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Marian W. Ropes, … , Elsie Rossmeisl, Walter Bauer

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Research Article

THE RELATIONSHIP BETWEEN THE ERYTHROCYTE SEDIMENTATION RATE AND THE PLASMA PROTEINS [1, 2]

By MARIAN W. ROPES, ELSIE ROSSMEISL AND WALTER BAUER

(From the Medical Clinic of the Massachusetts General Hospital, the Department of Medicine, Harvard Medical School, and the Massachusetts Department of Public Health, Boston)

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From the time of the early Greek physicians many observers noted a relationship between the sedimentation rate of the red cells and the concentration of fibrinogen or "phlegma" in the blood. However, no detailed studies were made until 1918 when Fåhraeus (5) studied the sedimentation rate in pregnancy and concluded that the increase in the rate was due to a lowering of the electric charge on the red cells. Since that time interest in the subject has been renewed. Numerous investigators have studied the variations in sedimentation rate that occur in disease and a few workers have attempted to determine also the factors underlying these variations. As a result of these investigations of the past twenty years, the sedimentation rate has become of definite clinical value, but there is no general agreement as to the factors involved in the aggregation and sedimentation of the red cells.

The majority of investigators have corroborated the long-standing impression that there is a suggestive relationship between the concentration of fibrinogen and the sedimentation rate. In fact, despite occasional marked exceptions to an exact linear relationship between the fibrinogen and the sedimentation rate, the majority of recent workers have concluded that the concentration of fibrinogen determines the sedimentation rate (1, 2, 4, 8, 10, 14, 16). The occurrence of occasional marked inconsistencies, however, has led a few workers to conclude that the relationship between fibrinogen and sedimentation rate is not one of cause and effect (9, 12, 13).

Various other constituents of the blood, notably globulin and lipoids, have been suggested as regulating factors in the sedimentation rate of the red cells. The majority of investigators agree that blood samples with high concentrations of globulin have high sedimentation rates.

In the course of our studies of the sedimentation rates and plasma protein fractions in arthritis, we occasionally obtained marked inconsistencies in the relationship between plasma proteins and sedimentation rates, in contrast with the majority of the findings reported in the literature. Because of these findings and the lack of agreement as to the correlation between the plasma proteins and the sedimentation rate, which is evident from a survey of the literature, we undertook a more detailed study of the relationship.

The present investigation includes chiefly studies in various types of arthritis, but it also includes a few studies in other diseases which produce abnormal rates, such as myelomatosis, carcinoma of lung, malignant lymphoma of Hodgkin's type, acute lupus erythematosus disseminatus, poikiloderma atrophicans vasculare, lymphogranuloma inguinale, and nutritional edema. The results are of special significance since they cover both the sudden and marked changes in sedimentation rates and in concentration of proteins that occur in acute infections such as gonorrheal arthritis, and the more gradual changes in chronic infections such as rheumatoid arthritis. In conditions in which the type of reaction is so different, the chemical changes produced by the infection would be expected to be different. Whatever the stimulating agent may be which is produced by the infection and which leads to changes in the proteins and the sedimentation rate, it acts more slowly and over a longer period of time in a chronic infection like rheumatoid arthritis. This makes it possible to study the relationship of the variations in rates to the variations in the concentrations of proteins more accurately than in the case of acute infections. For, in acute infections, the changes are so sudden and of such magnitude that a superficial relationship may be apparent but it may be impossible to follow the changes closely enough to

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determine the order of occurrence and draw conclusions as to the causal relationship.

METHODS

The subjects in this series included patients in the hospital and ambulatory patients seen in the clinic. The patients were fasting with the exception of the few cases indicated in the tables. The blood samples were withdrawn without stasis from the median basilic vein. Heparin (product of Hynson, Westcott and Dunning), in a concentration of 4 mgm. for approximately 4 cc. of blood, was used as an anticoagulant in the blood samples for the determination of sedimentation rates. Potassium oxalate, in a concentration of 2 mgm. per cc., was used as an anticoagulant in the samples for the fibrinogen determinations. No anticoagulant was used in the blood samples for the total protein and albumin determinations.

The erythrocyte sedimentation rates were determined by the method of Rourke and Ernstene (15), and corrected for hematocrit readings by the use of their correction chart. This method, by virtue of the length and diameter of the tube and by the determination of the rate during the period of most rapid fall, has been shown to avoid errors introduced in other methods from packing, counter flow, and inclusion in the rate of varying proportions of the initial slow period of aggregation and subsequent rapid period of settling (10). Furthermore, this method is the one which was found by Ham and Curtis (10) to give a higher statistical correlation with the fibrinogen content than the Wintrobe, Westergren, Cutler, or Linzenmeier methods. It was with the use of this method also that Gilligan and Ernstene (8) and Ernstene (4) obtained an approximately linear correlation between the sedimentation rate and the fibrinogen content.

The total protein was obtained by determination of the total nitrogen by a modified macro-Kjeldahl. The difference between the total nitrogen and the nonprotein nitrogen, determined by the method of Folin and Wu (7), was multiplied by the factor 6.25 to give the total protein. The albumin content was determined by the method of Howe (11), using 22.5 per cent sodium sulphate. The fibrinogen content was determined by precipitation as fibrin by the method of Cullen and Van Slyke (3) and determination of the nitrogen by digestion and nesslerization.

The following values have been accepted as the upper limits of normal:

Protein	8.0	grams per 100 cc.
Albumin	5.5	grams per 100 cc.
Globulin	3.0	grams per 100 cc.
Fibrinogen	.350	grams per 100 cc.

RESULTS

The blood samples included in this investigation were from the following sources: 46 from 8 cases

TABLE I

Relationship of sedimentation rate to plasma proteins

Case number*	Corrected sedimentation rate	Total protein	Albumin	Globulin	Fibrinogen
	mm. per minute	*grams per 100 cc.*	*grams per 100 cc.*	*grams per 100 cc.*	*grams per 100 cc.*
I 1	1.54	7.77	4.41	3.36	0.575
2	1.55	7.85	4.85	3.00	0.469
II	0.37	7.75	5.01	2.73	0.288
III 1	1.64	8.63	4.74	3.89	0.652
2	1.12	9.17	4.95	4.22	0.614
IV 1	1.95	10.40	3.30	7.10	
2	1.58	9.45	3.41	6.04	
3	1.36	8.59	3.64	4.94	0.631
V	1.24	7.82	4.92	2.91	0.366
VI	0.50	7.10	4.42	2.68	0.293
VII	1.40	8.19	4.95	3.25	0.625
VIII	1.27	8.74	4.91	3.83	0.375
IX	0.98	8.28	4.59	3.68	0.458
X 1	0.25	7.80	5.00	2.81	0.234
2	0.34	7.45	5.24	2.21	0.256
XI	0.37	7.12	4.94	2.14	0.308
XII	0.53	7.35	4.24	3.12	0.225
XIII	0.92	7.71	4.76	2.95	0.338
XIV 1	0.30	7.70	5.25	2.44	0.292
2	0.29	8.00	5.06	2.94	0.269
XV	0.80	7.57	4.96	2.61	0.658
XVI	0.12	7.07	4.97	2.10	0.236
XVII	1.43	7.06	3.84	3.22	0.511
XVIII	1.83	8.30	4.66	3.64	0.850
XIX 1	1.55	7.91	4.87	3.04	0.823
2	1.69	6.81	4.36	2.45	0.726
XX	1.63	8.10	4.13	3.97	0.568
XXI	1.96	7.98	4.07	3.91	0.972
XXII	0.68	7.66	4.51	3.15	0.264
XXIII 1	1.14	10.53	2.92	7.61	
2	1.19	10.36	2.84	7.52	0.306
3	0.75	11.77	3.35	8.43	0.511
XXIV†	1.77	12.60	3.64	8.96	0.418
XXV	1.42	8.39	3.83	4.57	0.313
XXVI†	1.80	8.57	2.81	5.76	0.483
XXVII	0.12	3.90	2.84	1.06	
XXVIII	1.16	7.35	4.64	2.71	0.420
XXIX	0.74	6.72	4.42	2.30	0.335
XXX	1.52	6.25	4.00	2.25	0.628
XXXI	0.90	7.62	5.22	2.40	0.504
XXXII	0.64	6.47	4.45	2.02	0.373
XXXIII	1.86	7.68	3.77	3.91	0.940
XXXIV	1.01	4.18	2.40	1.78	0.436
XXXV	0.15	7.10	4.62	2.49	0.289
XXXVI	1.40	7.48	4.37	3.12	0.366
XXXVII	0.52	7.84	5.22	2.62	0.315
XXXVIII	1.22	6.15	2.99	3.16	0.631
XXXIX	1.46	7.87	4.90	2.98	0.609

* Diagnoses: Cases I through XVI—rheumatoid arthritis; Cases XVII through XXI—gonorrheal arthritis; Cases XXII through XXVI—myelomatosis; Case XXVII—nutritional edema; Cases XXVIII, XXXI and XXXVI—arthritis of unknown origin; Case XXIX—Charcot's joint; Case XXX—carcinoma of lung with hypertrophic pulmonary osteo-arthropathy; Case XXXII—degenerative joint disease; Case XXXIII—malignant lymphoma of the Hodgkin's type; Case XXXIV—chronic glomerular nephritis; Case XXXV—lupus erythematosus disseminatus; Case XXXVII—poikiloderma atrophicans vasculare; Cases XXXVIII and XXXIX—lymphogranuloma inguinale.

† Patient not fasting.

of gonorrheal arthritis; 22 from 16 cases of rheumatoid arthritis; 7 from 5 cases of myelomatosis; 1 from 1 case of nutritional edema; 1 from 1 case of carcinoma of the lung with pulmonary osteoarthropathy; 1 from 1 case of Charcot's joint; 1 from 1 case of malignant lymphoma of Hodgkin's type; 3 from 3 cases of arthritis of unknown origin; 1 from 1 case of degenerative joint disease; 1 from 1 case of acute lupus erythematosus disseminatus; 1 from 1 case of poikiloderma atrophicans vasculare; 2 from 2 cases of lymphogranuloma inguinale, and 1 from 1 case of chronic glomerular nephritis.

The results given in Table I show that, in general, blood samples with high sedimentation rates have high concentrations of fibrinogen or of globulin, in accordance with the findings of numerous other workers. More detailed analysis of the figures, however, shows that there are many variations of greater or lesser degree in the relationship between the rates and the concentrations of the protein fractions.

Comparison of the sedimentation rates with the fibrinogen concentrations (see Figure 1) shows no clear-cut linear relationship such as that found by Gilligan and Ernstene (8), and by Ham and Curtis (10). There is only a suggestion of a linear relationship and at least one-third of the values are not consistent with such a relationship. A few of the inconsistencies may be explained, in part at

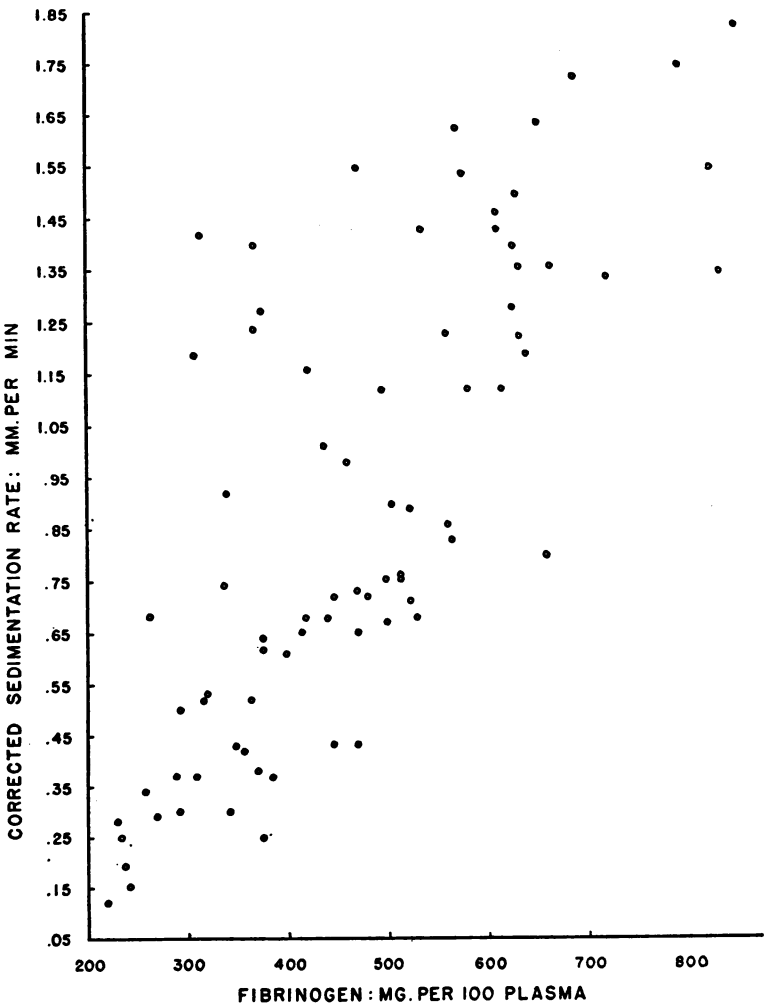

FIG. 1. CORRELATION BETWEEN THE CORRECTED SEDIMENTATION RATE AND THE PLASMA FIBRINOGEN

least, by abnormally high globulin concentrations. However, in some of the bloods that show higher sedimentation rates than would be expected from the fibrinogen content, the concentration of globulin is normal.

Comparison of the sedimentation rates with the total protein, albumin, and globulin concentrations and with the albumin/globulin ratios shows no linear relationship. Blood samples with high globulin contents tend to have elevated sedimentation rates, but there are even more inconsistencies than in the relation of fibrinogen concentration to sedimentation rate.

Analysis of individual blood samples shows clearly the lack of absolute correlation between the concentrations of fibrinogen and globulin and the rate of sedimentation of the red blood cells. The most marked variations are found in Case 5 (a girl of 15 who had had rheumatoid arthritis for 8 months and had had a recent acute exacerbation of joint symptoms). The corrected sedimentation rate rose to 1.24 mm. per minute, although the concentration of fibrinogen and of globulin remained at the upper limits of normal. Furthermore the results in Case 22 indicate that increased concentrations of fibrinogen or of globulin do not necessarily increase the sedimentation rate. With progress of the disease (myelomatosis) the fibrinogen increased from 0.306 to 0.511 gram per 100 cc. and the globulin from 7.5 to 8.43 grams per 100 cc., but the sedimentation rate dropped from 1.19 to 0.75 mm. per minute. In this case a 67 per cent rise in fibrinogen and a 12 per cent rise in globulin were associated with a 27 per cent fall in sedimentation rate.

Further evidence of lack of absolute correlation between the sedimentation rates and the fibrinogen and globulin concentrations is found in the following cases: Case 3 in which a 32 per cent drop in the sedimentation rate was associated with a slight fall (6 per cent) in the fibrinogen and a slight rise (4 per cent) in the globulin; Case 6 which showed a slight elevation in sedimentation rate with normal globulin and fibrinogen concentrations; Case 10 which showed a normal sedimentation rate with a fibrinogen concentration of 0.469 gram per 100 cc.

In order to study more thoroughly the correlation between plasma proteins and sedimentation rates, and to determine, if possible, whether the changes in protein precede or follow the alterations in sedimentation rate, successive determinations were made in 3 cases of gonorrheal arthritis during periods of clinical change. (The patients were receiving sulfanilamide.) The results are shown in Table II and Figure 2. The curves for fibrinogen concentration and sedimentation rate show the same general trend, but they are not superimposable. Changes in sedimentation rate did not consistently precede or accompany changes in either fibrinogen or globulin. For example, in Case 34 there was first a 26 per cent drop in sedi-

TABLE II

Relationship of sedimentation rate to plasma proteins

Case number*	Corrected sedimentation rate	Total protein	Albumin	Globulin	Fibrinogen
	mm. per minute	*grams per 100 cc.*	*grams per 100 cc.*	*grams per 100 cc.*	*grams per 100 cc.*
XL 1†	1.73	7.67	4.85	2.83	0.688
2	1.19	7.96	5.25	2.71	0.638
3†	1.28	7.38	4.74	2.64	0.625
4	1.34	7.22	4.38	2.84	0.721
5	1.43	7.48	4.52	2.96	0.610
6	1.23	7.57	4.65	2.91	0.558
7	0.86	7.39	4.39	3.00	0.559
8†	0.83	7.39	4.27	3.12	0.564
9	1.12	7.66	4.97	2.69	0.494
10	0.65	7.24	4.55	2.69	0.415
11	0.62	7.50	4.81	2.69	0.375
12	0.73	7.29	4.75	2.55	0.469
13	0.72	7.19	4.55	2.63	0.446
14	0.68	7.56	4.86	2.70	0.440
15	0.53	7.65	5.23	2.42	0.317
XLI 1	1.75	7.41	3.98	3.43	0.792
2	1.35	6.95	3.91	3.05	0.834
3	1.36	6.90	3.87	3.04	0.662
4	0.43	6.78	3.91	2.87	0.458
5	0.25	6.51	3.78	2.72	0.375
6	0.18	6.20	3.77	2.43	0.277
7	0.28	6.83	4.59	2.24	0.230
XLII 1	0.75	7.24	4.23	3.01	0.497
2	1.12	7.09	4.51	2.57	0.580
3	0.89	7.07	4.30	2.77	0.521
4	0.75	7.11	4.57	2.54	0.513
5	0.68	7.03	4.41	2.62	0.527
6	0.72	7.00	4.42	2.58	0.479
7	0.71	7.24	4.64	2.60	0.521
8	0.67	7.31	4.58	2.72	0.500
9	0.65	7.10	4.35	2.75	0.471
10	0.43	6.91	4.52	2.39	0.447
11	0.52	6.82	4.45	2.36	0.361
12	0.61	6.87	4.49	2.39	0.399
13	0.42	6.77	4.55	2.22	0.356
14	0.43	7.13	4.56	2.57	0.348
15	0.38	7.24	4.78	2.47	0.359
16	0.68	6.89	4.73	2.16	0.418
17	0.37	6.57	4.35	2.22	0.383
18	0.30	6.80	4.70	2.11	0.341

* Diagnosis in these 3 cases: gonorrheal arthritis.
† Patients not fasting.

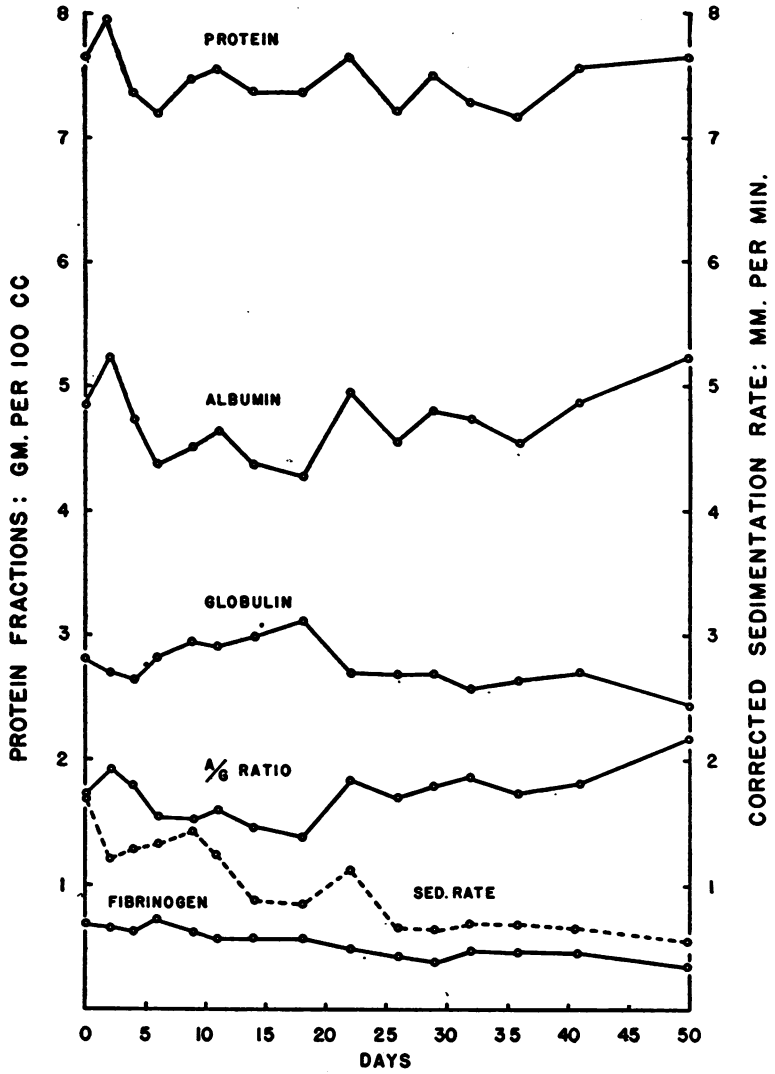

FIG. 2. THE VARIATIONS IN THE CORRECTED SEDIMENTATION RATE AND PLASMA-PROTEIN FRACTIONS IN A CASE OF GONORRHEAL ARTHRITIS TREATED WITH SULFANILAMIDE

mentation rate with a 5 per cent rise in fibrinogen, and then a 20 per cent drop in fibrinogen with no change in sedimentation rate. Similarly, in Case 33, a 30 per cent drop occurred in sedimentation rate with no change in the fibrinogen concentration.

The fact that the curves for fibrinogen, globulin and sedimentation rate show moderate correlation but are not superimposable indicates that the changes represent a direct response of all factors (fibrinogen, globulin and sedimentation rate) to the stimulating agent, rather than a response of one indirectly because of a change in one of the other factors.

Further experiments were undertaken to prove that changes in sedimentation rates are not necessarily associated with changes in the concentrations of any of the plasma proteins. The pH of one portion of a sample of heparinized blood was changed by addition of acid or alkali without significant alteration in the concentration of the proteins. The sedimentation rates of the two portions were then determined. The determinations of sedimentation rates were not done on blood taken under oil because of the difficulty in preventing errors in the rates due to the oil, and because of the fact that the pH at the time of the deter-

mination was the significant value rather than the pH of the blood as drawn. Colorimetric determinations of pH with various indicators were made. It was found possible to change the pH approximately 0.5 in either direction without causing clotting or hemolysis. When the pH was altered by acetic acid there were no significant changes in the corrected sedimentation rates (Table III). The uncorrected rates decreased but there was an associated increase in the hematocrits. By adding solid sodium carbonate to a concentration of 0.1 or 0.2 per cent, there were marked changes in the corrected rates, a decrease in 3 cases and an increase in 1 case. The uncorrected rates were approximately equal in 2 cases but there was a coincident change in the hematocrits so that the corrected rates were very different (Table IV). Even more conclusive results were obtained when sodium hydroxide was added. The uncorrected rates and the hematocrits both decreased so that the corrected rates in the alkaline samples were much lower than those of the original samples. Thus, marked changes in sedimentation rates were produced without any change in the concentration of the proteins.

TABLE III

Effect of acetic acid *

Case number	Corrected sedimentation rate	Hematocrit	Approximate pH
	mm. per minute	*per cent*	
I *a*†	0.99	42.0	7.8
b†	0.89	43.0	7.4
II *a*	1.01	42.0	7.8
b	0.99	44.0	7.6
III *a*	1.24	42.0	7.8
b	1.17	43.5	7.4
IV *a*	1.21	34.5	7.8
b	1.18	40.0	7.0
V *a*	1.30	41.0	7.8
b	1.39	43.5	7.4
VI *a*	0.76	36.5	7.6
b	0.69	40.0	7.0
VII *a*	0.65	46.0	
b	0.72	48.5	

* Acetic acid concentration approximately 0.01 N.
† *a* indicates original sample, *b* indicates sample to which acid has been added.

TABLE IV

Effect of alakli *

Case number	Corrected sedimentation rate	Hematocrit	Approximate pH
	mm. per minute	*per cent*	
VIII *a*†	0.74	34.0	7.5
b†	1.68	30.5	8.0
IX *a*	0.70	41.5	7.5
b	0.48	37.5	8.0
X *a*	1.98	39.0	7.5
b	0.45	31.5	8.0
XI *a*	0.66	40.5	7.5
b	0.35	30.0	8.0+
XII *a*	0.69	36.0	7.5
b	0.30	32.0	8.0
XIII *a*	1.91	39.0	7.5
b	1.50	35.5	8.0
XIV *a*	1.45	34.5	7.5
b	1.08	31.5	8.0
XV *a*	1.46	44.5	7.5
b	1.86	40.0	8.0
XVI *a*	1.25	41.0	7.5
b	0.78	37.5	8.0
XVII *a*	0.89	38.0	7.5
b	0.49	33.5	8.0

* Sodium carbonate (0.1 per cent) in Cases VIII and IX; sodium carbonate (0.2 per cent) in Cases X and XI; sodium hydroxide (approximately 0.01 N) in Cases XII to XVII.
† *a* indicates original sample, *b* indicates sample to which alkali has been added.

DISCUSSION

The numerous instances of lack of correlation between the erythrocyte sedimentation rate and the concentration of any of the plasma-protein fractions make it seem unlikely that an exact causal relationship exists.

In vitro experiments have proved that an increased concentration of fibrinogen or of globulin in any individual plasma does increase the sedimentation rate of the red cells in that plasma (2, 6, 14, 18). Fibrinogen has been found to have a greater effect than globulin. Albumin, on the other hand, has been found to have no effect or to decrease the rate. Such *in vitro* results, however, do not prove that increased concentrations of fibrinogen and globulin always cause increased rates *in vivo*, or that increases in these substances are the causes of the increased rates found in various

diseases. Coburn and Kapp (2), in their *in vitro* experiments, found that the sedimentation rates with added protein were never so high as those of the untreated sera with the same protein concentrations.

A concept with which all of the findings are consistent is that variations in sedimentation rate are due to variations in the physical state of the plasma colloids, with consequent changes in the electric charges on the proteins and red cells. With this hypothesis it is possible to explain the usual relationship between the concentration of fibrinogen and the sedimentation rate and also to understand the inconsistencies found by most workers. This theory also explains why so many factors have been found to influence the sedimentation rate.

The above concept is in accord with the original theory of Fåhraeus (5). He concluded that variations in sedimentation rate were due to changes in the magnitude of the electric charge on the red cells.

It is important to emphasize the fact that the results indicate that the stimulating agents produced in disease cause a change in the colloidal state of the plasma and a resulting increase in the sedimentation rate. They may coincidentally increase the fibrinogen or globulin, and any such change in the concentration of individual colloids naturally affects the colloidal state of the plasma. However, our results and those of other workers prove that the change in colloidal state and the resulting increase in rate may occur without any change in the concentration of fibrinogen or globulin. In other words, the agents may work partly through an increase in fibrinogen or globulin, or they may change the colloidal state without any change in the concentration of the proteins.

SUMMARY

1. The erythrocyte sedimentation rates and the plasma-protein fractions were determined in 89 blood samples from various diseases.

2. No absolute correlation was found between the sedimentation rate and any of the plasma-protein fractions. At least one-third of the findings were not consistent with a linear relationship between the fibrinogen concentration and the sedimentation rate.

3. In successive determinations during periods of clinical change, alterations in sedimentation rate did not consistently precede or accompany changes in either fibrinogen or globulin. In addition it has been shown that marked changes in the sedimentation rate can be produced without any alteration in the concentration of plasma proteins.

4. The only concept which explains all of the findings is that variations in sedimentation rates are due to variations in the colloidal state of the plasma with consequent changes in the electric charges on the proteins and red cells. Variations in the concentration of fibrinogen, globulin and other constituents affect the rate through their effect on the colloidal state of the plasma.

BIBLIOGRAPHY

1. Bendien, W. M., and Snapper, I., Zusammenhang zwischen der Senkungsgeschwindigkeit der roten Blutkörperchen und dem Eiweissspektrum. Biochem. Ztschr., 1931, **14**, 235.
2. Coburn, A. F., and Kapp, E. M., Observations on development of high blood sedimentation rate in rheumatic carditis. J. Clin. Invest., 1936, **15**, 715.
3. Cullen, G. E., and Van Slyke, D. D., Determination of fibrin, globulin, and albumin nitrogen of blood plasma. J. Biol. Chem., 1920, **41**, 587.
4. Ernstene, A. C., Erythrocyte sedimentation, plasma fibrinogen and leukocytosis as indices of rheumatic infection. Am. J. Med. Sc., 1930, **12**, 180.
5. Fåhraeus, R., Ueber die Ursachen der verminderten Suspensionsstabilität der Blutkörperchen während der Schwangerschaft (Vorläufige Mitteilung). Biochem. Ztschr., 1918, **89**, 355.
6. Fåhraeus, R., Suspension stability of blood. Physiol. Rev., 1929, **9**, 241.
7. Folin, O., and Wu, H.: System of blood analysis. J. Biol. Chem., 1919, **38**, 81.
8. Gilligan, D. R., and Ernstene, A. C., Relationship between erythrocyte sedimentation rate and fibrinogen content of plasma. Am. J. Med. Sc., 1934, **187**, 552.
9. Greisheimer, E. M., Johnson, O. H., and Ryan, M., Relationship between sedimentation index and fibrin content in relatively normal individuals. Am. J. Med. Sc., 1929, **177**, 816.
10. Ham, T. H., and Curtis, F. C., Sedimentation rate of erythrocytes; influence of technical, erythrocytic and plasma factors and quantitative comparison of five commonly used sedimentation methods. Medicine, 1938, **17**, 447.
11. Howe, P. E., The determination of proteins in blood. A micro-method. J. Biol. Chem., 1921, **49**, 109.
12. Jones, L. R., Plasma proteins, red-cell sedimentation and serum lability of blood in tuberculosis. Am. Rev. Tuberc., 1931, **23**, 325.

13. Moen, J. K., and Reimann, H. A., Plasma protein changes and suspension stability of blood in lobar pneumonia. J. Clin. Invest., 1933, **12**, 589.
14. Oakley, W., Erythrocyte sedimentation and plasma fibrinogen. Lancet, 1938, **1**, 312.
15. Rourke, M. D., and Ernstene, A. C., Method for correcting erythrocyte sedimentation rate for variations in cell volume percentage of blood. J. Clin. Invest., 1930, **8**, 545.
16. Westergren, A., Theorell, H., and Widström, G., Plasmaeiweiss, Blutlipoide, Erythrocyten und Senkungsreaktion. Ztschr. f. d. ges. exper. Med., 1931, **75**, 668.
17. Yardumian, K., Physicochemical factors influencing red cell sedimentation rate. Am. J. Clin. Path., 1937, **7**, 105.
18. von Zárday, I., and von Farkas, G., Quantitative Beziehungen zwischen Plasmaeiweissfraktionen und Blutsenkung. Ztschr. f. d. ges. exper. Med., 1931, **78**, 367.