

STUDIES ON HYPOALBUMINEMIA PRODUCED BY PROTEIN-DEFICIENT DIETS

III. THE CORRECTION OF HYPOALBUMINEMIA IN DOGS BY MEANS OF LARGE PLASMA TRANSFUSIONS

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Plasma transfusions are often used clinically to correct hypoproteinemia resulting from malnutrition although the results are often disappointing in the severe cases. It seemed advisable, therefore, to study experimentally the effect of intravenous plasma in dogs depleted by a non-protein diet which has been shown by Weech (1) and ourselves (2) to produce a rapid fall in the albumin fraction of the blood. Holman, Mahoney, and Whipple (3) were the first to study the metabolic effect of plasma transfusions in the dog and they showed that protein given in this way led to positive nitrogen balance but only when dog plasma was used. These findings were confirmed by later studies (4, 5). More recently Kremen *et al.* have reported similar findings with human plasma in human beings but not with bovine plasma (6). In protein-depleted dogs Shearburn (7) found that one plasma transfusion calculated to restore the plasma protein deficiency had only a transient influence on plasma volume and no effect on the hypoproteinemia, whereas smaller amounts given once or twice a day for 2 weeks led to a gradual return of the plasma protein to normal.

Procedures

The dietary method used to produce hypoalbuminemia was similar to that devised by Weech (1) except that a solution was used and administered by gavage twice daily (2). The energy value was 50 calories per kilo per day and the nitrogen intake due largely to vitamin B complex was under 20 mg. per kilo per day. A period of 3 weeks was used for depletion; the 4th week was used for therapy and the depletion then continued for 2 more weeks. Thus each experiment lasted 6 weeks. Under such a non-protein régime hypoalbuminemia rapidly develops except that occasionally it is masked by hemoconcentration which is revealed by a rise in the hematocrit reading (8). However, in the present experiments plasma volumes were measured to circumvent this state of affairs; the method used was described in a previous paper in this series (9).

The amount of plasma given during the 4th week was determined by measuring its nitrogen content. A dose of 0.5 gm. of nitrogen per kilo per day was given, which was the same we used in other regeneration experiments in which hydrolyzed protein was used (2). In terms of protein this represented a little over 3 gm. per kilo per day, which is somewhat greater than 2.5 gm. employed by Weech. It was

necessary to give about 500 to 600 cc. of dog plasma per day; the rate of injection was about 100 cc. per hour. No protein appeared in the urine. The plasma was obtained from donor dogs by centrifuging their citrated blood after bleeding. The methods for determining the hematocrit reading, and the albumin and globulin,

TABLE I

Blood Changes and Nitrogen Balance in Dietary Hypoalbuminemia As Influenced by Large Plasma Transfusions

Each dog received during the week (4) of therapy plasma amounting to exactly 0.5 gm. N/kg./day or roughly 600 cc. per day. N intake due entirely to vitamins and plasma.

Day	Blood changes					Nitrogen balance				Urine output	Remarks
	Hema- to- crit reading	Albu- min	Globu- lin	P.V.	T.C.A.	Week	Intake	Urinary output	Balance		
	per cent	gm. per cent	gm. per cent	cc.	gm.		gm.	gm.	gm.	cc.	
1	45.7	3.75	3.44	—	—	0	—	—	—	—	Dog C3 9.6 kg.
7	—	—	—	—	—	1	1.26	—	—	—	
14	44.3	3.23	4.06	—	—	2	1.26	—	—	—	
21	45.4	2.93	4.20	482	14.1	3	1.26	11.11	-9.85	4030	
28	39.8	4.73	4.32	616	29.1	4	35.69	12.32	+23.37	8530	
35	36.1	4.08	3.90	—	—	5	1.26	24.58	-23.32	4460	
42	39.6	3.29	3.05	379	12.5	6	1.26	—	—	—	
1	49.8	3.56	2.05	—	—	0	—	—	—	—	Dog C4 9.8 kg.
7	—	—	—	—	—	1	1.33	—	—	—	
14	47.1	3.08	2.26	—	—	2	1.33	—	—	—	
21	50.0	2.79	2.97	515	14.4	3	1.33	12.73	-11.40	4170	
28	33.0	4.32	3.61	746	32.2	4	36.35	15.88	+20.47	9480	
35	31.4	3.84	2.62	—	—	5	1.33	25.62	-24.29	4420	
42	36.5	3.16	2.42	515	16.3	6	1.33	—	—	—	
1	46.4	3.54	2.12	—	—	0	—	—	—	—	Dog D1 10.8 kg.
7	—	—	—	—	—	1	1.47	—	—	—	
14	52.3	3.01	2.37	—	—	2	1.47	—	—	—	
21	53.1	3.21	2.20	442	14.2	3	1.47	19.54	-18.07	3890	
28	37.3	4.10	3.97	690	28.3	4	39.27	16.43	+22.84	6610	
35	44.0	3.89	3.22	497	19.3	5	1.47	34.35	-32.88	5760	
42	—	—	—	—	—	6	1.47	27.40	-25.93	5180	

P.V.—plasma volume; T.C.A.—total circulating albumin.

have been described previously (2). During the periods of urine collection the dogs were kept in metabolism cages and the usual precautions taken.

FINDINGS

The really large plasma transfusions were tolerated without event. No symptoms or signs were noted in the dogs, aside from a pronounced diuresis.

Thus "toxic" symptoms as observed in other reported experiments (5) did not occur. The data on the blood changes and nitrogen balance are listed in Table I. The increase in the plasma proteins after the week of plasma was striking and affected both albumin and globulin, mostly the former. There was also a striking increase in plasma volume so that the total circulating albumin doubled in all experiments. Urinary nitrogen remained uninfluenced during the week of plasma injections, indicating a complete retention and the achievement of a remarkable positive nitrogen balance. However, during the weeks following the injections the output of urinary nitrogen increased and in one experiment was so great as to wipe out all of the nitrogen retained during the week of plasma injections. In the course of 2 weeks the plasma volume returned to its previous level as did the albumin and globulin concentrations. The diuresis which occurred during the week of plasma transfusions doubled the urinary secretion.

COMMENT

The findings in these experiments were striking and in some respects unexpected. That the plasma proteins and volumes should increase might have been foreseen but the magnitude of the changes was surprising. Doubtless the diuresis was a manifestation of the increased colloidal osmotic pressure produced by the large increases in the concentration of plasma proteins. Although nutritionally the introduced amount of plasma as nitrogen was not excessive, in terms of plasma transfusions it was tremendous. The protein intake was 3 gm. per kilo per day, which is a large but not an unusual amount from the nutritional point of view; yet it represents a volume of plasma greater than the plasma volume already present. In other words, the daily injection doubled the amount of normally circulating plasma. This contrast is of some interest when one considers plasma as a means of supplying protein nourishment parenterally.

Totally unexpected was the large excretion of urinary nitrogen following the week of plasma injections. One cannot escape the inference that all injected plasma,—at least in the large doses used in these experiments, was *not* utilized as nitrogenous nourishment for the rest of the body. By comparing the amount of plasma injected with the increase of circulating protein observed, it is obvious that during the week of injections but a small part of the injected plasma protein remained in the blood. The actual percentages are, in the three experiments, 9.9, 13.5, and 13.5 per cent (Table II). That the rest was taken up by the tissues seems obvious for there was no increase in urinary nitrogen during this period. It is conceivable, of course, that the protein was slowly catabolized in these tissues, the end products being stored for a while but eventually excreted in the urine. Nevertheless, the present data cast doubt on the assumption that the body is able to utilize plasma pro-

teins in the building of protein tissue elsewhere, at least when injected in large amounts. In contrast to these findings with plasma, previous experiments showed no increased nitrogen output in the week following the injection of the same amount of nitrogen as hydrolyzed casein. It is of interest to mention the findings of Schoenheimer *et al.* (10), who found in the rat that plasma proteins are being continuously destroyed and that their half life is about 2 weeks.

The present findings are not in agreement with the observations of Holman, Mahoney, and Whipple (3), who found no excessive nitrogen excretion during 5 days following a 2 week period of plasma transfusions. However, the daily amount of plasma they injected was only about one-third that used in the present experiments. If the difference is actually due to this circumstance, it suggests a limitation of the amount of plasma introduced intravenously which can be utilized each day as protein alimentation. The correction of nutritionally induced hypoalbuminemia with small repeated plasma injections

TABLE II
Proportion of Injected Protein Remaining in the Blood after the Week of Plasma Transfusions

Dog No.	Before plasma transfusions			Plasma protein injected	After plasma transfusions			Injected plasma protein remaining in plasma
	P.V.	T.P.	T.C.P.		P.V.	T.P.	T.C.P.	
	cc.	gm. per cent	gm.	gm.	cc.	gm. per cent	gm.	per cent
C3	482	7.13	34.4	215	616	9.05	55.7	9.9
C4	515	5.76	29.7	219	746	7.93	59.2	13.5
D1	442	5.41	23.9	236	690	8.07	55.7	13.5

P.V.—plasma volume; T.P.—total protein concentration; T.C.P.—total circulating protein.

already noted (7) is of interest in this connection. In view of the use of plasma transfusions to combat hypoproteinemia of nutritional origin in the human being, further observations seem indicated.

CONCLUSIONS

1. It proved possible to correct dietary hypoalbuminemia in dogs by large plasma transfusions (about 50 cc. per kilo per day). After 1 week of injections the increase of plasma protein exceeded the normal level although but 10 to 13 per cent of the injected protein remained in the blood. There was an associated increase in plasma volume and a marked diuresis. During the following 2 weeks the plasma volume and protein returned to their previous low levels.

2. The nitrogen introduced was retained and produced no change in urinary excretion during the week of plasma injections, but in the following 2 weeks there was an increased nitrogen output. The inference would seem to be that the large amounts of plasma injected in these experiments were not perma-

nently utilized by the body as nitrogenous nourishment but after some delay were largely excreted in the urine.

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