CHANGES IN THE VOLUME OF PLASMA AND ABSOLUTE AMOUNT OF PLASMA PROTEINS IN NEPHRITIS.

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In a preceding paper (1) it was shown that a considerable fall occurred in the concentration of protein in the plasma of persons suffering from nephrosis or from glomerulonephritis of the nephrotic type. In discussing this abnormality of the plasma proteins the question arose whether it was due in any degree to a process of dilution; whether a plasma previously normal in volume and protein concentration became greater in volume and poorer in proteins by the retention of extraneous water in the blood. This hypothetical condition has been named hydremic plethora, and it was tacitly assumed to be present in some stages of nephritis by most of the early workers who found a reduced concentration of the plasma proteins. In the absence of any definite means for distinguishing clinically between hydremic plethora and simple hydremia, that is between a dilute state of the blood with and without increase in total volume, these terms were vaguely used, and these early opinions were of little scientific value (2). An extension of this hypothesis connected the assumed changes of blood volume with the production of edema. Edema was thus believed first to involve the blood itself and then to implicate the tissues by reducing the osmotic pressure of the plasma. Similarly the anemia of nephritis was explained on the same basis as a dilution anemia. Brown and Roth (3), however, in a recent study concluded that the anemia of chronic nephritis is not due to dilution.

Whether low concentration of the plasma proteins also occurs independently of plasma volume change, or affords an indication of increased volume, remained undetermined. The data in the present paper appear to answer the question decisively. We have observed a series of nephritic patients with low plasma protein concentration,

with all degrees of edema, and have not found an abnormally large plasma volume per kilo of body weight, as determined by the vital red method of Keith, Rowntree, and Geraghty.

A number of observations on the blood and plasma volumes in nephritis have been published but none have come to our attention in which the plasma protein concentrations were simultaneously determined. Plesch (4), 1909, found an increased volume of blood in three cases of nephritis without edema and a marked decrease in one case with edema. He concluded that the increase was the decisive factor in the production of hypertension and that edema was a compensatory mechanism by which the effects of this increase on the blood pressure were mitigated. Keith, Rowntree, and Geraghty (5) reported nineteen measurements by the vital red method on cases of chronic nephritis and hypertension. In one case with considerable edema the plasma volume increased from 3,900 to 4,050, while the patient lost 11 kilos of edema. In the other cases they found an average of 42.8 cc. of plasma and 75 cc. of blood per kilo body weight, their normal figures being 42 to 56 and 78 to 97 respectively. There was, therefore, no increase. Plesch (6), 1922, using the carbon monoxide method found increases of blood volume in all cases of nephritis and arteriosclerosis. In two edematous patients the blood volume and hemoglobin increased as the edema decreased. Bock (7), 1921, reported observations by the dye method on three cases of nephritis, in two of which the plasma amounted to 4.8 and 6.0 per cent of the body weight. The third patient had great edema, the weight falling from 54.5 to 41 kilos in 1 month. The plasma per kilo observed body weight remained constant (4.0, 4.1, and 4.1), but the figures show a marked fall in absolute plasma volume (2,200, 1,900, and 1,690 cc.). Seyderhelm and Lampe (8) determined the rate of disappearance of trypan red from the circulation in normal people and in patients with nephritis. They found that in cases of great edema 50 per cent of the dye left the circulation in half an hour without any appreciable amount appearing in the urine during that time. In normal persons only 5 to 10 per cent disappeared in that time. They think that in such cases the dye must pass into the tissues. They failed to find increases in blood volume in nephritis (9) even when accompanied by anemia or edema, but state: "Eher war sogar die Gesamtblutmenge oft in hochgradigsten Status oedematosus mit sogenannter Hydrämie ausgesprochen vermindert."

Methods.

The methods useful for the determination of the absolute volumes of the plasma and blood in clinical practice are two: first, the carbon monoxide inhalation method, introduced by Gréhant and Quinquaud (10), applied to man by Haldane and Lorrain Smith (11), and improved by Van Slyke and Salvesen (12, 13), and second, the method

of injecting a non-diffusible dye, such as vital red, which was first employed by Keith, Rowntree, and Geraghty (5). These methods have been tested by a number of investigators (14–18), and their limitations have been thoroughly discussed, particularly by Whipple and his associates (14, 15) and by Lamson and Rosenthal (16). The conclusion appears to be that while neither method can be depended upon to give absolute results, either one may be used to observe variations in the blood volume of a given individual.

In this investigation the original vital red method of Keith, Rowntree, and Geraghty was used (5). The measurements were made about 2 hours after a breakfast which was arranged to contain as little fat as possible; by this precaution cloudiness of the plasma was greatly reduced. In consequence of the probable inaccuracy of the results depending upon the hematocrit we did not attach so much importance to the figures for the blood volume as to those for the plasma volume. Oxalate was employed as anticoagulant. In view of Lamson's criticism we made repeated observations on our patients when that was possible, but we found that the comparison of the findings from single determinations in other cases was not valueless. Keith, Rowntree, and Geraghty (5) found the plasma to vary in health between 43 and 54 cc. per kilo of body weight, and Bock (7) found it to be from 4.5 to 5.7 per cent of the body weight. For purposes of comparison we assumed a standard body weight for each patient, which was the weight reached when the patient became free from edema. This standard body weight was used in all the calculations for that individual. In some instances this weight was derived from the age, height, and weight tables because the patient did not become edema-free. The weight of a patient with nephritis when free from edema is liable to be less than it should be, as cachexia is a feature of the disease. No attempt was made to correct for this.

The patients used were those described in the preceding paper on the plasma protein concentration and the clinical details will not be repeated here. The same case numbers are used and the present results are recorded in the table. Charts illustrating some of the plasma volume findings will be found in the preceding paper.

Results of Plasma Volume Measurements.—Glomerulonephritis and Nephrosis: In four patients (Cases 1, 8, 15, and 16) observations

TABLE I.

Case. Diagnosis.	Date.	Actual weight.	Estimated weight. Edema-free.	Edema, etc.	Plasma volume.		Plasma protein in gm. per kilo body weight.			Red blood corpuscles in millions per c.mm.	Cell volume.	Blood volume.		Red blood corpuscles per kilo estimated body weight.
					Cc.	Percentage of body weight.	Albumin.	Globulin.	Total protein.			Cc.	Percentage of body weight.	
	1922	*kg.*	*kg.*								*per cent*			
(Normal.)						(5)	(2.05)	(1.3)	(3.35)	(5.0)	(43.0)		(8.8)	4.2×10^{11}
No. 1 (J. D.).	May 20	50.4	38	+++	2,060	5.42	0.86	1.14	2.00	4.15	31.0	2,980	8.24	3.25
Subchronic glomerulonephritis, nephrotic type.	June 7	39.0		+	2,060	5.42	1.25	0.98	2.23	—	32.5	3,120	8.62	—
	July 10	38.8		(+)	2,080	5.48	1.06	1.16	2.22	3.49	24.9	2,770	7.65	2.55
	Nov. 2	36.8		—	2 080	5.48	1.22	1.25	2.47	3.38	22.8	2,690	7.43	2.39
	1923													
	Jan. 5	38.2		—	1,960	5.32	1.37	1.03	2.40	2.95	19.8	2,440	6.74	1.89
	Mar. 9	41.6		—	2,270	5.98	1.36	1.39	2.75	2.48	17.6	2,750	7.60	1.80
No. 8. (M. P.).	Jan. 5	65.8	48	++++	2,470	5.30	1.18	1.18	2.36	3.52	27.7	3,420	7.48	2.51
Subacute glomerulonephritis, nephrotic type.	Feb. 2	54.8		++	2,790	5.99	1.24	1.89	3.13	2.60	18.3	3,420	7.48	1.85
	Mar. 9	47.9		—	2,650	5.69	1.36	1.77	3.13	3.08	23.7	3,475	7.60	2.23
	1922													
No. 15 (L. S.).	Oct. 9	82.4	64	++++	2,720	4.38	0.71	1.05	1.76	—	39.8	4,520	7.42	—
Acute nephrosis.	Nov. 19	74.3		+++	2,795	4.50	0.66	1.09	1.75	4.18	36.6	4,410	7.24	2.88
	1923													
	Feb. 2	64.8		—	2,960	4.76	1.68	1.04	2.72	4.82	38.8	4,840	7.94	3.65
	1922													
No. 16 (B. S.).	Nov. 6	34.9	35	+	1,980	5.83	0.63	1.94	2.57	5.08	38.5	3,210	9.64	4.66
Chronic nephrosis.	Dec. 21	33.1		—	1,520	4.48	0.70	1.35	2.05	4.75	37.7	2,440	7.32	3.31
	1923													
	Mar. 22	40.6		Ascites, etc., ++	1,650	4.86	0.47	1.58	2.05	4.72	37.0	2,620	7.86	3.53

	Apr. 9	39.4		Ascites, etc., +	1,520	4.48	0.33	1.24	1.57	5.50	42.0	2,620	7.86	4.12
	June 26	37.0		Absent.	1,620	4.77	0.54	1.19	1.73	4.65	34.9	2,490	7.5	3.31
	1922													
No. 3 (J. O'M.). Chronic glomerulonephritis, nephrotic type.	Nov. 3	41.2	42	—	2,350	5.76	1.61	1.39	3.00	3.82	27.6	3,250	7.7	2.95
	1923													
	Jan. 23	41.8		—	2,440	5.98	1.66	0.97	2.63	3.36	26.8	3,330	7.9	2.66
	Mar. 6	44.0		—	2,520	6.18	1.79	1.16	2.95	2.63	20.1	3,160	7.5	1.98
	1923													
No. 5 (S. L.). Chronic glomerulonephritis, nephrotic type.	Apr. 5	62.0	54	Ascites.	2,330	4.4	0.81	0.98	1.79	4.2	31.7	3,415	6.6	2.65
No. 9 (W. K.). Acute glomerulonephritis.*	Mar. 28	42.7	42.7	—	1,765	4.25	1.72	1.13	2.85	4.7	40.0	2,940	7.2	3.24
No. 11 (I. C.). Chronic glomerulonephritis, nephrotic type.	May 6	52.7	48	+	2,580	5.54	—	—	—	—	31.0	3,740	8.2	—
No. 20 (E. R.). Nephrosclerosis.	Apr. 7	71.0	71	—	3,330	4.84	1.92	1.35	3.27	—	38.0	5,380	7.9	—
No. 22 (H. L.). Nephrosclerosis.	Nov. 14	51.0	51	—	2,310	4.67	2.06	1.30	3.36	4.54	42.0	3,970	8.2	3.53
No. 13 (M. K.). Glomerulonephritis, vascular-interstitial type.	Oct. 9	42.3	42	(+)	2,880	7.08	2.15	1.57	3.72	1.6	13.5	3,330	8.3	1.27
No. 25 (H. B.). Functional proteinuria.	July 10	50.4	50.4	—	2,270	4.65	1.83	1.80	3.63	—	41.0	3,840	7.6	—

*Convalescent.

were made on the plasma volume before, during, and after the disappearance of extensive general edema. In the first case the plasma volume remained constant while the weight fell from 50.4 to 39 kilos in 17 days (Case 1, subchronic glomerulonephritis, Chart 1 of the preceding paper). In Case 8 (subacute glomerulonephritis, Chart 3), there were at the time of the initial observation general anasarca, pleural effusions, and ascites; with the steady improvement of the clinical condition, there was a definite small increase in the volume of plasma. In the third (Case 15, acute nephrosis, Chart 4), the observations were made before, during, and after a most striking diuresis and elimination of edema, and as in the preceding case, there was an increase in the volume of plasma as the edema disappeared. In the fourth case (Case 16, chronic nephrosis, Chart 5), the results were not so uniform. The initial figure which was obtained when the patient was slightly edematous was probably too high, but as no error in technique could be discovered the observation must stand. No adequate explanation was found to account for this high plasma volume and correspondingly high blood volume and number of red cells per kilo of body weight. If we neglect this observation, there remain four measurements, one before the development of considerable ascites, pleural effusion, and slight edema, one at their fullest development, one in the early stage of recovery, and finally one when all the effusions had disappeared and the patient had returned to a better state of nutrition. The plasma volume was constant at all these times within the limits of error of the method.

Consideration of these four cases shows that the volume of plasma was either uninfluenced by the presence of edema or else that it was actually diminished when the anasarca was extreme. In Cases 8 and 15 the increase which occurred as the edema disappeared was moderate but quite definite; a similar increase was found by Keith, Rowntree, and Geraghty in their case, but Bock as has been already noted found a decrease. The effect of the increased permeability of the capillaries for the dye in cases of great edema as observed by Seyderhelm and Lampe would be to introduce an error which would operate in the direction of increasing the observed plasma volume in the stage of edema. This consideration adds weight to the increases observed in our cases when the edema was absorbed.

Considering all the patients in this group we found that the plasma varied between 4 and 6 per cent of the body weight, but usually between 4.5 and 5.5 per cent. The table shows that in all those cases in which the plasma was above 5 per cent of the body weight, there was a considerable degree of secondary anemia with the red cell count reduced to less than 4.1 million per c.mm.; and, reversely, that in every case in which the plasma was less than 5 per cent anemia of this degree was lacking. To this statement there is one exception, namely the first observation on Case 16, the validity of which we doubt. The secondary anemia of chronic nephritis is frequently but a part of a general cachexia; the high percental weight of the plasma in nephritis with anemia is probably to be accounted for in part by this fact, as these patients are very likely to be under their proper normal weights when they are finally free from edema.

Only one observation was made in glomerulonephritis of the vascular type. This patient, Case 13, presented a very great increase in plasma, and with this an absolute increase in plasma proteins. This suggests that either there was an error in the determination or else the increase in plasma was of some standing and not merely a terminal event. Lorrain Smith (11), Plesch (4), and Keith, Rowntree, and Geraghty (5) report increases in blood volume in severe anemia. As this patient presented such an anemia, the red cells being reduced to 1.6 million per c.mm., it is probable that anemia was the cause of this increase in plasma volume. The volume of the whole blood in this case was not increased.

Nephrosclerosis: One determination was made on each of two cases of nephrosclerosis. In Case 22 the disease was in an early stage and in Case 20 it was well advanced; neither was complicated by heart failure. Both had normal amounts of plasma and of blood for their body weight.

Functional Proteinuria: A single observation fell within normal limits.

Results of the Measurement of Whole Blood and Corpuscle Content.—In consequence of the slight increase in plasma when anemia was well marked, the figures for the whole blood expressed per kilo of body weight were more constant than the corresponding figures for the plasma. They varied between 7 and 8.3 per cent, and were

therefore lower than the figures 8.2 to 10 per cent, given as normal by Keith, Rowntree, and Geraghty (5).

The figures for the red blood corpuscles calculated per kilo body weight lend support to the opinion that dilution of the blood is not the cause of the anemia in nephritis.

Results of the Determinations of the Total Plasma Proteins.—Glomerulonephritis and Nephrosis: If we accept the plasma in healthy adults to be 5.0 per cent of the body weight (4.3 to 5.4—Keith, Rowntree, and Geraghty (5); 4.5 to 5.7—Bock (7)), then, calculating from the figures for the normal plasma protein concentration given in our previous paper, we find that the figures for the absolute amount of albumin, globulin, and total protein are about 2.0, 1.3, and 3.3 gm. per kilo body weight respectively. From the table it is apparent that the low concentration of protein in the plasma was associated with a fall in the absolute amount of these proteins in the body. As for the plasma itself, the plasma proteins were calculated for a standard body weight for each individual, edema-free. In those patients with severe anemia there was a small increase in plasma per kilo, but this seldom exceeded the normal limits and was entirely insufficient to account for the low concentration of proteins on the basis of dilution, or hydremic plethora, as the absolute protein figures plainly demonstrated.

The total globulin varied very much less than the total albumin, a fact which tells very strongly against the explanation of the fall in protein concentration on the hypothesis of simple dilution. The albumin when abnormal was always decreased, never increased; a moderate fall appeared in all the cases of glomerulonephritis, and in most cases it was well marked, but extreme reductions to less than 0.8 gm. per kilo were only found in the two cases of active nephrosis (Nos. 15 and 16). The globulin usually showed a moderate decrease, the lowest figures, 0.98 gm. per kilo, being found in glomerulonephritis (Cases 1 and 5); but in some cases of glomerulonephritis and nephrosis it was increased to as much as 1.89 gm. per kilo (Cases 8 and 16).

Nephrosclerosis and Functional Proteinuria: In nephrosclerosis normal figures were found. In the patient with functional proteinuria there was an increase of globulin and of total protein with a

small decrease in albumin. Possibly the increase in globulin was due to septic absorbtion for he had hypertrophied and infected tonsils which required removal.

CONCLUSIONS.

1. We have not observed gross increases in plasma volume in glomerulonephritis, nephrosis, or nephrosclerosis, even when the concentration of plasma proteins was much below normal. Our results indicate the probability that "hydremic plethora" does not occur.

2. The low protein concentration frequently observed in the plasma in nephritis is not due to increased plasma volume but to a decrease of the total amount of plasma protein in the body.

3. Changes in plasma volume showed no constant relationship to changes in edema.

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