

ALBUMIN METABOLISM IN CHILDREN WITH PROTEIN MALNUTRITION¹

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Of the biochemical disturbances associated with protein malnutrition in man, hypoalbuminemia is undoubtedly one of those most consistently found (1, 2). The metabolic mechanisms operating to produce this hypoalbuminemia are not known. However, analysis of diets of children with severe protein malnutrition (kwashiorkor) has revealed that the protein intake of such children is less than half of the minimal protein requirement for age, even discounting the fact that the proteins ingested are primarily of vegetable origin and that caloric intake is inadequate as well (3, 4). While it is not possible to decide *a priori* that the hypoalbuminemia in this condition is attributable to decreased synthesis secondary to diminished amino acid intake, this possibility would seem the most likely; diminished albumin synthesis has been shown to occur in animals on comparable diets (5). However, since the plasma concentration of albumin represents a balance between synthesis, distribution in the body, and degradation, any or all of these factors could play a role. Consequently, this study was undertaken to evaluate the relative influence of each of these on the production of hypoalbuminemia in children with protein malnutrition.

METHODS

Patients. Fourteen children, admitted to the Hospital Infantil, Mexico City, with severe protein malnutrition, were selected for study (Table I). All of the children had a history of prolonged inadequate protein intake and repeated episodes of diarrhea during which total food intake was greatly reduced as well. Although extremely malnourished, 3 children had no edema upon admission

(Group I), while the other 11 children showed definite edema (Group II). Well-developed pellagroid skin lesions of the type seen in protein malnutrition were present in each of the 11 edematous children, but only small atrophic lesions were noted in the other three. Microscopic examination of feces revealed *G. lamblia* infestation in two children, L. B. F. and R. E. J. Patient J. M. J. died during the study, and postmortem examination revealed, among other things, the presence of bronchopneumonia.

Method of study. Each child was given five drops of Lugol's solution three times a day during the study. Within 48 hours of admission, I¹³¹-labeled human serum albumin was injected intravenously, and the disappearance of radioactivity from the serum was followed for about three weeks (Period A, Table I) in all patients except J. M. J., who died eight days after the start of the study. After an additional interval of three to four weeks, eight children were given a second injection of radioiodinated albumin, and its disappearance was again followed for about three weeks (Period B, Table I). The samples of iodinated albumin used were, for the most part, prepared as described elsewhere (6), but in several instances, two preparations obtained from Abbott Laboratories were used. In each of the eight children studied on two occasions, a different iodinated albumin preparation was used for the first and second periods. The specific activities of the labeled albumins were such that a maximum of 1 mg. of iodinated albumin was injected, or no more than 1.5 microcuries per kilogram of body weight.

The condition of the children upon admission was considered to be too serious to warrant continued protein restriction. Consequently, with but one exception, during the study the patients were given either milk, later supplemented with sugar, or milk supplemented with bananas, meat, eggs and vegetables. One patient, A. V. M., was given a diet similar to that eaten before admission, namely beans and cornmeal cakes, during the first study period and then milk supplemented with meat and vegetables after this.

Three of the children, S. S. F., H. T. J. and C. R. V., were restricted to metabolic beds during the study periods for the collection of urine.

The amount of radioactivity in samples of serum or urine was determined with a well-type sodium iodide crystal scintillation counter. Proteins in the samples

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TABLE I
Albumin studies in patients with protein malnutrition

Patient	Age	Sex	Study period	Weight*	Serum* albumin	Plasma volume	Albumin in vascular system†	Albumin half-life
	yrs.			Kg.	Gm. %			days
Group I								
S. S. F.	3	M	A	7.10- 8.45	1.50-3.25	452	0.42	9.3
			B	9.50- 9.76	3.95-4.07	688	0.38	9.4
H. T. J.	3	M	A	5.82- 7.10	1.85-3.58	448	0.42	9.8
			B	8.30- 8.76	3.60-3.75	697	0.32	10.8
B. T. L.	5½ ₂	F	A	6.80- 8.30	1.65-3.75	398	0.53	6.3
Group II								
M. X. D.	1½ ₂	M	A	6.90- 8.50	1.85-4.10	373	0.54	6.6
			B	9.30- 9.30	4.30-4.30	562	0.37	7.0
J. M. J.	2	M	A	4.80- 4.50	1.55-1.87	256	0.47	7.6
L. B. F.	1¼ ₂	M	A	6.90- 7.60	1.50-4.10	380	0.31	10.4
			B	8.10- 8.30	3.13-3.43	498	0.27	10.8
G. M. E.	1¾ ₂	F	A	5.60- 6.75	2.16-3.20	401	0.31	9.0
			B	7.00- 8.00	3.75-3.75	498	0.30	10.8
C. R. V.	1¾ ₂	M	A	5.92- 6.70	2.62-3.05	418	0.28	8.8
			B	7.40- 8.10	3.75-4.30	468	0.32	9.5
R. E. J.	1½ ₂	F	A	7.30- 7.50	2.16-3.75	455	0.34	9.3
			B	8.00- 8.25	3.43-3.43	467	0.32	8.5
A. V. M.	2¼ ₂	M	A	8.78- 7.85	1.92-2.35	420	0.40	14.5
			B	10.8 -11.9	4.30-4.75	561	0.30	11.3
P. B. G.	1½ ₂	M	A	6.44- 5.40	0.80-1.32	518	0.22	11.0
T. H. C.	5	M	A	9.30-11.8	0.85-3.65	720	0.53	7.8
R. M. A.	6½ ₂	F	A	12.0 -14.0	1.07-3.95	712	0.52	8.5
R. O. M.	3¼ ₂	F	A	7.50- 8.90	2.75-3.95	362	0.40	7.8

* At beginning and at end of study period.

† As fraction of total exchangeable albumin.

were precipitated in 10 per cent tricholacetic acid and the precipitates and supernates assayed for radioactivity.

Albumin concentrations in serum samples were estimated immunochemically (7).

RESULTS

The albumin half-lives in these children as determined from the serum disappearance curves are shown in Table I. The disappearance of radioiodinated albumin from the serum of some of the children is illustrated in Figures 1 to 3. There was no significant difference in the half-life of radioiodinated albumin during the second study period as compared to the first period (Table I). In the eight children who were studied twice, the half-life of albumin ranged from 6.6 to 14.5 days,

with an average of 9.7 days in the first period, and from 7.0 to 11.3 days, with an average of 9.8 days in the second. The fraction of total exchangeable albumin found in the vascular compartment in these children, as estimated by extrapolation of the catabolic phase of the serum disappearance curve to zero time, is indicated in Table I. In three of the eight children studied twice, this fraction decreased appreciably from the first study period to the second (H. T. J., M. X. D., and A. V. M.); it decreased only slightly, if at all, in four children (S. S. F., J. M. J., G. M. E., and R. E. J.) and increased slightly in one child (C. R. V.). The percentage of radioiodinated albumin catabolized per day by H. T. J., S. S. F., and C. R. V., as calculated from the urinary data

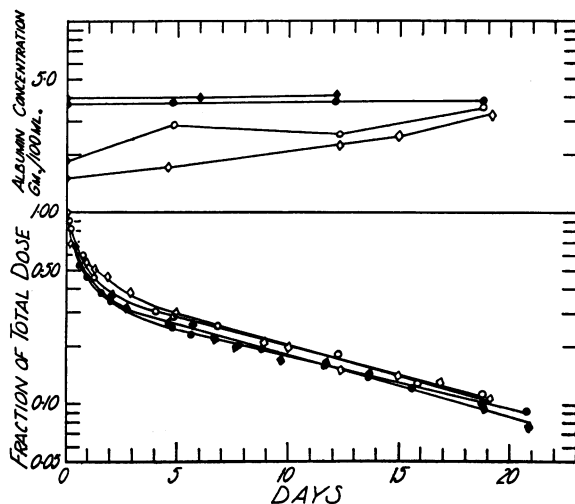


FIG. 1. SERUM ALBUMIN CONCENTRATIONS AND DISAPPEARANCE OF RADIOIODINATED ALBUMIN FROM THE SERUM IN TWO CHILDREN WITH THE NONEDEMATOUS FORM OF PROTEIN MALNUTRITION

In this and in all subsequent figures, the open symbols represent the first study period and the solid symbols indicate the second study period.

Circles, H. T. J.; diamonds, S. S. F.

by the method of Berson, Yalow, Schreiber, and Post (8), was found to be, respectively, 6.0, 5.6 and 5.8 per cent during the first study period, and 5.8, 6.8 and 5.8 per cent during the second; these

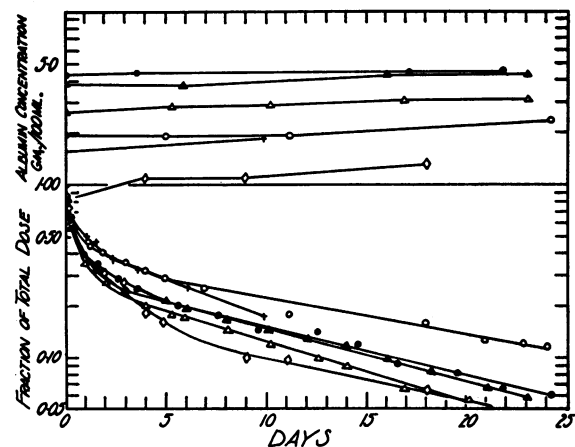


FIG. 2. THE SERUM DISAPPEARANCE OF RADIOIODINATED ALBUMIN AND THE SERUM CONCENTRATION OF ENDOGENOUS ALBUMIN IN FOUR CHILDREN WITH THE EDEMATOUS FORM OF PROTEIN MALNUTRITION IN WHOM THE SERUM ALBUMIN ROSE LESS THAN 0.52 GM. PER CENT DURING THE FIRST STUDY PERIOD

Circles, A. V. M.; diamonds, P. B. G.; triangles, C. R. V.; and crosses, J. M. J.

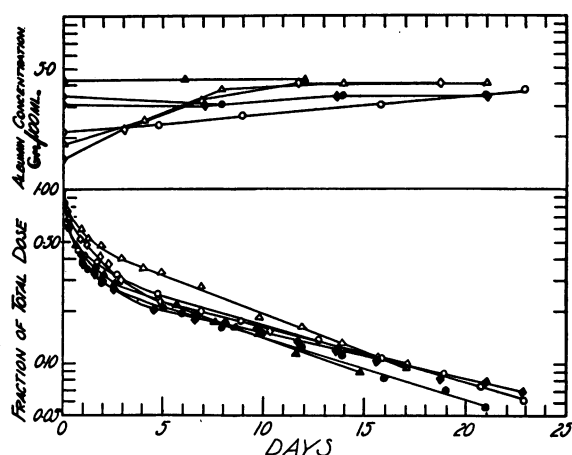


FIG. 3. THE SERUM DISAPPEARANCE OF RADIOIODINATED ALBUMIN AND THE SERUM CONCENTRATION OF ENDOGENOUS ALBUMIN IN THREE CHILDREN WITH THE EDEMATOUS FORM OF PROTEIN MALNUTRITION IN WHOM THE SERUM ALBUMIN ROSE MORE THAN 1 GM. PER CENT DURING THE FIRST STUDY PERIOD

Circles, R. E. J.; diamonds, L. B. F.; and triangles, M. X. D.

values correspond to albumin half-lives of 11.5, 12.4 and 11.9 days in the first period, and 11.9, 10.2 and 11.9 for the second. In these patients no more than 10 per cent of the administered radioactivity was excreted during the first day of the study.

Serum albumin concentrations rose continuously and significantly during each first study period; the total increment in this time was from 0.32 to 0.52 Gm. per cent in four children and from 1.04 to 2.88 Gm. per cent in the others (Table I). During the second period, albumin concentrations remained rather constant, having reached relatively normal values by this time; the maximum gain in albumin during the second study period was 0.55 Gm. per cent.

DISCUSSION

Upon admission and during the study, all but one of the children were fed a diet higher in protein and calories than that which had led to their malnourished state. The effects of the diet were apparent in clinical improvement and return of serum albumin concentrations toward normal levels. Under these circumstances then, before the results of the study can be evaluated, it is necessary to decide whether the half-life of albumin deter-

mined during the initial study period truly represents the turnover of albumin in these children *before* they entered the hospital. Can it be assumed that the improved diet did not cause an immediate change in the half-life of albumin? It should be noted first that the results obtained cannot be attributed to peculiarities of an individual radioiodinated albumin preparation since several were used and in no case was the same one used for the first and second study periods. In Patients J. M. J., C. R. V., A. V. M., and P. B. G., the rise in serum albumin concentration was only 0.32 to 0.52 Gm. per cent during the study period and yet the albumin half-life in these children (Figure 2) was similar to that in the other children in whom the rise in albumin was three to six times as great during the same period of time (Figures 1 and 3). In addition, in the three of these four patients who survived, the return of serum albumin concentrations to normal occurred chiefly during the interval between the two study periods; the albumin half-life in each of the two periods was similar. And finally, although in A. V. M. the albumin half-life was similar to that in the other children, his diet during the first study period was qualitatively the same as that eaten before he entered the hospital and consisted of beans and cornmeal cakes. It would seem, therefore, that the half-lives of albumin observed initially were not drastically altered by the diet, and that the hypoalbuminemia initially observed in the children studied was attributable to some factor other than simply increased catabolism of albumin. With no loss of albumin in the urine, it may be concluded that the hypoalbuminemia was due primarily to decreased albumin synthesis.

The vascular fraction of the total exchangeable albumin in some of these children appeared to be somewhat smaller than that usually observed in normal children.² The urinary data suggest that this was not due to excessive albumin catabolism during the initial part of the study period in at least three of the children (H. T. J., S. S. F., and C. R. V.). In addition, the same iodoalbumin

preparation that gave low vascular : total exchangeable albumin ratios in some children gave normal ratios in others. Finally, a different iodoalbumin preparation in the second study period gave low ratios in the same children in whom low ratios were obtained in the first period. In one patient, P. B. G., the serum disappearance curve (Figure 2) does suggest that albumin catabolism was faster in the initial week of study than was observed later; unfortunately, urinary excretion data in this patient were not obtained and a second study was not done. It is interesting that in at least three patients, the fraction of total albumin present in the vascular system decreased significantly from the first study period to the second. This observation is in accord with that of Yuile, Lucas, Neubecker, and Whipple, who found that protein depletion in dogs was accompanied by a decrease in extravascular plasma protein greater than that of the vascular plasma protein (9).

The average albumin half-life and the lower limits of the observed range in these children were somewhat less than those usually found in normal children.² The reasons for this were not apparent. Those children with an unusually rapid turnover of albumin in the first study period showed a similarly rapid albumin turnover during the second study period a month later. Whether the decreased albumin half-life could be attributed to undisclosed infection (10), or to the fact that the children had not yet fully recovered, is not known.

It is noteworthy that the metabolic response of children to protein deprivation seems to be quite different from that observed in lower animals. In mice, decreased caloric and protein intake leads to decreased albumin synthesis, but this is partially compensated by a significant increase in the half-life of albumin, reflecting a decreased rate of catabolism (5). The children observed in this study did not seem to compensate for decreased albumin synthesis in this manner.

In the three patients with the atrophic or non-edematous form of protein malnutrition, initial levels of serum albumin were lower than in many of the children in the edematous state. As has been indicated by a number of investigators, the presence of edema in this condition is not dependent solely upon the serum concentration of albumin (11, 12).

² In normal children the vascular compartment contains about 35 to 50 per cent of the total albumin pool and the range of half-lives for iodinated albumin is about 9 to 17 days with an average of about 12 days, depending upon the preparation used.

SUMMARY

The metabolism of serum albumin was studied in 14 children with severe protein malnutrition, using I^{131} -labeled albumin as a tracer. The half-life of albumin in these children during the hypoalbuminemic period did not change when the serum albumin concentration rose to normal values. Hypoalbuminemia in these children with low protein intakes appears to be due primarily to a decreased rate of albumin synthesis.

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