STUDIES ON HYPOALBUMINEMIA PRODUCED BY PROTEIN-DEFICIENT DIETS

I. HYPOALBUMINEMIA AS A QUANTITATIVE MEASURE OF TISSUE PROTEIN DEPLETION*

By L. A. SACHAR, M.D., ABRAHAM HORVITZ, M.D., AND ROBERT ELMAN, M.D.
(From the Department of Surgery, Washington University School of Medicine, and Barnes Hospital, St. Louis, Missouri)

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The realization within recent years of the prevalence and seriousness of protein deficiency has emphasized the need for some simple means of recognizing the presence and degree of such a condition. The only proteins capable of direct clinical measurement are those in the blood. Yet there has, so far, been no evidence that a lowered plasma protein concentration reflects accurately anything but a deficiency in the blood alone.

During the course of other experiments, evidence was adduced indicating the existence of a constant relationship between losses in the total circulating plasma albumin and in the body protein as a whole. This, of course, immediately suggested a means of recognizing and evaluating total body protein deficiency. Of the plasma proteins it is only the albumin fraction which consistently decreases during an inadequate protein intake (1-3); for this reason consideration may be confined to this fraction alone. The total circulating serum¹ albumin can be readily obtained by multiplying the albumin value by the plasma volume which may be estimated from the body weight or determined directly. By subtracting this total circulating serum albumin from the normal, the number of grams of albumin by which the serum is depleted is obtained. The depletion in the tissue protein is, of course, readily measured by determining the total nitrogen loss in the urine and feces. Now if the relationship between total serum albumin depletion and total tissue protein depletion is represented by the equation
$$\frac{\text{Total serum albumin depletion}}{\text{Total protein depletion}} = K,$$
 the value of K is readily calculated. On the other hand if K is known and the serum albumin measured the only unknown would be the tissue protein depletion for which the equation could then be solved.

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¹ Because fibrinogen comes out in the globulin fraction, serum albumin and plasma albumin are practically the same; the terms will be used interchangeably in this paper.

TABLE I

Data Showing the Approximate Quantitative Relationship (K) between Dietary Changes in Total Serum Albumin and Tissue Protein

Author	Dietary procedure	Plasma volume	Loss of serum albumin and tissue protein		
			Total albumin loss (gm.)	Total tissue protein loss (gm. total urinary N $\times$ 6.25)	$K \left(\frac{\text{serum albumin loss}}{\text{tissue protein loss}} \right)$
Weech, Goettsch, and Reeves (2)	Low protein—carrot diet 30 days	Assumed 1/20th of body weight	Not recorded	Not recorded	0.04 (approximate)
Holman, Mahoney, and Whipple (4) Dog 22-131	Glucose by gavage for 24 days	Directly determined (dye)	11.9	292*	0.04
Madden <i>et al.</i> (5) Dog 39-223	Fasted 1 wk.	Directly determined (dye)	3.28	82.6	0.04
Madden <i>et al.</i> (5) Dog 39-234	Fasted 1 wk.	Directly determined (dye)	5.14	101.25	0.05
Present data	Low protein diet for 21 days	Assumed 1/20th of body weight	5.28	176	0.03
Average					0.04
			Gain in serum albumin and tissue protein		
			Total albumin gain (gm.)	Total tissue protein gain (gm. N retained $\times$ 6.25)	$K \left(\frac{\text{serum albumin gain}}{\text{tissue protein gain}} \right)$
Elman, Sachar, Horvitz, and Wolf (6) average of 4 dogs	4 gm. of casein hydrolysate per kg. per day by mouth for 1 wk.†	Assumed 1/20th of body weight	1.76	71.87	0.02
Average of 5 dogs	4 gm. of casein hydrolysate per kg. per day for 1 wk. intravenously†	Assumed 1/20th of body weight	1.4	32.6	0.04

* Loss in last 5 days estimated.

† Calories supplied with karo syrup.

In this paper we shall present evidence indicating that such a constant relationship between the total circulating serum albumin and the tissue proteins does exist under conditions of inadequate protein intake, and that in dogs at least the value for K is in the neighborhood of 0.04. Indeed, there are reasons for believing that the same equation applies to the distribution of nitrogen intake during replenishment of the depletion.

Although no previous studies could be found devoted to the topic of this communication data of several workers have been used in calculations which seem to confirm the thesis presented in this paper. These calculations are simple. Total serum albumin loss is obtained by multiplying the plasma volume by the change in the concentration of serum albumin nitrogen during the experimental period. The loss in tissue protein was measured by determining the total negative nitrogen balance during the same period. By comparing these two figures of nitrogen loss, the proportion of total nitrogen loss was obtained which could be accounted for by the serum albumin change. When the plasma volume was not actually determined, it was assumed to be one-twentieth of the body weight.

Weech, Goettsch, and Reeves (2) noted that about 4 per cent of the nitrogen lost by dogs on a low protein diet could be accounted for by the decline in total circulating serum albumin. Calculations made of the data presented in the papers of Holman, Mahoney, and Whipple (4) and of Madden, Zeldis, Hengerer, Miller, Rowe, Turner, and Whipple (5) showed a decline in the total circulating albumin of fasted dogs which also represented about 4 per cent of the total nitrogen lost. It was interesting to note that the same percentage was reached if one calculated in the same way data obtained while regeneration of serum albumin was produced by feeding protein. During the correction by protein alimentation in experimentally induced hypoproteinemia of dogs, Elman, Sachar, Horvitz, and Wolf (6) found that only about 4 per cent of the nitrogen which the dogs retained could be accounted for by the increase of serum albumin thus produced. These previous observations are summarized in Table I.

PRESENT OBSERVATIONS

Five dogs were placed on a protein-poor diet containing karo syrup, Ringer's solution, and a vitamin B complex concentrate for 3 weeks. A constant intake was achieved by feeding the dogs by gavage twice daily a solution prepared as follows: 200 gm. of a vitamin B complex concentrate (labco)² and 5,000 gm. of karo syrup were made up to 10,000 cc. with 4 times concentrated Ringer's solution. Each feeding consisted of enough of this stock solution to provide 25 calories per kilo body weight; *i.e.*, 12.5 cc. per kilo diluted 4 times with water and given by gavage. The total daily energy intake was therefore 50 calories per kilo.

Plasma albumin determinations and concomitant nitrogen balance studies were carried out while the dogs were on the diet described above. The chemical and experimental procedures have been described in a previous paper (6).

² Obtained from the Borden Company, Bainbridge, New York.

EXPERIMENTAL FINDINGS

The results of the present experiments are tabulated in Table II and are really self-explanatory. In brief they show that of the total nitrogen lost by the dogs during 3 weeks on a low protein diet, a relatively small but constant percentage averaging about 3 per cent, represented the fall in serum albumin. The calculations employed were those previously described. The value found in these experiments compares fairly well with those derived from the literature as tabulated in Table I.

TABLE II
Quantitative Relation (K) between Total Tissue Protein Loss and Serum Albumin Loss during 3 Weeks of a Protein-free Diet (Plasma Volume Assumed to be 1/20th of Body Weight)

Dog	Loss in body weight	Fall in serum albumin concentration	Loss in total serum albumin	Loss in total tissue protein (gm. total urinary N $\times$ 6.25)	$K = \frac{\text{loss total serum albumin}}{\text{loss total tissue protein}}$
	kg.	gm. per cent	gm.		
Z10	1.2	1.82	9.5	199	0.047
Z24	0.9	0.89	4.3	182	0.024
Z14	0.6	0.59	2.7	135	0.020
T56	1.8	0.69	6.5	237	0.027
T67	0.7	0.81	3.4	129	0.026
Averages.....	1.04	0.96	5.28	176	0.030

DISCUSSION

On the basis of the evidence presented (both our own observations as well as those of others) an hypothesis is offered that a relatively constant relationship (about 25 or 30 to 1) exists between dietary induced changes in the total tissue protein and changes in the total circulating serum albumin. In other words, loss (or gain) of tissue protein and of serum albumin caused by diet parallel each other. This conception is based on the existence of a fixed partition between tissue protein and serum albumin; *i.e.*, loss or gain in one is accompanied by a proportional loss or gain in the other. Thus this hypothesis denies the existence of "deposit protein" or of reserves of protein which became available during dietary deficiencies. (When loss of serum albumin occurs in other ways such as hemorrhage, burns, etc., another situation exists which presents other mechanisms.)

It would seem that the existence of such a parallelism between serum albumin and tissue proteins makes it possible to detect the presence and extent of a tissue protein deficiency simply by determining the amount of serum albumin. Since it is also probable that the same parallelism, or biological partition,

exists in the process of replenishment of depleted tissue protein and serum albumin, such information may be of practical value in calculating the amount of protein which must be fed in order to overcome the deficiency.

If this idea is correct it is possible, as stated previously, to develop a formula by which the total protein loss may be calculated, if the serum albumin concentration is known. Let the serum albumin-tissue protein parallelism be represented by the equation:
$$\frac{\text{Serum albumin depletion in grams}}{\text{Tissue protein depletion in grams}} = K.$$
 The serum albumin depletion in grams will be equal to the normal serum albumin concentration (2) of dogs (3.6 gm.) minus the observed serum albumin concentration (S.A.) times the plasma volume (P.V.). When the albumin concentration is given in terms of grams per 100 cc. of serum, the plasma volume should be the number of 100 cc. of plasma present. This figure for the plasma volume is obtained by direct dye determination or estimated by dividing the normal body weight in kilos by 20 and multiplying this figure by 10. Stated again:

Serum albumin depletion (grams)

$$= (3.6 - \text{observed albumin concentration S.A.}) \frac{(\text{body weight in kilos} \times 10)}{20}$$

Inasmuch as K (Table I) is approximately 0.04, one obtains by substituting our first equation:

$$\frac{(3.6 - \text{S.A.}) (\text{body weight in kilos}) (10)}{(20) (\text{tissue protein depletion in gm.})} = 0.04, \text{ or simplifying, tissue protein}$$

$$\text{depletion in gm.} = (3.6 - \text{S.A.}) (\text{normal body weight in kilos}) (12.5)$$

The relationship of 1 to 25 (or 30, *i.e.* $K = 0.04$ or 0.03) between serum albumin loss and tissue protein loss was compared with the available data on the relative amounts of each in the intact human body. The amount of serum albumin is easily estimated as 161 gm. (3500×4.6). Let us assume that nearly all tissue protein is muscle; from Vierordt (7) the weight of the muscles in an average adult is about 28 kilos of which $1/5$ is protein or 5600 gm. Of course only the parenchyma of the muscle tissue is lost during starvation so that the active protein tissue is less than this. Nevertheless 5600 gm. is but slightly more than 30 times the amount of serum albumin. It seems not unlikely that the relationship for K may be the same as the relative masses of these two protein compartments of the body.

Certain obvious limitations of the hypothesis here formulated must be emphasized. It applies only when the tissue proteins and serum albumin are altered as a result of diet. It cannot be expected to hold in cases of hypo-proteinemia due to blood loss, burns, nephrosis, or liver disease. Another factor is also important, *i.e.* in depleted patients the measurement of serum albumin concentration may not accurately measure the degree of hypoalbu-

minemia if the normal plasma volume shrinks. For example, if the patient is dehydrated, the resultant hemoconcentration produces a rise in the value of serum albumin and minimizes or even masks completely the existence of the deficiency. This masking effect of dehydration was pointed out clearly by Peters and his coworkers (8) in 1925. It is probable that the persistence of more or less normal plasma albumin concentrations, noted by several observers, in animals placed on certain low protein diets or fasted is the result of such hemoconcentration. Indeed, this phenomenon was noted in experiments on fasting dogs performed in this laboratory (9).

Although the present data are confined to dogs, there is no reason to believe that a similar relationship does not hold true for human beings. There are in the literature but few data of the sort herein discussed. A rough calculation of the data of Bruckman, D'Esopo, and Peters (12) who measured the serum albumin concentration and made concomitant nitrogen balance studies of a malnourished individual during a period of replenishment indicates a value for K of about 0.02. Nevertheless if we assume that the value for K for humans is the same as for dogs, and accept as the normal serum albumin concentration the lower limit, 4.6 gm. per cent, given by Hawk and Bergheim (10) the equation describing the protein depletion of a malnourished human is: grams protein depletion = $(4.6 - S.A) (\text{normal body weight in kilos}) (12.5)$.

The practical application of the conception herein presented concerns to a large extent the problem of replenishment of chronic protein deficiencies which are of frequent clinical occurrence. For example, a patient whose body weight in health is 60 kilos and whose serum albumin is 3.6 gm. per cent would be deficient by $(4.6 - 3.6) (60) (12.5) = 756$ gm. protein. If such a patient retained but half of the nitrogen consumed, he would require twice 756 gm. or 1512 gm. Thus a period of over 2 weeks on a diet providing 100 gm. protein per day would be required to reach this amount. To this must be added the requirements for endogenous nitrogen metabolism which would be at least 4×6.25 or 26 gm. per day. Viewed in this way the therapeutic problem presented by a protein-deficient patient is largely a quantitative one; only by giving a large amount of protein can it be solved. This is particularly difficult when the nitrogen-containing nutriment must be given intravenously or parenterally or when but a short period of time is available for correction. The immense quantities of protein required make the use of human plasma or serum transfusions for this purpose an altogether impractical procedure at least in severely depleted patients. The most promising approach at present is the use of hydrolyzed protein of high biological value (6, 11).

SUMMARY

In five dogs placed on a protein-poor diet for 3 weeks, the decline in total circulating plasma albumin was a small (3 per cent) but relatively constant

part of the total nitrogen lost. These data together with observations on dogs by others indicate that there is a constant relationship or partition in the loss (or gain) between plasma albumin and total body protein induced by diet. Based on this relationship a formula is developed for estimating the degree of total tissue protein deficiency from the value of the serum albumin concentration alone. This formula would also apply to the replenishment of protein deficiencies of dietary origin and it indicates that for every gram of increase in serum albumin desired about 30 gm. must be retained for increases in other proteins of the body.

BIBLIOGRAPHY

1. Peters, J. P., Wakeman, M. A., and Eisenman, A. J., *J. Clin. Inv.*, 1927, **3**, 491.
2. Weech, A. A., Goettsch, E., and Reeves, E. B., *J. Exp. Med.*, 1935, **61**, 299.
3. Elman, R., and Heifetz, C., *J. Exp. Med.*, 1941, **73**, 417.
4. Holman, R. L., Mahoney, E. B., and Whipple, G. H., *J. Exp. Med.*, 1934, **59**, 251.
5. Madden, S. C., Zeldis, L. J., Hengerer, A. D., Miller, L. L., Rowe, A. P., Turner, A. P., and Whipple, G. H., *J. Exp. Med.*, 1941, **73**, 727.
6. Elman, R., Sachar, L. A., Horvitz, A., and Wolf, H., *Arch. Surg.*, in press.
7. Vierordt, H., *Anatomische, physiologische und physikalische Daten und Tabellen*, Jena, Gustav Fischer, 3rd edition, 1906, 44.
8. Peters, J. P., Eisenman, A. J., and Bulger, H. A., *J. Clin. Inv.*, 1925, **1**, 435.
9. Elman, R., Horvitz, A., and Sachar, L. A., unpublished observations.
10. Hawk, P., and Bergheim, O., *Practical physiological chemistry*, Philadelphia, P. Blakiston's Son and Co., Inc., 11th edition, 1937.
11. Elman, R., *Ann. Surg.*, 1940, **112**, 594.
12. Bruckman, F. S., D'Esopo, L. M., and Peters, J. P., *J. Clin. Inv.*, 1930, **8**, 577.