SERUM ALBUMIN TURNOVER IN LAENNEC'S CIRRHOSIS AS MEASURED BY I^{131}-TAGGED ALBUMIN [1]

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Many investigations of Laennec's cirrhosis of the liver have dealt with the low serum albumin concentration and its physiological significance. Information on the dynamics of albumin formation in this disease should contribute to the understanding of the metabolic derangements. In the present work the turnover rate of serum albumin was measured by following the disappearance from the circulation of albumin labelled with radioiodine (1).

MATERIAL AND METHODS

Case material. The cases selected were considered clinically typical of Laennec's cirrhosis. Most of them had been under observation for more than a year, and histologic confirmation had been obtained by laparotomy or needle biopsy in several instances. The patients were studied during hospitalization or during follow-up as outpatients.

At the time of study the clinical status ranged from asymptomatic to severely ill. The patients were classified in gross categories as follows:

Ambulatory, asymptomatic: J. D., F. B.

Ambulatory, with mildly to severely limited activity: S. E., E. L., C. S., J. C., F. S.

Severely ill, hospitalized: E. A., J. M., C. M. (J. M. had cirrhosis, chronic alcoholism, and Wernicke's encephalopathy.)

In addition to cases of Laennec's cirrhosis, other individuals with low serum albumin were studied. In two instances hypoalbuminemia was associated with liver diseases other than cirrhosis. R. O. had severe macrocytic anemia and a fatty liver associated with alcoholism. The enlarged liver regressed markedly in size on rest and dietary management prior to the time of study. R. W. had typical homologous serum hepatitis of moderate severity.

Two other patients had hypoalbuminemia without significant proteinuria and without evidence of hepatic disorder. M. G. had coronary atherosclerosis with angina pectoris, previous myocardial infarction, and rheumatic heart disease. He was in mild congestive heart failure at the time of study. J. M. had severe pulmonary emphysema, hypertensive cardiovascular disease and rheumatic heart disease, and pyelonephritis related to benign prostatic hypertrophy. He was in severe congestive heart failure at the time of study. The particular clinical pictures these two patients presented were not a subject of investigation as such. They were intended as "hospital controls" for possible non-specific effects of chronic illness.

A series of 21 male medical student volunteers (1) served as normal controls.

None of the subjects had significant proteinuria.

Technical methods. The details of the use of I^{131}-tagged albumin and tests performed to establish its similarity to native protein have been described separately (1). Ultracentrifugal analyses,[3] immunochemical tests, and studies of the rate of metabolism in rabbits were carried out. The most sensitive criterion that the labelled albumin was not significantly changed from the starting material was satisfactory homogeneity on ultracentrifugal analysis. Iodo-albumin showing significant alteration from the native protein was discarded.

Determinations of serum albumin concentration were carried out by the quantitative precipitin technique by Gitlin's method (2). The values obtained were within 10% of the results of electrophoretic analyses.[4] Howe sodium sulfate fractionations were done as a preliminary approximation.

Radioactive assays were performed in duplicate on 1 ml. samples of plasma dried at room temperature. To correct for radioactive decay, each subject's plasma samples and appropriately diluted aliquots of the injected iodo-albumin were counted within a few hours at the end of the study.

Radiation dosage. The routine administration of 20 microcuries of I^{131} as iodo-albumin approximated a total dose of 0.22 rep in a 70 kg. man. The calculation (1) from the equations of Marinelli, Quimby, and Hine (3) was based on the conservative assumptions of no excretion and localization of radioactivity in the extracellular fluid.

Plan of studies. The subjects' diets were adequate in protein and calories, usually 70 grams of protein and 2,500 calories. Body weight was relatively stable throughout. In patients with ascites, restriction of sodium intake re-

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tarded fluid accumulation so that gain in weight during the two weeks of study was often negligible. With one exception, weight gain did not exceed 2 kg. E. A., who had been subjected to abdominal paracentesis four days prior to study with loss of 3.6 kg., regained this weight during the two weeks of study. Mercurial diuretics were omitted and paracenteses were not done during the studies, because shifts in body fluids or significant protein losses would have altered the steady state conditions.

Determinations of serum albumin concentration at the beginning and end of the two week studies showed no significant changes (mean difference 0.2 gram %). The subjects were therefore considered to be in a steady state with respect to serum albumin concentration. Therefore the rates of albumin synthesis and degradation were assumed to be equal.

Lugol's solution (15 drops daily) was given two days prior to and during the studies routinely to prevent thyroid uptake and promote excretion of I^{131} liberated on degradation of the iodo-albumin.

After intravenous injection of 1 to 10 mg. of labelled protein, blood samples were taken in heparinized syringes, usually on alternate days, for approximately two weeks.

Different lots of I^{131}-tagged albumin were tested for uniformity. As a further precaution, parallel groups of patients and normals were studied simultaneously to exclude artificial differences due to slight variation in iodo-albumin lots.

RESULTS AND INTERPRETATION

The disappearance curves of injected iodo-albumin were obtained from assays of plasma radioactivity. When plotted semi-logarithmically the points obtained after the second day approximated a straight line (Figure 1). The slope of the line was interpreted as the rate of replacement of tagged by untagged albumin, hence the turnover rate.

The 24 hour point invariably and the 48 hour point usually fell above the line drawn through the remaining points. The points above the line signified that distribution of tagged protein in the extravascular albumin was not yet complete at that time.

The half-time of disappearance of labelled albumin was obtained graphically, and the turnover rate was computed. The "exchangeable albumin pool" was calculated by the isotope dilution principle. The product of this quantity and the turnover rate yielded the turnover of albumin in grams per day. Calculations are reported separately (1).

The 11 cases of Laennec's cirrhosis were compared with the 21 normal controls (Table I). The mean half-time in the cirrhosis group was

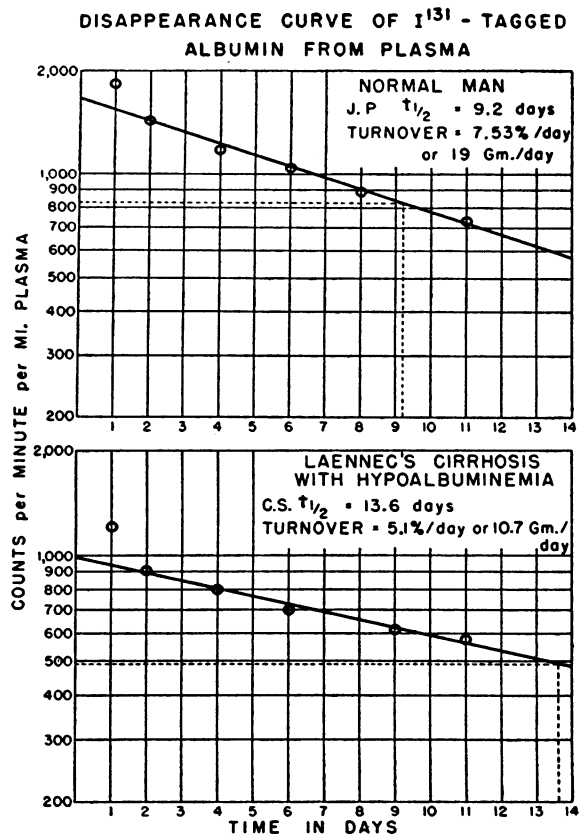

FIG. 1. SEMI-LOGARITHMIC PLOT OF PLASMA RADIOACTIVITY AFTER INTRAVENOUS INJECTION OF I^{131}-TAGGED ALBUMIN

The half-time of albumin turnover ($t_{1/2}$) is obtained graphically as shown by the horizontal and vertical dotted lines. The turnover rate may be computed from the half-time or obtained graphically from the slope of the disappearance curve.

12.9 days as compared with the shorter normal mean half-time of 10.5 days. The mean albumin turnover rate was slower in the cirrhosis group: 5.49% per day as compared to 6.7% per day in the normals; 11.9 grams per day compared to 17.2 grams per day; and 11.9 grams per 1.73 m^2 (surface area) per day compared to 15.4 grams per 1.73 m^2 per day. The differences between the above means were highly statistically significant ($P < 0.01$ by Fisher's "t" test). There was some overlap between the two groups. This may be attributed in part to the inclusion of mild and asymptomatic cases.

The differences appear more pronounced in the patients with very low serum albumin concentrations. The last four cases of cirrhosis listed in

TABLE I

Albumin turnover data in Laennec's cirrhosis compared with other pathologic states and normal mean values

	Subject	Age	Sex	Ascites	Wt. (*kg.*)	Surface area (m^2)	Serum albumin (*grams %*)	Exchangeable albumin pool (*grams*)	Albumin/kg. (*body wt.*)	Albumin/1.73 m^2 (*surface area*)	$t_{\frac{1}{2}}$ (*half-time in days*)	Albumin turnover rate			
												%/day	Grams/day	Grams/kg./day	Grams/1.73 m^2/day
11 cases of Laennec's cirrhosis	J. D.	72	♂	0	69.6	1.83	3.8	221	3.18	209	11.6	5.98	13.2	0.190	12.5
	S. E.	63	♂	0	81.4	1.91	3.5	266	3.27	241	13.1	5.30	14.1	0.173	12.8
	E. L.	54	♀	+	59.1	1.63	3.5	220	3.73	234	10.2	6.80	15.0	0.254	15.9
	F. B.	72	♂	0	64.0	1.77	3.4	178	2.78	174	9.6	7.22	12.9	0.201	12.6
	J. S.	51	♂	0	56.0	1.63	3.4	214	3.82	227	15.0	4.62	9.9	0.176	10.5
	J. C.	53	♀	+	48.2	1.43	3.1	199	4.13	241	14.0	4.95	9.9	0.204	11.9
	F. S.	35	♂	+	89.5	1.97	3.0	378	4.22	332	13.3	5.21	19.7	0.220	17.3
	C. S.	57	♂	+	84.2	1.94	2.5	210	2.50	187	13.6	5.10	10.7	0.127	9.5
	J. M.	50	♂	0	57.2	1.69	2.5	203	3.55	208	16.3	4.25	8.6	0.151	8.8
	E. A.	43	♂	+	64.8	1.72	2.0	158	2.44	159	13.4	5.17	8.2	0.126	8.2
	C. M.	58	♀	+	47.3	1.46	1.9	154	3.26	183	12.0	5.77	8.9	0.188	10.6
	Mean						3.0	218	3.35	218	12.9	5.49	11.9	0.183	11.9
	Standard deviation							62	0.61	47	2.0	0.89	3.5	0.039	2.8
	Standard error of mean							19	0.18	14	0.6	0.27	1.1	0.012	0.8
21 Normals	Mean						4.4	259	3.54	232	10.5	6.70	17.2	0.233	15.4
	Standard deviation							40	0.61	34	1.5	0.93	2.7	0.032	2.0
	Standard error of mean							9	0.13	7.5	0.3	0.02	0.6	0.007	0.4
Hepatitis	R. W.	67	♀	0	52.0	1.40	3.4	121	2.33	150	7.4	9.37	11.3	0.218	14.1
Fatty liver	R. O.	60	♀	0	54.0	1.61	2.5	141	2.61	151	9.0	7.70	10.9	0.201	11.6
Other low albumin	M. G.	55	♂	0	52.0	1.56	3.5	200	3.85	222	9.1	7.62	15.2	0.293	16.9
	J. M.	70	♂	?+	63.0	1.73	2.9	151	2.40	151	6.2	11.2	16.9	0.269	16.9

Table I, C. S., J. M., E. A., and C. M., had serum albumin concentrations of 2.5 grams % or less, the lowest in the group. The albumin turnover rates of these four patients ranged from 8.2 to 10.6 grams per 1.73 m^2 per day in contrast to the normal mean of 15.4 grams per 1.73 m^2 per day. The curves of paired subjects shown in Figure 1 were selected to illustrate this difference.

The expressions in terms of body weight (Table I) were possibly distorted considerably by edema and ascitic fluid. The turnover rates in grams per 1.73 m^2 surface area per day were considered less subject to this distortion.

The exchangeable albumin pool in the cirrhosis group was not markedly below the normal, except for the diminution exhibited by the cases with pronounced hypoalbuminemia.

The data on F. S. indicated an abnormally large exchangeable albumin pool, greater than that obtained in any of the normals. Although the turnover rate of 5.21% per day was slow, the product of this figure and the large exchangeable albumin pool gave a turnover in grams per day in the high normal range. No explanation for the divergent data in this case was evident.

The other two cases of hepatic disease, R. W. and R. O., with homologous serum hepatitis and fatty liver, respectively, exhibited a different picture from the cirrhosis group. The exchangeable albumin pool was quite low, but the percentage turnover rate was rapid (faster than normal in R. W.). The turnover in grams of albumin per day was low due to the small albumin pool rather than because of diminished daily fractional turnover, as in cirrhosis.

The cases of cardiac failure, M. G. and J. M., exhibited diminution of the exchangeable albumin pool, but rapid percentage turnover rate (faster than normal in J. M.) resulting in normal turnover in grams per day.

The cases other than the cirrhosis group were included for purposes of comparison rather than in the effort to study these conditions *per se*. The findings in the cases of cardiac failure were inter-

preted as evidence that non-specific effects of illness alone did not account for the observed differences between the cirrhosis group and the normals.

DISCUSSION

The finding of diminished albumin turnover rates in the cases of Laennec's cirrhosis is compatible with but does not prove the existing conceptions of impaired albumin synthesis in this disease. The studies dealt with subjects in a steady state with respect to serum albumin concentration, hence the findings constitute a description of this hypoalbuminemic state. The method and the assumptions involved (1) limit its applicability to such a steady state where albumin synthesis and degradation are equal. In the circumstance of constant hypoalbuminemia in cirrhosis it would appear that degradation of albumin is retarded in balance with diminished formation. The present data do not provide information on the pathogenesis of the hypoalbuminemic state or its remission. It would, however, be reasonable to assume that discrepancies between the rates of synthesis and degradation, which might be small in magnitude, result in the alterations of serum albumin concentration observed during the course of cirrhosis. Further information on the kinetics of such changes would be desirable. Future work will be required to evaluate the possible role of a large accumulation of ascitic fluid albumin in retarding the turnover rate.

In a given instance of hypoalbuminemia, there is no reason to suspect *a priori* that the findings of a turnover study would necessarily conform to the present results in Laennec's cirrhosis. Indeed, it is theoretically possible to have a high or low concentration of serum albumin with a rapid or slow turnover, provided only that the rates of formation and degradation are equal. The present study illustrates instances of hypoalbuminemia with normal and faster than normal turnover rates in the cases other than the cirrhosis group.

The relatively minor diminution of exchangeable albumin pool in the cases of cirrhosis studied was of interest; possible error in this estimation due to incomplete distribution of iodo-albumin would give falsely *low* values. The finding of unexpectedly high pools suggested that low serum albumin concentration was offset by protein in the expanded interstitial fluid space, especially in ascitic fluid. In the paired studies illustrated in Figure 1 the plasma radioactivity extrapolated to zero time was markedly lower in the cirrhosis case, indicating a larger volume of distribution. (The albumin specific activity in this patient with hypoalbuminemia was somewhat higher than that of the normal.) If the possibility of marked hypervolemia be rejected, it follows that the patient with cirrhosis had an increased proportion of the albumin pool located in extravascular sites. This inference is compatible with existing information on the proteins of ascitic fluid (4–8), but requires amplification by intra- and extravascular albumin estimations (1) and studies of the ascitic fluid.

As previously described (1) the plasma radioactivity fell at a relatively rapid rate during the first 24–48 hours, followed by a gradual exponential decay representing turnover. The initial phase was attributed to distribution of labelled protein in the exchangeable albumin pool. Although a complete curve of the distribution phase was not obtained in the cirrhosis group, the 24 hour and usually the 48 hour points were above the line through the remaining points. These points above the line served to delimit the maximum duration of the distribution phase, and did not differ significantly in the normal and cirrhosis groups. The presence of ascitic fluid did not therefore appear to delay equilibration of the tagged protein (9). Short-term disappearance curves concomitantly with studies of ascitic fluid radioactivity may be expected to yield further information on these matters.

SUMMARY

1. The serum albumin turnover rate of a group of 11 cases of Laennec's cirrhosis was studied by following the disappearance rate of intravenously administered I^{131}-tagged albumin.

2. The cases of cirrhosis exhibited a longer half-time and slower turnover rate than the normal controls.

3. In cases with serum albumin of 2.5 grams % or less, the deviations from normal were more pronounced.

4. The exchangeable albumin pool was not markedly below the normal, except in cases with pronounced hypoalbuminemia.

5. Examples of other diseases with hypoalbuminemia were studied and the findings did not coincide with the picture in Laennec's cirrhosis.

6. Possible implications of the albumin turnover data are discussed.

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