The Metabolism of Serum Albumin in Man During Brief Starvation

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PROTEINS which are eaten, digested, and absorbed face only two alternatives: incorporation into tissue protein or catabolism to nitrogen, carbon, and sulfur residues. However, when plasma proteins are administered by vein, a third possibility exists: the proteins may circulate unaltered in the blood, lymph, and interstitial fluid for significant periods of time.[1,2] It is for this reason that a short-term positive nitrogen balance following parenteral administration of plasma proteins does not prove their incorporation into tissue proteins. Studies from this laboratory[3] indicated that the magnitude of this metabolic "dead space" following albumin administration was considerable. The present investigation was designed to secure information as to whether the catabolism of albumin increased under conditions promoting the catabolism of tissue protein in general. Starvation was employed, since it is a potent stimulus to the breakdown of protein so that glucose may be made available.

Experiment: The experiment was planned to compare the metabolism of amino acids and of albumin under similar circumstances. The volunteer subject was a healthy 23-year-old medical student, 6 feet, 3 inches tall and weighing 87 kg. Except for the test protein materials the subject took no nourishment of any kind during the study; drinking water was not limited. A multivitamin capsule and 4 g of sodium chloride were given daily. Activity was restricted, in part by weakness.

The first portion of the experiment consisted of three periods:

(1) Fast, four days.

(2) Daily administration of 25 g of amino acid nitrogen* given intravenously in two divided doses—two days.

(3) Fast—three days.

A month was then allowed to elapse for the subject to regain his normal nutritional state. During this month, other experiments in albumin metabolism[3] were carried out in the course of which subjects developed congestive failure with a week's time from receiving 75 g intravenous albumin daily. It was clearly unsafe to administer the isonitrogenous dose of 150 g a day (25 g of albumin nitrogen) projected for the second portion of the experiment; for this reason, the two portions of the study are comparable but not identical. The second part of the experiment therefore consisted of the following three periods:

(1) Fast—four days.

(2) Daily administration of 12 g of albumin nitrogen† given intravenously in two divided doses—four days.

(3) Fast—three days.

Studies: The subject was weighed daily. 24-hour urine collections were made. These were analyzed for total nitrogen, urea, potassium, and inorganic sulfate as in a previous study.[3] A qualitative test was done for acetonuria. Determination of the respiratory quotient was made on several occasions, using 20-minute gas collection periods.

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* A lyophilized supplemented acid hydrolysate of casein containing alpha amino acid nitrogen as 75 per cent of the total nitrogen. A more extensive description of this material is provided by Hoffman *et al.*[4] Our supply was provided by the manufacturer, The Interchemical Corporation, of Union, New Jersey.

† 75 g of human serum albumin with 3 g DL-acetyltryptophan, supplied by the American National Red Cross.

RESULTS

The experiment progressed without untoward events except for the sixth day of the albumin study, when the subject developed a headache and temperature of 101° F. Since the effects of fever and starvation upon protein breakdown should be similar, this unforeseen complication should not interfere with the interpretation of the study. Acetone was consistently found in the urine after the first day, indicating that the subject was under an adequate stress to encourage protein breakdown and the formation of endogenous glucose. Respiratory quotient determinations varied from 0.69 to 0.72; there was no increase on the second day of amino acid administration.

Figure 1 and Table I permit a comparison of the amino acid and the albumin experiments. After amino acid administration urinary nitrogen doubled. In view of the output of urea, only a small fraction of this could have represented aminoaciduria. After albumin administration, in contrast, urinary nitrogen did not increase. The retention of sulfur during the albumin experiment in contrast to the amino acid study confirms the nitrogen balance trends. It is apparent that even under the stress of starvation albumin is not readily catabolized.

It is of interest to infer the proportion of administered albumin that was catabolized during the study. Because albumin contains 2 per cent sulfur[5] while most body and dietary protein have only 1 per cent, the extra associated sulfur constitutes a natural tag, the ratio of nitrogen to sulfur in the urine indicating the proportion of these elements derived from albumin. Urea and inorganic sulfate have a comparable status in the urine, each reflecting exogenous metabolism to a greater extent than the continuing metabolism in protein turnover,[6] and it is the ratio of these elements that is given. The ratios suggest that although nitrogen excretion following albumin failed to increase, a large fraction of the urinary nitrogen present both during and after albumin administration did arise from albumin rather than from other body tissues.

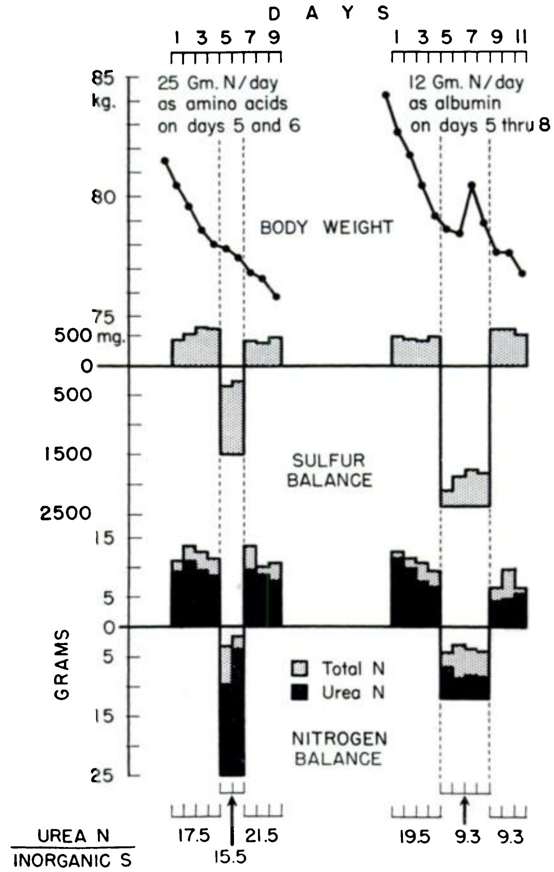

Fig. 1. In the portions of the graph showing sulfur and nitrogen balance, the method of Albright is employed; intake is indicated by a line below the baseline and output is charted upward from the intake line.

DISCUSSION

In normal subjects with normal amounts of circulating albumin, studies with I^{131}-labeled albumin have indicated a half-life of 10 days for this protein.[7] Similar studies with N^{15}-labeled albumin indicated a half-life of not more than 20 days.[8] The question for investigation has been whether excessive amounts of albumin will undergo more rapid catabolism under the influence of stress.

After phlorhizinizing dogs, Howland and Hawkins[9] administered plasma orally and intravenously. Although oral plasma was followed by increases in urinary nitrogen and glucose that made evident the availability of ingested plasma for gluconeogenesis, parenteral infusion was followed by no increases. It was concluded that even under marked carbohydrate deprivation the plasma proteins were

TABLE I

Comparison of Amino Acid and Albumin Experiments

Day	Intake		Urinary excretion				Ratio, urea nitrogen/ SO_4 sulfur, for period
	Nitrogen g	Sulfur mg	Total nitrogen g	Urea nitrogen g	Potassium meq	SO_4 sulfur mg	
Amino acid study							
1	—	—	11.4	9.1	65	430	
2	—	—	13.2	11.0	31	520	
3	—	—	11.6	9.6	39	590	
4	—	—	11.2	8.4	45	590	17.5
5	24.1	1,440	21.0	18.3	28	1,160	
6	25.4	1,520	23.7	21.2	15	1,230	15.5
7	—	—	13.3	9.7	6	400	
8	—	—	10.0	8.0	7	360	
9	—	—	10.5	7.4	15	440	21.5
Albumin study							
1	—	—	12.4	11.5	75	460	
2	—	—	11.2	9.4	32	460	
3	—	—	10.8	7.5	29	400	
4	—	—	9.4	6.6	35	310	19.5
5	12.2	1,500	7.7	5.5	24	300	
6	12.2	1,500	8.6	3.6	48	450	
7	12.2	1,500	7.7	3.9	25	590	
8	12.2	1,500	7.3	3.8	13	540	9.3
9	—	—	7.8	4.4	8	550	
10	—	—	9.2	4.7	5	560	
11	—	—	7.9	5.5	6	500	9.3

not available for degradation. The patients whom Fletcher *et al.*[10] infused with human serum albumin under the stress of a recent major operation also failed to increase their urinary nitrogen, unlike similar patients given protein hydrolysates.[11]

The present study indicates that even in starvation albumin continues to be slowly metabolized. It seems reasonable to conclude that either the system for the catabolism of excess albumin is limited, or it is insensitive to the methods of provoking it that have been attempted. It is interesting to speculate upon the proper interpretation of the precipitous drop in the urea nitrogen/inorganic sulfate sulfur ratio following albumin administration. Although it probably represents albumin catabolism, it might also represent rejection of sulfur-containing amino acids by the tissues incident to transformation of albumin into the proper composition of cellular proteins. Tagging of the nitrogen would be necessary to obtain a conclusive answer.

SUMMARY AND CONCLUSIONS

Evidence of protein and amino acid catabolism was sought for in a starving healthy subject who received intravenously human serum albumin in one experiment and an amino acid mixture in another. Following administration of the amino acid mixtuıe the urine contained almost equivalent amounts of nitrogen and sulfur. In contrast, although some catabolism of albumin occurred, the majority of the albumin was retained by the subject. This finding indicates that even under the stimulus to protein catabolism posed by starvation, the rate of albumin breakdown is relatively slow.

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