THE PLASMA PROTEINS IN RELATION TO BLOOD HYDRATION

I. IN NORMAL INDIVIDUALS AND IN MISCELLANEOUS CONDITIONS

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INTRODUCTION

During the last two years an extensive investigation has been made of the water and electrolyte changes occurring in the blood in nephritis and diabetes and in other diseases which presented analogous phenomena. As part of this study the oxygen-capacity, cell volume and plasma proteins have been determined simultaneously in an attempt to gain some insight into the causes of the variations in the protein content of the serum and their relation to the hydration of the blood and the tissues.

Most of the determinations of blood proteins reported in the literature have been carried out on serum. In the present studies plasma has been employed almost exclusively. At first sight one would expect the values obtained from plasma to be somewhat higher than those from serum, because fibrinogen has been removed from the latter. That this is not actually the case has been shown by Gëttler and Baker (5). They found that the total nitrogen of serum was somewhat greater than that of plasma. The apparent paradox may be explained by the fact, demonstrated by Gram and Norgaard (6) and others, that the addition of anticoagulant amounts of oxalate to blood causes a shrinking of the cells.

Eisenman and Peters (4) have shown that this effect is demonstrable and amounts to a change of about 2 volumes per cent of cell volume, even if only 0.2 per cent of neutral potassium oxalate is used. In an attempt to verify the actual value of the change they compared cell

volume and plasma protein values. The results of these experiments appear in table 1.

METHODS AND RESULTS

Cell volumes were determined in duplicate with a Daland hematocrit of the type manufactured by the International Instrument Company for their centrifuges. With this instrument duplicates usually check within one volume per cent. In order that the effect of fibrinogen might be eliminated and that only the effect

TABLE 1

Case number	Oxygen capacity	Cell volume	Serum proteins	Relative change of serum volume		Treatment of serum
				From oxygen capacity and cell volume	From serum proteins	
	<i>vols. per cent</i>	<i>vols. per cent</i>	<i>per cent</i>			
29123	20.27	48.41	7.24*	1.00	1.00	Without oxalate
	20.47	43.58	6.92*	1.08	1.05	With 0.2 per cent potassium oxalate
29397	19.76	45.55	6.67	1.00	1.00	Without oxalate
	19.76	43.55	6.28*	1.04	1.06	With 0.2 per cent potassium oxalate
18433	10.05	23.95	6.83	1.00	1.00	Without oxalate
	10.10	20.35	6.44*	1.05	1.06	With 0.2 per cent potassium oxalate

* Non-protein nitrogen was not determined on these samples, but the values for total nitrogen, in terms of per cent protein, were reduced by 0.19, corresponding to a blood non-protein nitrogen of 30 mg. per 100 cc., or were assumed to be identical with those of the specimens without oxalate.

of oxalate might be active a specimen of blood was first defibrinated. To one portion of the blood neutral potassium oxalate was added. Both samples were brought into equilibrium with 40 mm. of CO₂ in air at 38°C. A portion of each was then used for the determination of oxygen capacity and cell volume; from another portion the plasma was removed for analysis. All procedures were carried out by the technique previously described (9), to prevent exposure to air. In this way variations in cell volume which might have resulted from differences of CO₂ tension were avoided. The total nitrogen of each sample of plasma was determined in duplicate by a macro-Kjeldahl method, using $\frac{1}{2}$ cc. of plasma. In some instances no correction was made for the non-protein nitrogen of the plasma.

Instead a blood non-protein nitrogen value of 30 mg. per 100 cc. was assumed and the total nitrogen of the serum was reduced accordingly. This course was pursued throughout this work in the interests of economy. Whenever there was any reason to suspect a change in the non-protein nitrogen the latter was separately determined. The error introduced by the omission of this procedure probably never exceeds 0.1 per cent.

It is evident that in every case the addition of oxalate to the blood results in a contraction of the cells and a reduction of the serum protein concentration. The change in volume of the serum calculated from the serum protein values is of the same order of magnitude as that calculated from cell volumes and hemoglobin. This is quite in keeping with the theory that the cell membrane is impervious to proteins.

TABLE 2

Subject	CO ₂ tension	Cell volume	Plasma proteins	Relative plasma volume from cell volume	Relative plasma volume from plasma proteins
	<i>mm.</i>	<i>vols. per cent</i>	<i>per cent</i>		
J. P. 5a	30	41.4	6.59*	1.00	1.00
	60	41.5	6.65*	0.998	0.991
J. P. 5b	30	52.0	9.16*	1.00	1.00
	60	52.2	9.17*	0.996	0.999

* Non-protein nitrogen was not determined on these samples, but the values for total nitrogen, in terms of per cent protein, were reduced by 0.19, corresponding to a blood non-protein nitrogen of 30 mg. per 100 cc.

The average diminution of the proteins, 0.37 per cent, is equal to or possibly a little greater than the average normal concentration of fibrinogen in the plasma.

As changes in CO₂-tension are known to cause alterations in the volume of the cells one would expect corresponding alterations in the plasma proteins. The difference in both cell volume and plasma proteins produced by varying the CO₂-tension between 30 and 60 mm. is shown in table 2. At least in this experiment it is negligible. If we assume that there is no interchange of protein across the cell membrane in vitro the variations of protein produced can be calculated from the change in cell volume alone, for which considerable data are available. In 34 experiments the average cell volume at 30 mm. of CO₂ was 40.5 volumes per cent; at 60 mm. it was 41.2 volumes per

cent. The plasma volume therefore varied from 59.5 volumes per cent at 30 mm. to 58.8 volumes per cent at 60 mm. This would produce a difference of about 1 per cent in the concentration of the proteins, which would be greater at a higher tension. Variations in oxygen will, also, of course, affect the cell volume and therefore the concentration of plasma proteins. The quantitative effect of oxygenation and reduction has not been investigated by us; but the work of Warburg (14) and of Van Slyke, Wu and McLean (13) indicate that it is relatively small. In general it may be said that the changes in CO₂ and O₂ tension usually encountered in the blood have a demonstrable but inconsiderable effect on the cell volume and on the plasma proteins.

TABLE 3

Subject	Oxygen capacity	Cell volume	Plasma proteins	Relative plasma volume calculated		Remarks
				From oxygen capacity and cell volume	From plasma proteins	
	<i>vols. per cent</i>	<i>vols. per cent</i>	<i>per cent</i>			
J. P. 1	18.61	42.7	6.90*	1.00	1.00	Without stasis
	22.45	51.2	9.32*	0.71	0.74	With stasis
J. P. 2	18.42	41.5	6.62*	1.00	1.00	Without stasis
	22.72	52.1	9.17*	0.66	0.72	With stasis

* Non-protein nitrogen was not determined on these samples, but the values for total nitrogen, in terms of per cent protein, were reduced by 0.19, corresponding to a blood non-protein nitrogen of 30 mg. per 100 cc.

In 1915-16 Rowe (10) demonstrated the fact that the production of venous stasis in a limb increased the plasma proteins in the venous blood of the part. In his experiments the serum albumin increased more than the globulin. This led him to believe that the change could not be due only to a transfer of water from the blood to the tissues. That such a transfer does occur has been suggested by Dautrebande, Davies and Meakins (3) and by one of us (8).

In the two experiments presented below (table 3) venous stasis was produced in the arm of a normal individual by means of a tourniquet which was applied with sufficient pressure to obstruct the venous return without completely obliterating

the arterial pulse. Blood was withdrawn from the arm vein immediately before the tourniquet was applied and again after the tourniquet had been in place for about five minutes.

In these and other similar experiments a considerable increase in hemoglobin, cell volume and plasma proteins occurred. If it is assumed that these changes were due only to inspissation of the blood, the amount of water lost to the tissues may be calculated. From the hemoglobin and hematocrit values it appears that the blood has lost considerable water, predominantly at the expense of the plasma. If the change of plasma volume be calculated from the differences in plasma protein figures of the same order of magnitude are obtained. It seems hardly reasonable to doubt that the chief mechanism responsible for these alterations in proteins and blood cells is loss of fluid to the tissues and that this fluid carries with it little or none of the proteins. To be sure the plasma volume changes calculated from hemoglobin and cell volume do not in either case agree exactly with those derived from the protein values.¹ In these two experiments the latter method indicates less change, which suggests that a part of the protein has escaped from the vessels. In other similar experiments discrepancies of the opposite sign have been found. It is, of course, possible that an exchange of proteins may occur in either direction; but it is just as reasonable to suppose that the stasis has tended to filter out a certain proportion of the blood cells in the capillaries.

The agreement between the hemoglobin-hematocrit and the plasma protein calculations is so close that one is almost forced to disregard the slight variations in *albumin : globulin* ratio found by Rowe (10) and to believe that the increases of plasma protein resulting from venous stasis are due to a concentration of the blood which affects predominantly the plasma and that even under the drastic conditions of these experiments the vessels remain practically impermeable to the proteins.

Rowe (12) found that the serum protein concentration was increased by exercise and Barr and Himwich (2) have noted a similar rise of hemoglobin. In some experiments of which one is submitted in table

¹ The failure to correct for non-protein nitrogen is recognized as a source of some error, but is probably negligible.

4 the changes observed have been neither as considerable nor as constant as those reported by Rowe and by Barr and Himwich. Their experiments differed from ours in one respect especially. They withdrew the blood immediately after the cessation of general exercise. In the experiment here presented blood was taken from the veins of the exercised part during the course of the exercise.

Both arms and forearms were thoroughly warmed, before the experiment, by immersion in hot water. The right hand was then exercised by the alternate extension and flexion of the wrist and hand with a weight of about ten pounds suspended from the tips of the fingers. When the exercise had been continued to the point of painful exhaustion blood was simultaneously withdrawn from the veins of both arms without stasis.

Table 5 shows the results of over-ventilation carried to the point where tetany developed.

Both hands and forearms of the subject were warmed thoroughly by immersion in hot water. Venous blood was then withdrawn from the arm vein. Immediately after the blood had been obtained the subject began breathing as hard as possible. Definite carpo-pedal spasm and other evidences of tetany developed in about five minutes. When these symptoms had become quite marked a second sample of blood was taken from the same arm vein. Over-ventilation was continued until the blood had been removed.

Although changes occur in hemoglobin, cell volume and plasma proteins there is nothing characteristic in them. It would, in all probability, be possible to multiply examples of conditions associated with alterations in blood water ad infinitum.

Dautrebande, Davies and Meakins (3) have demonstrated the fact that cold, stasis and certain diseased conditions, notably cardiac decompensation, cause the blood to give up an excessive amount of fluid to the tissues. So rapid are these changes that they may result in the production of appreciable differences in hemoglobin, cell volume and plasma proteins between arterial and venous blood. One of us (8) has already presented data confirming this work and showing that under other circumstances the blood may gain water from the tissues.

Whether these changes in plasma protein are expressions of alteration in blood hydration or not, their bearing on the determination of plasma protein values is the same. If plasma proteins are to be

TABLE 4

Subject	Oxygen capacity	Cell volume	Plasma proteins	Relative plasma volume calculated		Remarks
				From oxygen capacity and cell volume	From plasma proteins	
J. P. 1	<i>vols. per cent</i> 18.30	<i>vols. per cent</i> 38.1	<i>per cent</i> 6.60*	1.00	1.00	Venous blood from unexercised arm
	18.74	41.4	6.67*	0.93	0.99	Venous blood from exercised arm
J. P. 2	18.21	42.6		1.00		Venous blood from unexercised arm
	18.73	43.9		0.95		Venous blood from exercised arm

* Non-protein nitrogen was not determined on these samples, but the values for total nitrogen, in terms of per cent protein, were reduced by 0.19, corresponding to a blood non-protein nitrogen of 30 mg. per 100 cc.

TABLE 5

Subject	Oxygen capacity	Cell volume	Plasma proteins	Relative plasma volume calculated		Remarks
				From oxygen capacity and cell volume	From plasma proteins	
J. P. 1	<i>vols. per cent</i> 19.11	<i>vols. per cent</i> 42.1	<i>per cent</i> 6.55*	1.00	1.00	Venous blood before overventilation
	18.78	41.2	6.67*	1.03	1.00	Venous blood during overventilation
J. P. 2	18.86	43.9	6.76*	1.00	1.00	Venous blood before overventilation
	19.87	43.9	7.27*	0.95	0.93	Venous blood during overventilation

* Non-protein nitrogen was not determined on these samples, but the values for total nitrogen in terms of per cent protein, were reduced by 0.19, corresponding to a blood non-protein nitrogen of 30 mg. per 100 cc.

interpreted with any degree of accuracy determinations must be made under standard conditions with precautions to avoid stasis, cold, exercise and any other unusual circumstances. Arterial plasma is preferable to venous plasma in most cases.

The values for the plasma proteins of the venous blood of five normal individuals, members of the hospital and laboratory staff, in table 6, agree with those published by other observers and are quite variable. Unfortunately the blood from the first four subjects and the first four specimens from the last subject were taken with no special

TABLE 6

Subject	Date	Plasma protein
		<i>per cent</i>
H. A. B.		7.25*
		7.98*
K. B.		7.92*
H. J. S.		7.61*
M. S.		6.52*
J. P. P.	November 28, 1922	6.70*
	January 22, 1923	6.72*
	March 20, 1923	6.94*
	March 11, 1924	6.71*
	March 18, 1924	6.43*
	March 27, 1924	6.42*
	April 3, 1924	6.41*
	April 10, 1924	6.46*
	April 16, 1924	6.57*

* Non-protein nitrogen was not determined on these samples, but the values for total nitrogen, in terms of per cent protein, were reduced by 0.19, corresponding to a blood non-protein nitrogen of 30 mg. per 100 cc.

precautions and much of the variation may be due to this fact. The five last specimens from J. P. were all taken without stasis at approximately the same time of day, after a preliminary rest period and after the arm and hand had been warmed by immersion in hot water. The constancy of the proteins in these experiments is quite striking in contrast to the previous ones. In some of these experiments the plasma proteins were determined after the blood had been brought into equilibrium at 38°C. with 40 mm. of CO₂ in air. In the others the blood was centrifuged and the plasma removed with precautions to prevent all contact with the air. There is no systematic difference

between the two sets of figures, confirming the previous statement that the changes of gas tension in the blood encountered under ordinary circumstances have no significant effect on the plasma proteins.

Such normal figures are hardly comparable to those obtained from patients in the ward, restricted in their activities and diet and presenting too often a variety of functional disturbances that may affect the water content and the plasma proteins of the blood. Before attacking the problems of diabetes, nephritis and edema, therefore, it seemed advisable to study patients with miscellaneous pathological conditions. Some of these were selected as control material because there seemed no reason to expect any disturbance of the plasma proteins; others because it seemed quite possible in the light of previous reports or certain clinical phenomena that the proteins might be abnormal.

The technique followed was similar to that described above. In some cases venous blood was used, in others arterial. Sometimes the blood was brought into equilibrium with 40 mm. of CO_2 in air at $38^\circ\text{C}.$; sometimes it was withdrawn and analyzed with precautions against contact with air. The nature of the blood (whether venous or arterial) and its treatment are indicated in the last column of each table. *Art.* and *Ven.* stand for arterial and venous blood respectively; *cap.* means that the blood was saturated with 40 mm. of CO_2 while *cont.* means that the blood was analyzed as drawn, without exposure to the air.

The patients in the first part of table 7 were suffering from nervous conditions that presumably would not affect the plasma proteins. The range of variation does not differ appreciably from that of the normals shown in the preceding table.

In the second part of the table appear four patients with arteriosclerosis and hypertension without evidences of functional disturbances of heart or kidney. With one exception these patients showed normal plasma proteins. No. 22158, at the time of the first observation had very high proteins in his plasma. At this time, three days after his admission to the hospital, he was in coma, difficult to feed, and his fluid intake was small. Five days later, with some improvement, the plasma proteins, hemoglobin and hematocrit had fallen together. Calculations of the relative plasma volumes made on the basis of the hemoglobin and hematocrit figures show that the blood plasma had been diluted 11 per cent. Similar calculations based on

TABLE 7

Case number	Oxygen capacity	Cell volume	Plasma proteins*	Character and treatment of blood	Remarks
Section 1					
	<i>vols. per cent</i>	<i>vols. per cent</i>	<i>per cent</i>		
12016	22.4	47.0	7.71.	Ven. Cap.	Neurasthenia. Wassermann test positive
29189	20.9	45.1	6.94*	Ven. Cap.	Syphilis of central nervous system
15004	20.2	43.4	7.94*	Ven. cap.	Psychoneurosis
10875	20.6	43.7	7.69*	Ven. cap.	Neurasthenia. Wassermann test positive
10859	18.2	39.9	7.17*	Ven. cap.	Hysteria
26871	17.3	38.9	6.73*	Ven. cap.	Glioma of left parietal lobe.
26451	21.1	48.0	7.52*	Ven. cap.	Cataract. Chronic frontal sinusitis
Section 2					
26362	16.4	36.5	7.31	Art. cont.	Arteriosclerosis, hypertension, old hemiplegia
22158	22.1	48.3	8.60	Ven. cap.	Arteriosclerosis, hypertension, cerebral hemorrhage, hemiplegia and coma
	20.7	46.1	7.81	Ven. cap.	5 days later
6657	18.5	41.1	7.61	Ven. cap.	Hypertension, obesity
18081	29.3	39.1	6.54	Art. cont.	Arteriosclerosis, hypertension
Section 3					
10702	18.7	40.8	7.00*	Ven. cap.	Methyl alcohol poisoning. In convulsions. Has received large amounts of sodium bicarbonate
29658	20.6	46.4	7.97	Ven. cont.	Obstructed ventral hernia. Intestinal obstruction.
9420	21.6	44.7	7.81*	Ven. cap.	Acute colitis. Moderately severe
10495	17.9	35.5	6.70*	Ven. cap.	Acute alcoholic gastritis
26690	10.9	24.4	5.52	Art. cont.	Arteriosclerosis with hypertension. Carcinoma of the ascending colon with intestinal obstruction
22798	15.90	34.6	4.89	Art. cont.	Extensive burns of trunk. Has been given enormous amounts of water and salt solution by every means until generalized subcutaneous edema developed

TABLE 7—Continued

Case number	Oxygen capacity	Cell volume	Plasma proteins*	Character and treatment of blood	Remarks
Section 3—Continued					
26515	vols. per cent 17.0	vols. per cent 34.7	per cent 6.30	Ven. cont.	Toxic vomiting of pregnancy. Cellulitis—no edema—fluid intake by parenteral routes large
Section 4					
18725	20.1	43.3	8.63	Ven. cap.	Hemorrhagic pachymeningitis. Bronchopneumonia. Patient stuporous and having frequent convulsions on the day of the examination
33564	15.3	36.0	7.03	Ven. cont.	Chorea major. Patient in coma
15712	21.2	43.6	7.66	Ven. cap.	Carbon monoxide poisoning. Influenza. Patient in coma
15703	20.1	42.1	6.62	Ven. cap.	Lobar pneumonia. Fourth day
10744	16.2	40.9	6.77	Ven. cap.	Acute tracheitis, broncho-pneumonia, fibrous pericarditis, one day before death
26343	15.9	38.2	7.01	Ven. cap.	Acute mediastinitis
Section 5					
5196	18.4	39.9	6.73	Ven. cap.	Arsphenamine poisoning with central necrosis of the liver
1536	10.4	24.9	7.53*	Ven. cap.	Seven year old boy with anemia and unexplained jaundice
5238	21.4	50.1	7.40	Ven. cap.	Atrophic cirrhosis of liver. Moderate ascites. Hypertension
34777			5.52	Ven. cont.	Female, aged 53, with obstruction of the common bile duct and an ascending bile duct infection. Extremely toxic. Blood non-protein nitrogen 80 mg. in 100 cc. Intense jaundice

* Non-protein nitrogen was not determined on these samples, but the values for total nitrogen, in terms of per cent protein, were reduced by 0.19, corresponding to a blood non-protein nitrogen of 30 mg. per 100 cc.

plasma protein values show a 10 per cent dilution. The high protein of the first observation was apparently merely a product of blood concentration, possibly due to his low fluid intake, and was not directly referable to the diseased condition. Hypertension and arteriosclerosis in themselves seem to have no specific effect on the plasma proteins.

In the third portion of the table is a group of miscellaneous cases. Nos. 10702, 9420, 10495 and 26515 were chosen for study in the hope that they would show dehydration from loss or deprivation of fluids. All of them had, however, received adequate fluids before the time of the examination. No. 29658, an old woman with an obstructed ventral hernia who had been vomiting continuously for more than 24 hours, does show some elevation of the plasma proteins with a high normal hemoglobin. Unfortunately no other observation was made on this patient.

No. 26690 had a carcinoma of the ascending colon which had become obstructed shortly before admission. At the time of the blood examination the intestinal obstruction had been overcome, vomiting had ceased and large amounts of fluid had been given the patient. He had, however, had a profuse hemorrhage from the bowel and appeared exhausted and toxic. How far the hemorrhage may be held responsible for the low proteins and how much dilution of the blood had been caused by the forcing of fluids it is impossible to say.

No. 22798, a middle aged man who had received extensive burns of the face, trunk and extremities was not examined until a few days before death. For four days before the blood study his fluid intake by mouth and by hypodermoclysis had been from 4500 to 9000 cc. At the time of the examination he had a moderate generalized edema and a liquid diarrhea. His hemoglobin, which had been determined daily by the Cohen and Smith method, had fallen from 140 per cent (Haldane scale) to 45 per cent. Although no other observations of the proteins were made it seems more than likely that the low value found in this case was largely due to dilution of the blood. It should be added that none of the patients of this series had blood non-protein nitrogens above 50 mg. per 100 cc. of blood.

In the fifth section of table 7 appear four observations on subjects with diseased conditions of the liver, all but one of which have normal

plasma proteins. Atchley, Loeb, Benedict and Palmer (1) noted a reduction of serum protein in three patients with cirrhosis of the liver and ascites. That such a reduction is not characteristic of this condition is evident from case no. 5238. In one case with low proteins, no. 34777, the reduction may well have been referable to the general state of intoxication and shock, and not to the liver injury.

Rowe (11) and others have found that in acute infectious conditions there is an increase of the globulin of the serum, associated with a

TABLE 8

Case number	Oxygen capacity	Cell volume	Plasma proteins*	Character and treatment of blood	Remarks
	<i>vols. per cent</i>	<i>vols. per cent</i>	<i>per cent</i>		
18859	3.57	11.0	6.97*	Ven. cap.	Adenomyoma of uterus. Secondary anemia
8169	2.65	5.4	5.89*	Ven. cap.	Pernicious anemia. Slight generalized, subcutaneous edema
	2.89	6.1	6.57*	Ven. cap.	Same patient, 9 months later. Edema is again present
9734	4.23	12.8	7.49*	Ven. cap.	Secondary anemia. Cause undetermined
22272	4.90	18.6	3.68	Ven. cont.	Advanced pulmonary tuberculosis. General anasarca
22114	3.71	9.4	5.52*	Ven. cap.	Adenoma of uterine cervix. Slight edema of ankles
33106	3.61		5.42*	Ven. cont.	Pernicious anemia. General anasarca
10210	10.4	23.0	6.95*	Ven. cap.	Pernicious anemia
22780	28.7	65.4	7.23*	Ven. cap.	Polycythemia
	27.6	61.0	6.34	Ven. cont.	Same patient, 2 weeks later

* Non-protein nitrogen was not determined on these samples, but the values for total nitrogen, in terms of per cent protein, were reduced by 0.19, corresponding to a blood non-protein nitrogen of 30 mg. per 100 cc.

reduction of the albumin, with the result that the total proteins are normal or slightly reduced. In the fourth section of table 7 are shown a few cases with severe infections. Nothing can, of course, be said about the relation of globulin to albumin in these plasmas, but the total protein, at any rate, shows no tendency to reduction. In many of these cases the diminution may have been masked by a concentration of the blood caused by inadequate fluid intake, but the hemo-

globin values give no indication of such a concentration. In no. 10744 such an explanation is certainly unsatisfactory because the patient was almost anuric and had received large amounts of fluid by mouth and subcutaneously. The increase of fibrinogen which is such a constant finding in pneumonia and other infectious conditions would of course tend to make the plasma proteins relatively higher than the serum proteins.

Low serum proteins have been reported in severe anemias by Kahn and Barsky (7) and others. In eight observations on seven patients shown in table 8 low proteins were found in the plasma five times. It is interesting that in four of these five instances the patients presented subcutaneous edema. The association of edema and low proteins appears, however, to be merely coincidental because one of the same patients, no. 8169, on a second occasion had normal proteins in the presence of edema. The low proteins, furthermore, do not seem to depend on the presence, severity or type of anemia. In one case of polycythemia the plasma proteins were normal.

SUMMARY

1. Determination of the proteins in normal oxalated plasma gives values appreciably lower than those obtained from the analysis of serum, in spite of the fact that the latter lacks fibrinogen. This is due to the shrinking of the blood cells produced by oxalate.

2. The changes in carbon dioxide and oxygen tension of the blood encountered under ordinary conditions cause demonstrable but inconsiderable changes in the plasma proteins.

3. The production of venous stasis results in an increase of the proteins in the venous plasma of the affected part which is due to a transfer of water from the blood to the tissues.

4. Exercise may cause concentration of the venous plasma that is reflected in an increase of the plasma proteins.

5. Under certain conditions the exchange of water between the blood and the tissues in the capillaries may be so greatly accelerated that the concentration of proteins in arterial and in venous plasma may differ to a significant degree.

6. The degree of variation of the plasma proteins in a group of five normal individuals taken under various conditions was considerable

and agreed with the reports of other observers. The degree of variation observed in a single individual over a period of two years was very slight. The same individual, observed under standardized conditions over a shorter period presented even smaller variations in the proteins of his venous plasma. Seven patients with neurologic or psychopathic disorders which presumably would not affect the plasma proteins showed values similar to those found in the normal group.

7. Arteriosclerosis and hypertension in themselves appear to have no effect on the plasma proteins. One patient with cerebral hemorrhage, in coma, had high proteins in his plasma. As his condition improved proteins, hemoglobin and cell volume fell simultaneously. The high cell volume and proteins were evidently due to a concentration of the blood, possibly caused by an inadequate fluid intake.

8. The administration of excessive fluids to a patient with severe burns resulted in the production of hydremia with a consequent reduction of the plasma proteins. Edema also developed.

9. In a series of five cases with severe acute infections the plasma proteins were normal or slightly elevated.

10. The effects of factors which may alter the water content of the blood must not be neglected in the interpretation of values of the proteins of the plasma.

11. Normal plasma proteins were encountered in three patients with diseases of the liver, in one instance in the presence of ascites.

12. Although low plasma proteins appeared four times in seven observations on patients with profound anemia, there seemed to be no relation between the reduction of the proteins and the presence, severity or type of anemia. Edema, which so commonly occurs in these cases, is not necessarily associated with a diminution of the plasma proteins.

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