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**STUDIES WITH IODINE-TAGGED
 ALBUMIN IN CIRRHOTIC PATIENTS***

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Patients with cirrhosis of the liver show alterations in many metabolic functions. In those patients who develop ascites one of the chief factors is believed to be the lowered concentration of serum albumin, since the albumin fraction is known to be the one which exerts the greatest intravascular osmotic attraction.

Many investigators have demonstrated a correlation between the presence of ascites and a lowered serum albumin level in cirrhotic patients.^{1,2} It has been suggested that the prognosis in patients with cirrhosis is directly related to levels of albumin and other protein fractions.^{1,3,4} Several observers have administered large amounts of human serum albumin up to 1,000 grams over a six-month period to patients with portal cirrhosis and ascites, and have studied the long-range effects.^{5,6,7} None of these investigations allowed observations on the rate at which protein molecules are utilized or move about.

The body proteins are in a dynamic state.⁸ Urinary nitrogen determinations furnish an index to the day-to-day utilization of dietary protein. Serum protein levels, when followed over long periods, may serve as an indication of the over all protein metabolism. These studies reflect the

balance between the synthesis and breakdown of protein. It now appears that within the total protein content of the body there is an exchange between the cellular protein, that being synthesized, utilized and in the circulation. The plasma protein represents the labile exchange medium of the body's total protein pool.

Extensive experimental study has indicated that the liver is the chief source for the formation of plasma proteins.^{9,10,11} This deduction has been supported by clinical studies in patients with liver disease.¹² Evidence has been produced to show that, in dogs, the mass of protein in the extravascular, extracellular fluid is approximately equal to the proteins in circulation.¹³ In human patients with cirrhosis of the liver clinical recovery may be correlated with the ability to maintain a normal total circulating albumin.¹⁴ The total circulating albumin seems to be a reflection of the body's total store of labile albumin.

Human serum albumin may be "tagged" with radioactive iodine (I^{131}) and injected into the body in very small amounts to serve as a tracer.¹⁵ This permits dilution of negligible, yet detectable quantities of albumin with the body pool without altering homeostasis, and is a method by which the metabolism of native albumin can be measured and labile stores estimated.

MATERIALS AND METHODS

In the present study, a tracer dose of tagged human serum albumin* was injected into 11 control patients† without liver disease (Group 1), 7 cirrhotic patients (Group 2) without ascites, and 5 patients with portal cirrhosis and ascites (Group 3) (Table 1). Diuretics and parenteral fluids were not administered before or during the study period. Patients with ascites were studied before paracentesis.

The degree of radioactivity in the serum was determined at 24, 48 and 72 hours after injection of the tagged albumin.

The plasma volume was determined from the degree of radioactivity after 10 to 15 minutes was allowed for intravascular mixing. This

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period has been found to be sufficient for equilibration within the vascular compartment.¹⁶ The serum albumin concentration was measured by a standard chemical method (Kjeldahl). The total circulating albumin was calculated from the plasma volume and the serum albumin level.

In a previous study in human patients it was found that significant radioactivity without albuminuria was detectable within three hours following the intravenous injection of tagged albumin.¹⁶ This finding was interpreted as evidence that demonstrable catabolism of the injected albumin molecule had occurred. In order to use the concentration of tagged albumin in the serum as an index to the rate of metabolism of albumin, it was necessary to allow tagged molecules to reach a state of equilibrium with the body pool. It was found that a period of 24 to 48 hours was required for equilibration between the serum and the ascitic fluid in the patients with cirrhosis and ascites. The decrease in the serum level of tagged albumin between the 48 and 72 hour determinations was therefore used as an index to the rate of metabolism.

RESULTS (Table 2)

There was no significant difference in the mean plasma volumes of the three groups.

The serum albumin concentration in both groups of cirrhotic patients was significantly re-

duced as compared with the controls. The albumin level in the group with ascites was also significantly lower than that in the group of cirrhotic patients without ascites.

In the patients with cirrhosis and ascites the total circulating albumin was significantly less than the values found in cirrhotic patients without ascites. In Groups 1 and 2 the mean values for circulating albumin were comparable.

During the first 48 hours the rate of disappearance of the tagged albumin from the vascular compartment was similar in the three groups. At 48 to 72 hours, however, the rate of disappearance in the patients with cirrhosis and ascites (Group 3) was significantly less than that in the other two groups. A typical curve from each group is seen in Fig. 1.

COMMENT

The reduced rate of disappearance of the injected tagged albumin from the vascular compartment in the patients with portal cirrhosis and ascites is interpreted as indicating a slower rate of albumin metabolism in these patients.

The reduction in the serum albumin concentration of cirrhotic patients confirms the observations of other investigators.^{17 18} Of further significance is the decrease in the serum albumin

CLINICAL DATA

Group	No. of Pts.	No. of Det.	Males	Females	Age	Follow up
I Controls	11	11	10	1	21-44	All living and well.
II. Cirrhosis without Ascites	7	8	4	3	23-56	One dead with hemorrhage; others living and improved.
III. Cirrhosis with Ascites	5	6	4	1	35-69	4 dead 2-4 weeks after study. One unknown.

TABLE 1

TYOR AND CAYER: CIRRHOTIC PATIENTS

level of patients with cirrhosis and ascites, as compared with the cirrhotic patients who did not have ascites.

The data also indicate that those individuals with cirrhosis who show no evidence of ascites have an essentially normal total circulating al-

COMPARISON OF RESULTS

	Plasma Volume	Serum Albumin Concentration	Total Circulating Albumin	Albumin Metabolism
Controls				
Cirrhotics $\bar{\text{A}}$ Ascites	↔	↓	↔	↔
Cirrhotics $\bar{\text{C}}$ Ascites	↔	↓	↓	↓
Cirrhotics $\bar{\text{S}}$ Ascites				
Cirrhotics $\bar{\text{C}}$ Ascites	↔	↓	↓	↓

↔ Similar Values
 ↓ Significant Reduction

TABLE 2

Rate of Disappearance of I¹³¹ Albumin from the Vascular Compartment
 Illustrative Cases

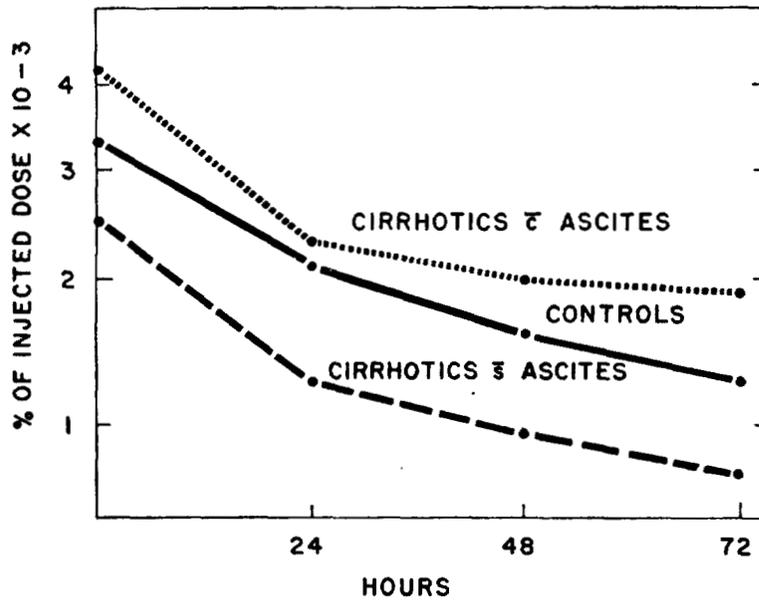


FIG. 1

bumin. In the patients with cirrhosis and ascites, however, this value was significantly reduced indicating depletion of albumin stores.

During the 72 hours in which the patients were studied, there was no detectable alteration in body homeostasis. The reduction in the serum albumin concentration, the total circulating albumin, and the rate of albumin metabolism in the patients with ascites would suggest a decrease in the synthesis of albumin.

The data presented are consistent with the concept of a labile protein reserve, which has been depleted in patients with portal cirrhosis and ascites. It is felt that the reason for the depletion of this store is a reduction in the rate of albumin synthesis. When the labile stores of protein are depleted, the homeostatic mechanisms regulating the distribution of body fluids are altered, and ascites develops. Our data suggest that the defect in albumin metabolism is of primary importance in the pathogenesis of ascites, although factors such as portal hypertension, alterations in electrolyte metabolism and the possible influences of endocrines and lymphatics are significant and contributory.

The patients with ascites had a uniformly poor prognosis. Four died within six weeks after the study. The lower rate of albumin metabolism in ascitic patients, as compared to that of cirrhotic patients without ascites would appear to indicate that albumin metabolism proceeds at a constant, relatively normal rate, despite impairment of other less vital liver functions, until the terminal stages of liver disease.

SUMMARY

Following the injection of tracer amounts of albumin tagged with I^{131} , the plasma volume, serum albumin concentration, total circulating albumin, and rate of disappearance of albumin from the vascular compartment (albumin metabolism) were determined in patients without liver disease and in cirrhotic patients with and without ascites.

The serum albumin concentration of cirrhotic patients, with and without ascites, is significantly reduced.

In patients with cirrhosis and ascites the levels of serum albumin and total circulating albumin, as well as the rate of albumin metabolism were significantly less than those of patients without liver disease or cirrhotic patients without ascites.

These data demonstrate that depletion of labile albumin stores can be correlated with the presence of ascites, and suggest that albumin metabolism proceeds at a constant rate and is demonstrably altered only in the terminal stages of liver disease.

REFERENCES

1. Post, J.; and Patek, A. J., Jr.: Serum Proteins in Cirrhosis of the Liver: Relation to Prognosis and Formation of Ascites. *Arch. Int. Med.*, **69**:67, 1942.
2. Myers, W. K.; and Keefer, C. S.: Relation of Plasma Proteins to Ascites and Edema in Cirrhosis of the Liver. *Arch. Int. Med.*, **55**:349, 1935.
3. Foley, E. F.; Keeton, R. W.; Kendrick, A. B.; and Darling, D.: Alterations of Serum Proteins as an Index of Hepatic Failure. *Arch. Int. Med.*, **60**:64, 1937.
4. Brinkhous, K. M.: Plasma Prothrombin; Vitamin K. *Medicine*, **19**:329, 1940.
5. Kunkel, H. G.; Labby, D. H.; Ahrens, E. H., Jr.; Shank, R. E.; and Hoagland, C. L.: The Use of Concentrated Human Serum Albumin in the Treatment of Cirrhosis of the Liver. *J. Clin. Invest.*, **27**:305, 1948.
6. Patek, A. J., Jr.; Mankin, H.; Colcher, H.; Lowell, A.; and Earle, D. P., Jr.: The Effects of Intravenous Injection of Concentrated Human Serum Albumin upon Blood Plasma, Ascites and Renal Function in Three Patients with Cirrhosis of the Liver. *J. Clin. Invest.*, **27**:135, 1948.
7. Thorn, G. W.; Armstrong, S. H., Jr.; and Davenport, V. D.: Chemical, Clinical and Immunological Studies on the Products of Human Plasma Fractionation. The Use of Salt-Poor Concentrated Human Serum Albumin Solution in the Treatment of Hepatic Cirrhosis. *J. Clin. Invest.*, **25**:304, 1946.
8. Madden, S. C.; and Whipple, G. H.: Plasma Proteins: Their Source, Production and Utilization. *Physiol. Rev.*, **20**:194, 1940.
9. Knutti, R. E.; Erickson, C. C.; Madden, S. C.; Reckers, P. E.; and Whipple, G. H.: Liver Function and Blood Plasma Protein Formation. *J. Exper. Med.*, **65**:455, 1937.
10. Whipple, G. H.; Robschert-Robbins, F. S.; and Hawkins, W. B.: Eck Fistula Liver Subnormal in Producing Hemoglobin and Plasma Proteins on Diets Rich in Liver and Iron. *J. Exper. Med.*, **81**:171, 1945.
11. Drury, D. R.; and McMaster, P. D.: The Liver as a Source of Fibrinogen. *J. Exper. Med.*, **50**:569, 1929.
12. Post, J.; and Patek, A. J., Jr.: Serum Proteins in Relation to Liver Disorders. *Bull. N. Y. Acad. Med.*, **19**:815, 1943.
13. Yuile, C. L.; Lamson, B. G.; Miller, C. J.; and Whipple, G. H.: Conversion of Plasma Protein to Tissue Protein without Evidence of Protein Breakdown. Results of Giving Plasma Protein Labeled with Carbon-14 Parenterally to Dogs. *J. Exper. Med.*, **93**:539, 1951.
14. Hiller, G. I.; Huffman, E. R.; and Levey, S.: Studies in Cirrhosis of the Liver. I. Relationship Between Plasma Volume, Plasma Protein Concentrations and Total Circulating Proteins. *J. Clin. Invest.*, **28**:322, 1949.
15. Fine, J.; and Seligman, A. M.: Traumatic Shock. VII. A Study of the Problem of the "Lost Plasma" in Hemorrhagic, Tourniquet, and Burn Shock by the Use of Radioactive Iodo-Plasma Protein. *J. Clin. Invest.*, **23**:720, 1944.
16. Tyor, M. P.; Aikawa, J. K.; and Cayer, D.: The Plasma Disappearance and Urinary Excretion Rate of I^{131} Albumin in Patients with Cirrhosis. Unpublished Data.
17. Cayer, D.; and Nabors, G. C.: A Clinical Evaluation of the Total Blood Proteins and the Albumin and Globulin Fractions in Hospitalized Patients. An Analysis of Data in 300 Cases. *South. Med. Jour.*, **40**:744, 1947.
18. Tumen, H.; and Bockus, H. L.: Clinical Significance of Serum Proteins in Hepatic Diseases Compared with other Liver Function Tests. *Am. J. M. Sc.*, **103**:788, 1937.