15.7	1.10	3	4
	5/11/44	51.4	5.6	11.1	12.7	6.7	12.5	1.32	3	3
	10/19/44	59.5	4.6	9.5	12.7	5.9	7.8	0.33	3	2
	6/13/46	46.0	6.9	13.3	11.9	10.9	11.0	1.24	3	4
	1/21/47	46.7	7.0	12.3	12.4	7.6	14.0	0.68	3	4
	1/15/48	48.0	6.3	10.8	14.5	8.5	11.9	0.84	3	4
	2/17/49	44.3	7.1	12.4	13.0	9.3	13.9	1.12	3	4
	7/20/49‡	47.8	6.5	12.2	15.9		17.6	1.56	3	4
	9/1/49‡§	55.9	5.1	11.2	13.3		14.5	0.15	3	2
	12/24/49‡§	57.0	6.7	12.7	16.6		7.0	0.14	3	2
	1/4/50‡	49.5	8.3	15.8	18.5		7.9	1.24	3	4
	1/20/50‡	47.6	6.5	12.5	17.5		15.9	1.26	3	4
	3/2/50‡	56.8	5.4	10.1	14.3		13.4	0.70	3	3
2 A. P. 216602	12/19/46	42.1	7.6	5.3	11.9	8.5	24.6	1.22	3	2
	3/6/47	45.9	7.5	8.3	8.7	9.7	19.9	0.86	3	2
	12/11/47	50.7	8.6	6.2	10.5	6.4	17.6	0.43	3	1
3 W. M. 567613	4/22/47	46.1	5.3	13.3	14.7	6.9	13.7	0.84	1	4
	1/8/48	57.3	4.4	12.9	13.9	5.5	6.0	0.18	1	2
	12/16/48	53.5	5.1	13.4	14.0	6.5	7.5	0.42	1	1
4 G. R. 319835	10/21/42	47.2		12.6	11.9	12.8	15.5	0.67	1	2
	9/28/32	46.2	4.9	9.6	13.1	6.6	19.6	1.00	1	2
	6/1/44	59.7	5.3	7.5	11.4	5.7	10.4	0.30	1	1
5 E. B.	4/11/44	48.6	5.7	10.4	13.7	6.5	15.1	1.05	1	2
	1/28/47	54.0	4.4	4.9	17.2	6.6	12.9	0.26	1	1
6 E. H. 311289	7/27/43	42.5	6.4	9.3	14.4	7.6	19.8	1.09	2	3
	1/8/48	50.7	4.9	9.0	14.2	7.5	13.7	0.62	1	1
7 A. M. 393050	8/12/43	46.7	7.3	15.1	10.9	9.2	10.8	1.00	2	3
	6/22/44	42.1	7.8	15.3	11.4	10.3	13.1	0.79	2	3
	3/1/45	45.6	7.2	14.0	11.4	8.9	12.9	1.24	2	2
	8/1/46	42.0	7.8	15.7	11.7	10.6	12.2	1.45	2	3
	2/14/47	45.5	7.3	15.3	10.2	9.2	12.5	1.18	2	3
	12/6/49	33.7	9.0	17.1	10.5	13.1	16.6	1.93	3	4
	7/6/50	44.4	6.6	13.4	11.2	9.8	14.6	1.72	3	3

\* Protein concentrations: 1.8 per cent; in sodium diethylbarbiturate buffer of pH 8.6 and 0.1 ionic strength.

† Previously reported (34).

‡ Electrophoresis carried out on serum.

§ Patient treated with ACTH.

|| In potassium phosphate buffer.

¶ See footnote 4 to text.

1949) a marked alteration in the electrophoretic pattern was associated with a rise in the sedimentation rate. A return toward a more normal electrophoretic pattern and a considerable improvement clinically occurred in 1950, with relatively little change in the sedimentation rate. In two other cases, not listed in Table IV, in which only sera were analyzed, a similar dissociation was found. The serum pattern reflected decreasing activity of the disease in one case during 1945 and 1946, and subsequently reached its most abnormal level after an exacerbation in 1948. Throughout this period the sedimentation rate varied only from 1.2 to 1.7 mm. per minute and was the same, 1.7 mm. per minute, both at the time of the partial remission in 1946 and during the exacerbation in 1948. Decreasing activity of the disease in 1948 in the other case was associated with a return toward a normal electrophoretic pattern, but the sedimentation rate continued to rise at this time.

Clinical remission of rheumatoid arthritis, whether spontaneous or induced by ACTH or cortisone, is usually associated with lessening of the abnormalities in the electrophoretic pattern. A return to a normal distribution of the components, occasionally with the relative concentration of the  $\gamma$ -globulin somewhat below the normal concentration, may occur when the remission is relatively complete (see Cases 1, 4, and 5, Table IV). Similar observations have been reported by other workers in rheumatoid arthritis (9, 12, 15, 38, 39), as well as in rheumatic fever (7, 35, 40), disseminated lupus erythematosus (41, 42), and scleroderma (42).

Numerous attempts have been made to correlate alterations in the sedimentation rate with changes in the concentration of individual plasma protein fractions. A major role has been ascribed to elevations of fibrinogen or of the  $\alpha_1$ -,  $\alpha_2$ -, or  $\gamma$ -globulin, respectively (4, 33, 43-45). In the present study a correlation between the sedimentation rate and high concentrations of fibrinogen and  $\gamma$ -globulin and low concentration of albumin is apparent with coefficients of .61, .60, and - .58, respectively.<sup>5</sup>

A relationship of the alterations in protein frac-

<sup>5</sup> The "correlation coefficient" is a measure of the degree of linear relationship between two quantitative variables. The coefficient can range in value from - 1 to + 1, the two extremes indicating, respectively, an exact inverse and an exact direct linear relationship.

tions to severity of the disease was apparent only in the case of the albumin and of the fibrinogen. With increasing severity the albumin concentration fell from an average of 50.1 per cent in the mild cases to 41.1 in severe cases. Concomitantly, there was a rise in fibrinogen from 6.9 per cent in the mild cases to 9.8 in the severe ones.

The electrophoretic patterns of plasma of patients whose disease is of varying duration indicate no definite correlation between any of the protein fractions and the duration of the disease. There is a slight tendency toward a higher  $\gamma$ -globulin, 19.9 per cent, in the patients of over ten years' duration, as compared with 15.7 per cent in patients whose disease is of less than one year.

#### DISCUSSION

The consistent finding in the present study that in cases of active rheumatoid arthritis the relative concentrations of  $\alpha_1$ -,  $\alpha_2$ -,  $\gamma$ -globulin and fibrinogen are increased and that of albumin decreased correlates well with those of previous reports. A tendency is apparent for the  $\alpha$ -globulins to rise early in the disease followed by an elevation of the  $\gamma$ -globulins. The causes for the alterations in a given individual protein fraction, however, are unknown, although there is evidence that the  $\alpha$ -globulins are increased whenever considerable inflammation or tissue destruction is present and that a rise of  $\gamma$ -globulin may be associated with enhanced antibody formation. However, a direct correlation between protein variations and the pathogenic mechanisms of rheumatoid arthritis is not possible.

#### SUMMARY

The electrophoretic distribution of proteins in 88 plasmas from 32 patients with rheumatoid arthritis has been determined.

An elevation of the concentrations of  $\alpha_1$ -,  $\alpha_2$ -, and  $\gamma$ -globulins and of fibrinogen and a lowering of the albumin were observed in active rheumatoid arthritis.

Reversal to a normal electrophoretic pattern may occur during remission of the activity of arthritis.

#### ADDENDUM

##### *Electrophoretic Distribution of Proteins in Plasma in Other Rheumatic Diseases*

Adequate comparison of the electrophoretic distribution of plasma proteins in rheumatoid arthritis

with that in other joint diseases cannot be made because of the paucity of studies of these other diseases. Some interesting similarities and dissimilarities, however, are disclosed by the few studies available.

In plasma from seven patients with disseminated lupus erythematosus studied in this laboratory, the changes in the  $\alpha$ -globulins were less than those noted in rheumatoid arthritis. In two cases the  $\alpha_1$ -globulins were slightly elevated, and in one case 14.5 per cent  $\alpha_2$ -globulin was recorded. One patient on two occasions had increased  $\beta$ -globulins, 21 and 23 per cent, respectively. The elevation of fibrinogen and  $\gamma$ -globulin was similar to that found in rheumatoid arthritis except for the fact that in two cases the levels of  $\gamma$ -globulin, 39 and 45 per cent, were greater than any observed in our series of rheumatoid patients. The albumin contents in these two cases were 34 and 24 per cent. Coburn and Moore (46) in two patients, Walker and Benditt (47) in nine, and Lever, Schultz, and Hurley (42) in nine noted similar patterns with slight or no abnormality in the  $\alpha$ -globulin fractions and slight to marked elevation of  $\gamma$ -globulin. The distribution found by Reiner (41) in five cases was similar except for considerable increase in  $\alpha_2$ -globulin.

Electrophoretic studies of plasma from four patients with mild to moderate dermatomyositis showed no elevation of the  $\alpha_1$ -globulin and only a slight increase in the  $\alpha_2$ -globulin and fibrinogen. In two patients the  $\gamma$ -globulin was normal; in the other two, however, it was increased to 19 and 20 per cent, respectively, and accompanied by a simultaneous decrease of albumin to 41 and 49 per cent. Similarly, in four advanced cases, Walker and Benditt (47) found only slight changes in the globulin fractions, in contrast to the usual finding in rheumatoid arthritis, but noted a moderate decrease in the albumin concentration. Lever, Schultz, and Hurley (42) reported similar changes in two severely ill patients but in another found marked increase in  $\alpha_1$ - and  $\alpha_2$ -globulin.

In rheumatic fever the findings in the three plasmas analyzed in this laboratory correspond to those reported by other investigators (7, 8, 15, 35, 47-51). In all cases a moderate to marked decrease in albumin concentration was associated with an increase in the  $\alpha$ - and  $\gamma$ -globulin fractions. In some cases the  $\alpha_2$ -globulin was much higher

than that found in rheumatoid arthritis, and in others a marked rise in  $\gamma$ -globulin was observed; occasionally only a slight elevation in either the  $\alpha$ - or  $\gamma$ -globulin was found. Wilson and Lub-schetz (51) concluded that the  $\gamma$ -globulin was elevated only when there had been an antecedent illness. Svartz and Olhagen (8) found high  $\gamma$ -globulin levels in recurrent cases or in cases manifesting involvement of organs other than joints.

In the serum from one patient with gout, the  $\alpha$ -globulins were slightly increased, the  $\gamma$ -globulin fraction moderately increased, and the albumin concentration moderately lowered. This pattern resembled many of those found in rheumatoid arthritis.

Two sera from patients with Reiter's syndrome showed a considerable elevation in the  $\alpha_1$ - and  $\alpha_2$ -globulin fractions with only a slight elevation of  $\gamma$ -globulin and a moderate decrease in albumin. The level of the  $\alpha$ -globulin components was higher, whereas that of the  $\gamma$ -globulin was lower than those observed in the majority of the rheumatoid patients. The distribution patterns resembled those reported by Svartz and Olhagen (8).

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### ANNOUNCEMENTS OF MEETINGS

The 46th Annual Meeting of the American Society for Clinical Investigation will be held in Atlantic City, N. J., on Monday, May 3, 1954, with headquarters at the Chalfonte-Haddon Hall. The scientific session will begin at 9 a.m. at the Steel Pier Theater.

The annual meeting of the Association of American Physicians will be held at the Chalfonte-Haddon Hall on Tuesday, May 4, and Wednesday, May 5, 1954.