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Research Article

AN EVALUATION OF HUMAN SERUM ALBUMIN IN THE TREATMENT OF CIRRHOSIS OF THE LIVER[1, 2]

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INTRODUCTION

The recent development of normal human serum albumin for intravenous administration has led to its use in treating clinical states marked by hypoalbuminemia, including chronic liver disease (1–4). Previous work with this therapeutic agent has been confined to relatively short-term studies. The present study was undertaken to determine the effect of salt-poor human serum albumin on ascites and edema in chronic liver disease when administered in sufficient amounts to raise the serum albumin concentration and maintain it at or near normal over long periods of time. The results of such therapy attempted in 29 patients with cirrhosis of the liver are presented in this communication.

METHODS

Patients were selected who had marked evidence of hepatic cirrhosis by history, physical examination, and liver function tests, and who had ascites, edema, and hypoalbuminemia. In a few patients the diagnosis was confirmed by liver biopsy or at post-mortem examination. In most instances patients were chosen in whom there was no response to other forms of therapy. In the majority of cases, the need for repeated paracenteses was established before treatment was initiated. During the period of study no other therapeutic agents were given except for a nutritious diet which the patients were urged to eat. A few patients were given mercurial diuretics at infrequent intervals but with only a temporary effect on the course of their fluid retention. The salt-poor concentrated (25 per cent) human serum albumin was given intravenously, diluted with an equal volume of 5 or 10 per cent dextrose solution. Quantities of albumin necessary to raise the serum albumin concentration to between 3 and 4 grams per 100 cc. varied: usually from 50 to 100 grams daily were given over a five to ten day period. The majority of patients received 75 grams per injection and thereafter 75 grams once, 50 grams twice or 25 grams three times weekly. If marked improvement in ascites was not observed during the first ten days of treatment, maintenance injections were continued for from three weeks to eight months. In three patients the effect of a low sodium diet was studied during albumin therapy.

Abdominal paracentesis was performed as necessary and whenever possible the protein concentration was determined on the fluid obtained. The serum protein concentration and albumin and globulin fractions were determined at weekly intervals; total protein by micro-Kjeldahl analysis and albumin and globulin separation by Howe precipitation (5). Serum thymol turbidity (6) and serum bilirubin (7) were determined at weekly intervals. The percentage of bromsulphalein retention, 45 minutes following a 5 mgm. per kilogram dose, was determined at less frequent intervals. Most of the patients were weighed daily and frequent abdominal girth measurements were made. The latter were found to correlate well with weight gain and ascites formation.

RESULTS

Twenty-nine patients received albumin in varying amounts during periods of from four days' to eight months' duration. Table I shows the statistical results of the series. Twenty-five patients had both edema and ascites before therapy was begun and the remaining four had ascites alone. A history of heavy intake of alcoholic beverages was obtained in 25 cases, two admitted only a moderate alcoholic intake, while two denied drinking. In nine cases albumin administration had to be stopped because of untoward reactions, lack of cooperation, or untimely demise. Therefore, of

[1] The serum albumin used in this study was processed by the American National Red Cross from blood which it collected from voluntary donors. This is one of a series of investigations on serum albumin being carried out with material supplied by the American National Red Cross. As soon as sufficient data become available to justify final conclusions concerning its therapeutic value a full report to the medical profession on the use of serum albumin in medical practice will be published.

[2] This study was aided in part by a gift to Harvard University from the Abbott Laboratories, North Chicago, Illinois.

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TABLE I

Results of albumin administration to patients with cirrhosis of the liver

Patient	Total albumin given *grams*	Period of therapy	Paracenteses necessary*			Period of follow-up since therapy and end result
			Before therapy	During therapy	After therapy	
Immediate improvement						
S. P.	450	6 days	0	0	0	Free of ascites—11 months.
F. F.	375	5 days	0	0	0	Free of ascites—5 months.
S. H.	300	6 days	0	0	0	Died of bleeding varices 1 week after treatment.
J. G.	400	4 days	0	0	0	Recurrence of edema and ascites after 6 weeks. Died in coma 4 months later.
Slow improvement						
G. D.	1000	3 months	2(*16*)	0	0	Free of ascites—16 months.
P. B.	675	5 weeks	1	0	0	Free of ascites—10 months.
J. M.	1075	7 weeks	3(*17*)	1	0	Moderate ascites not requiring tap—8 months.†
A. D.	1500	6 weeks	1	0	0	Recurrence of edema after 6 weeks. Free of ascites—11 months.
H. H.	600	8 days	3(*6*)	0	–	Recurrence of edema and ascites after 6 weeks. Refractory to retreatment. Died of bleeding varices during therapy.†
Delayed improvement						
J. S.	1975	6 months	6(*15*)	4(*24*)	0	Free of ascites—6 months.
W. M.	3675	7½ months	4(*23*)	6(*29*)	0	Free of ascites—8 months.†
Improvement only with low sodium diet						
E. G.	2405	6 months	2(*28*)	3(*33*)	1	Died in coma 2 months later.
V. L.	1825	2 months	2(*14*)	1	–	Died of bleeding varices during therapy.
C. M.	4000	7 months	2(*15*)	9(*28*)	–	Still reforming ascites—under treatment.
Failure						
M. C.	1750	3 months	2(*30*)	7(*15*)	4(*19*)	Ascites increased with therapy. Died in coma 3 months later.
F. G.	350	5 days	3(*30*)	0	0	No apparent early benefit. Died in coma 2½ months later.
H. G.	900	3 weeks	4(*34*)	1	–	No apparent benefit. Died of bleeding varices 6 weeks later.
N. C.	900	3 weeks	3(*16*)	2(*7*)	–	Died in coma during therapy.
R. A.	525	18 days	1	1	–	Died of epistaxis 48 hours after last albumin.
P. W.	2300	4½ months	1	6(*20*)	–	Died in coma during therapy.
Indeterminate						
C. F.	425	12 days	3(*33*)	1	–	Pyrogenic reaction—coma. Died in coma 8 days later.
J. C.	450	7 days	1	0	–	Died during treatment from diphtheria infection of abdominal skin.
H. K.	450	9 days	2(*15*)	0	–	Pleural fluid increased with therapy. Left against advice—no follow-up.
R. V.	400	26 days	0	0	0	Intestinal obstruction during therapy. Died of int. obs. 2 months later.
B. B.	375	5 days	0	0	0	Improvement possibly spontaneous. Free of ascites—9 months.
L. B.	150	2 days	4(*30*)	0	0	Pulmonary edema with therapy. Spontaneous diuresis. Free of ascites—7 months.
J. Q.	225	6 days	0	0	0	Diuresis before therapy begun. Died in coma 2 weeks later.
P. M.	150	2 days	0	0	–	Pulmonary edema with therapy. Died in cardiac failure 1 day later.
F. H.	300	12 days	0	0	0	Improvement possibly spontaneous. Free of ascites—2 months.

* Average interval (days) between paracenteses given in parenthesis.

† Sodium balance studies were done on these patients who received a low sodium diet for short periods of time.

the total number, 20 patients are considered to have had sufficient therapy and follow-up to determine the effect of treatment. Improvement was judged on the basis of diminution in ascites and edema and other signs of improvement clinically and by laboratory tests. There was often a discrepancy between the decrease in fluid retention and improvement in other manifestations of liver disease. In this study the change in ascites and edema was used as the prime criterion of improvement.

The results presented in Table I can be divided into four main types: (*1*) immediate improvement with diuresis seen within the first ten days of treatment; (*2*) slow improvement with fluid retention disappearing (diuresis taking place) during one to three months of therapy; (*3*) delayed improvement with relief of ascites and edema occurring over six and eight month periods; and (*4*) failure to improve. Three patients were treated with a low sodium diet in conjunction with the albumin and are therefore classed separately.

Prompt diuresis occurred in four patients with complete relief of ascites and edema (Table I). This took place during or immediately following the administration of from 300 to 450 grams of albumin. Weight loss began in each instance before a sustained rise in serum albumin concentration was detected. The course of one patient typical of the group is shown in Figure 1. It can be seen that weight loss began in this patient before the serum albumin concentration rose above

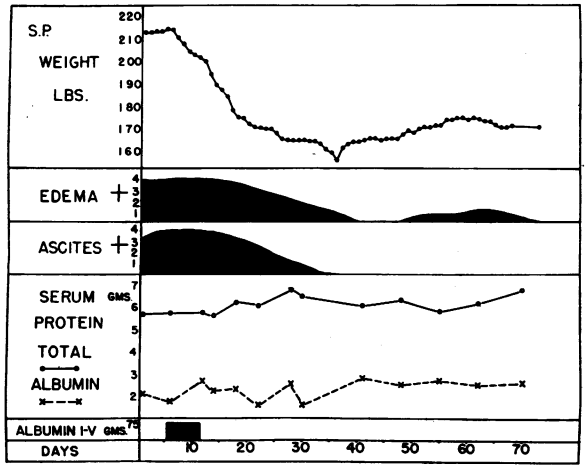

FIG. 1

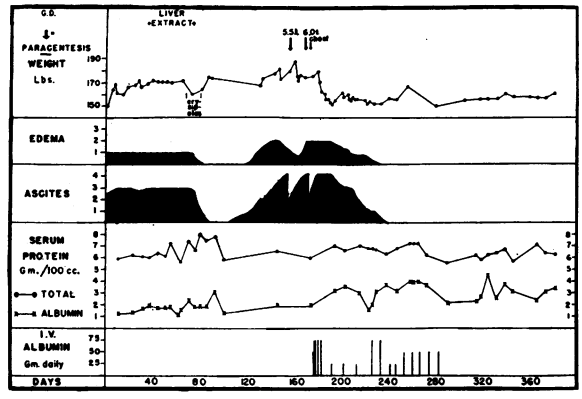

FIG. 2

3.0 grams per 100 cc. Edema and ascites recurred in one patient with this type of response six weeks after therapy was stopped. Improvement was apparently permanent in two others who have been followed for five and 11 months, respectively. The fourth patient had a fatal hemorrhage from esophageal varices one week after the last administration of albumin.

Definite improvement at a slower rate was seen in five patients after therapy had been continued for from eight days to three months (Table I). The response shown by this group is typified by the findings in one patient (G. D.) shown in Figure 2. Of these five patients, recurrence of ascites and edema took place in one (H. H.) approximately six weeks after the last injection of albumin. This patient was subsequently refractory to retreatment and died of hemorrhage from esophageal varices during therapy approximately five months after the initial albumin was given. A second patient (A. D.), although free of ascites for 11 months, noted a recurrence of peripheral edema six weeks after the cessation of albumin. Varicose veins in both lower extremities undoubtedly contribute to the edema in this patient. The improvement of the remaining three is maintained at eight, 10, and 16, months' follow-up examinations.

The two patients in whom disappearance of ascites and edema occurred only after prolonged treatment received albumin injections over periods of six and eight months, respectively (Table I). At the end of this time each had stopped reforming ascites in spite of having required numerous paracenteses before and during treatment.

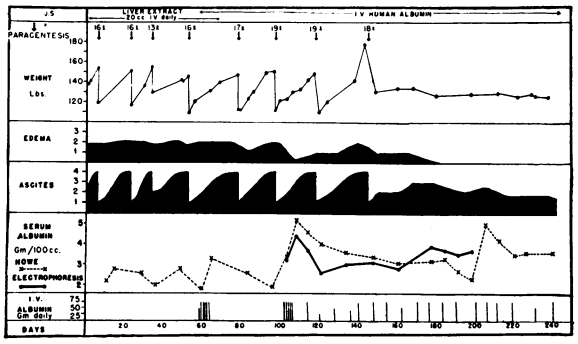

FIG. 3

One of these patients, J. S., seen six months after therapy was discontinued, showed no ascites in spite of the resumption of a large intake of alcohol, and the second has been seen eight months after cessation of albumin therapy, still free of ascites. The hospital course of the first of these is shown in Figure 3. It may be seen that electrophoretic analysis [5] of the serum albumin concentration was generally lower than that determined by the Howe separation. Thus, the level at which the serum albumin was actually maintained was considerably lower than was supposed. Moreover, reaccumulation of fluid ceased coincident with a rise in serum albumin concentration (electrophoretic analysis) which was not associated with an increase in albumin administered. Whether this rise resulted from cessation of ascites formation and removal, or from increased production of albumin by the liver, cannot be ascertained from these data. The ineffectiveness of albumin in the amount administered is demonstrated.

Because of rapidly reforming ascites in spite of albumin administration, three patients were treated with low sodium diets [6] while receiving maintenance injections of albumin (Table I). One of these was well controlled without paracentesis for two months while previously he had required paracentesis at two-week intervals. At the end of this period, five days after the last albumin administration, he bled from esophageal varices and expired. A second patient was followed for eight months, during which time only one paracentesis, three months after the diet was begun, was required. Previous to the low sodium regimen, in spite of albumin therapy, paracentesis had been necessary twice a month. Figure 4 shows part of the course of the latter patient. The third patient, now under treatment for seven months, continues to reform ascites but at a considerably reduced rate while receiving a diet restricted in sodium. The importance of sodium in cirrhosis has been the subject of a separate investigation (8).

Despite continued therapy with albumin for from five days to four months, six of the 20 patients in whom the effect of albumin could be evaluated must be considered failures. During the period of treatment the attainment of significantly increased serum albumin concentrations did not improve ascites although edema of the lower extremities was decreased. The end results and reasons for cessation of therapy in this group of failures are shown in Table I. Reformation of ascites was accentuated in one patient by albumin administration, as shown in Figure 5. None of this group is still living.

An indeterminate group also included in Table I has been so classified because treatment could not be continued or the follow-up was insufficient to enable judgment of the result. None of these patients is now receiving albumin. Two may be considered to have received some benefit but other factors cannot be definitely ruled out. One patient, B. B., began to form ascites while recovering from jaundice after a prolonged bout of drinking. During the five-day period when albumin was given, weight loss occurred but this may have been

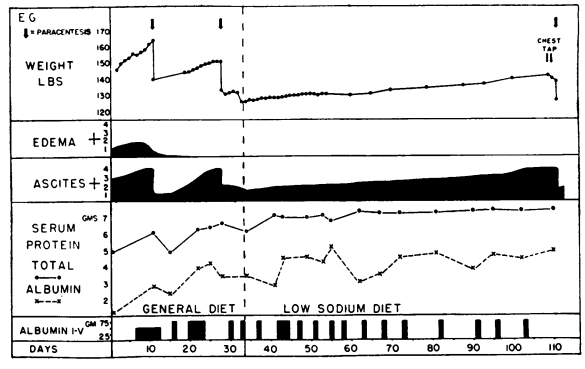

FIG. 4

[5] Per cent of the total serum protein (Kjeldahl) appearing as albumin in the Tiselius pattern. The authors express their appreciation to Dr. Frank H. Clarke, Lederle Laboratories Division, American Cyanamid Company, Pearl River, New York, for these determinations.

[6] The low sodium diet provided approximately 100 grams protein and 3,000 calories but only 21 mEq. Na (1.2 grams NaCl) daily.

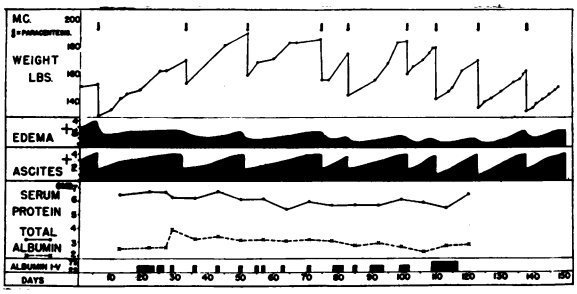

FIG. 5

spontaneous. The second, F. H., was a patient with known esophageal varices for which a splenorenal anastomosis had been done. Post-operatively, ascites formation became apparent and albumin was therefore administered. Weight loss and disappearance of the peritoneal fluid took place but the factor of diminished portal pressure following the shunt procedure may have been operative in this case.

Untoward effects of albumin administration

The intravenous administration of concentrated albumin as a therapeutic agent in cases of hypoproteinemia has been accompanied by certain untoward reactions which should be emphasized. In this series of 29 cases, reactions which albumin may have precipitated were seen in ten. As mentioned above, fatal hemorrhage from esophageal varices occurred in three patients during the period of albumin therapy. One occurred one week after the last previous albumin infusion, one five days after, and the third patient had hematemesis six hours after an infusion which was pyrogenic. Although in cirrhosis with varices hemorrhage may occur at any time, albumin may have been a precipitating factor by increasing the plasma volume (9).

Hematemesis occurred in one patient after albumin administration, with recovery. Subsequently, a duodenal ulcer was demonstrated as the probable source of the bleeding. In a patient with frequent epistaxis prior to treatment, fatal hemorrhage from the nose took place after he had received 525 grams of albumin over an 18-day period. Such incidents as these two must also be considered possible sequelae of albumin therapy.

One patient (P. M.) with a previous history of cardiac failure during an attack of acute glomerulonephritis developed pulmonary edema during the second daily infusion of 75 grams of albumin, although he showed no physical signs of cardiac disease at the beginning of treatment. He died in cardiac failure 12 hours thereafter. A 65-year-old female also developed pulmonary edema during the second day of albumin therapy (75 grams daily); albumin was discontinued and she recovered. Two patients, both elderly women, developed pleural effusion while receiving albumin and required thoracenteses. In the first (H. K.), severe dyspnea was noted after one week's administration and treatment was discontinued, while the second (E. G.) showed slowly progressive dyspnea in spite of the maintenance of a low sodium intake. Cessation of albumin therapy resulted in control of pleural fluid formation. With the exception of the first of these patients, P. M., no history or sign of cardiac disease had been noted prior to treatment and cessation of therapy was not followed by residual signs of heart disease. However, the dyspnea seen in patients H. K. and E. G. was due to the pleural effusion and probably was not of cardiac origin.

Pyrogenic reactions following albumin administration have been rare, and in no case has the albumin supplied been directly implicated. However, the dangers of such pyrogenic reactions in advanced cirrhosis are amply illustrated by the one fatality occurring under these circumstances. C. F., a 56-year-old female, received albumin for 12 days with what appeared to be a good response. On the 12th day she was given 50 grams of albumin mixed with liver extract and glucose solution. A severe chill and fever followed and hepatic coma ensued from which she did not recover. No instances of homologous serum hepatitis were observed following the intravenous administration of human serum albumin in this study.

Factors influencing the retention of albumin

In attempting to determine which patients with cirrhosis will show a diuresis following albumin, the number of paracenteses necessary, the effect of entry of albumin into the ascitic fluid, and the amounts of protein lost in ascitic fluid when paracentesis is necessary have been analyzed for the patients in this series. In addition, a study was carried out of the efficacy of a low sodium diet in reducing the transfer of albumin into ascitic fluid, and subsequent loss by paracentesis.

The relationship between the number of paracenteses necessary before albumin therapy and the response obtained after treatment is shown in Table I. As can be seen, the patients who had not yet reached the stage where paracentesis was absolutely necessary had an immediate diuresis when given albumin. In these subjects, the edema of lower extremities, penis and scrotum was massive while the ascitic fluid collection was not usually severely distressing. Comparing the groups who responded to therapy with those showing no response, only seven of the 11 patients who were improved had previously required one or more paracenteses while all of the patients who required the use of a low sodium diet or who failed to improve had had paracentesis prior to treatment. If, as is generally accepted, the necessity for abdominal fluid removal is an indication of the severity of liver disease, then it is apparent that those patients whose disease is more severe have the poorest therapeutic result when albumin is given.

Mankin has shown that the osmotic pressure changes of ascitic fluid and serum parallel each other under varying conditions in patients with liver disease and ascites (10). The protein values of serum and ascitic fluid obtained from 15 patients in this series before and during albumin therapy are listed in Table II. The total protein concentration in the ascitic fluid rose in all patients as albumin was administered intravenously. Moreover, this occurred in patients F. F. and J. G., both of whom had a prompt diuresis with disappearance of ascites and edema. The protein content of edema fluid (obtained by Southey tubes)

TABLE II

Changes in protein concentration of ascitic fluid and serum during albumin administration

Patient	Total albumin given *grams*	Interval between determinations *days*	Serum total protein *grams/100 cc.*		Serum albumin *grams/100 cc.*		Ascitic fluid total protein *grams/100 cc.*	
			Before therapy	During therapy	Before therapy	During therapy	Before therapy	During therapy
Immediate improvement								
F. F.	375	5	5.8	6.1	1.8	3.6	0.6	2.0
J. G.	400	4	6.3	5.8	2.0	3.1	0.8	2.0
Slow improvement								
G. D.	425	6	6.5	7.0	2.7	3.9	0.8	2.6
P. B.	375	9	6.7	7.0	2.2	4.3	1.2	3.6
J. M.	450	8	5.3	7.0	2.3	4.1	*	4.0
H. H.	300	6	6.4	7.3	1.9	4.1	0.5	2.1
Delayed improvement								
J. S.	450	15	6.5	6.2	3.2	3.7	1.3	2.4
W. M.	300	25	4.7	6.8	1.7	2.8	1.6	3.1
Improved only with low sodium diet								
E. G.	300	9	4.9	6.1	1.2	2.8	*	2.9
V. L.	300	9	6.6	7.4	2.1	3.1	*	2.2
C. M.	825	16	6.7	6.9	1.5	4.6	1.8†	4.4
Failure								
M. C.	350	30	6.8	6.2	2.5	3.2	*	2.2
H. G.	975	25	7.8	7.5	2.6	2.7	*	3.2
N. C.	825	16	6.9	7.4	2.9	3.7	1.0	3.7
P. W.	1200	55	6.9	6.6	2.8	3.4	*	2.7

* Determination not done.
† Two days after albumin started.

TABLE III

Changes in protein concentration of edema fluid, ascitic fluid, and serum in three patients with prompt diuresis during albumin administration

Patient	Albumin administered between determinations	Day of study	Serum		Ascitic fluid		Edema fluid	
			Total protein	Albumin	Total protein	Albumin	Total protein	Albumin
	grams		*grams/100 cc.*	*grams/100 cc.*	*grams/100 cc.*	*grams/100 cc.*	*grams/100 cc.*	*grams/100 cc.*
F. F.	0	0	5.8	1.8	0.6	0.0	0.1	0.0
	75	1	6.1	1.5	0.7	0.0	0.2	0.0
	75	2	5.8	2.0	1.1	0.3	0.2	0.0
	75	3	5.7	3.2	1.2	0.4	1.0	0.3
	75	4	5.4	2.3	2.1	0.5	0.8	0.3
	75	5	6.1	3.6	2.0	1.4	1.1	0.6
J. G.	0	0	6.3	2.0	0.8	0.3	0.2	0.0
	100	1	6.2	1.6	0.9	0.3	0.4	0.0
	100	2	6.0	2.5	0.9	0.3	1.0	0.2
	100	3	6.6	2.5	1.9	0.5	1.4	*
	100	4	5.8	3.1	2.0	0.5	*	*
S. P.	0	0	5.7	1.7	0.8	0.0	0.2	*
	450	11	6.3	2.3	*	*	0.7	*

* Determination not done.

from these two patients and from a third, S. P., also rose during treatment (Table III, Figure 6).[7] It is apparent that the entry of protein into the ascitic fluid occurred regardless of the final result and that a rise in protein content of edema fluid did not interfere with its reabsorption.

The entry of protein into the ascitic fluid is a source of protein loss in patients with cirrhosis because of repeated removal by paracentesis.[8] The total protein lost in ascitic fluid removed was compared in five patients with the total amount of albumin administered since the previous paracentesis. The results of this "balance" between parenteral protein administered and ascitic fluid protein removed are shown in Table IV. While it is realized that this is but a rough estimate and is subject to many variables, it may be seen that the total loss of protein by entry into the ascitic

[7] A variable and undetermined portion of the increase in concentration of protein in the edema fluid and ascitic fluid of patients undergoing rapid diuresis may result from more prompt reabsorption and mobilization of the water and electrolytes than of the protein. It is impossible to ascertain, therefore, to what extent the intravenously administered albumin contributed to the final concentration by its entry into these fluids.

[8] Albumin administered intravenously does not usually appear in the urine as whole protein. Although a large portion of injected albumin may be excreted into the urine of patients with preexisting renal disease, only a negligible amount escapes through the normal kidney even after several days of repeated daily infusions. Determinations for protein were made in the urine of several of the patients in this study. A total proteinuria of 5 to 10 grams was occasionally noted during the initial period when approximately 500 grams of albumin were administered within a week to raise the serum albumin concentration to normal, but was not subsequently observed while maintenance injections of approximately 75 grams weekly were required to maintain the serum albumin concentration. Thus, the loss of albumin into the urine of the patients reported in this study did not constitute a significant loss of administered protein.

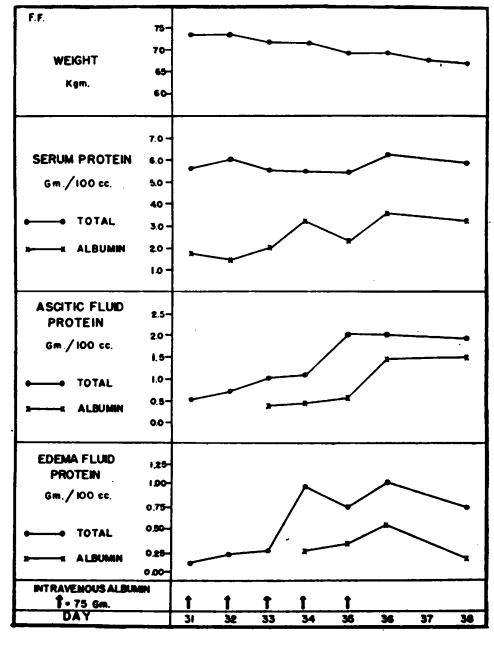

FIG. 6

TABLE IV

Protein loss in ascitic fluid during albumin administration

Patient	Interval between paracenteses	Fluid removed	Protein concentration of ascitic fluid	Total protein lost	Albumin given between paracenteses
	days	*liters*	*grams/100 cc.*	*grams*	*grams*
J. S.	19	15.0	1.3	195	425
	19	10.5	1.8	189	0
	22	18.5	2.4	444	450
	27	18.0	1.6	288	200
	Total			1116	1075
W. M.	18	16.0	3.1	496	250
	18	13.0	2.2	286	175
	9	9.0	3.0*	270	450
	37	13.0	4.1	533	375
	40	14.0	4.0*	560	675
	49	14.0	4.1	574	1125
	Total			2719	3050
H. H.	12	9.0	1.7	153	150
	33	10.1	3.2	323	800
	12	10.5	2.3	242	150
	Total			718	1100
M. C.	7	8.0	2.2	176	350
	21	14.0	2.0	280	150
	11	8.2	2.3*	189	200
	21	15.0	2.6	390	200
	17	12.0	2.7*	324	400
	9	17.5	2.8	490	375
	Total			1849	1675
P. W.	6	7.5	2.0*	150	450
	49	11.0	2.7	297	750
	17	15.0	2.5*	375	375
	11	15.0	3.0	450	450
	21	15.0	2.3	345	325
	Total			1617	2350

* Estimated—determination not done.

fluid during albumin therapy is large and may even surpass the amount of protein given intravenously as albumin.

The formation of ascites was not improved in three patients in this series by the intravenous administration of albumin until a low sodium diet was simultaneously provided (Table I). It was observed that reducing the sodium intake slowed the formation of ascites, prolonged the period between paracenteses, and thus diminished protein loss. Table V shows the findings in two of the patients given albumin to maintain normal serum albumin concentrations. Ascitic fluid was collected when paracentesis became necessary, both after a period of high salt intake and again after a period of low salt intake. Although the protein loss in ascitic fluid was not markedly changed in quantity at any one paracentesis, it is apparent that the period between paracenteses was prolonged by the low sodium diet and that less albumin per day was required to maintain the serum albumin at normal concentrations during the low sodium period.

Changes in liver function tests following albumin administration

The effect of albumin administration on three liver function tests is shown in Table VI. Serum bilirubin and thymol turbidity were determined at regular intervals whereas bromsulphalein retention was done less frequently. The results were extremely variable and no consistent picture was shown. It has been demonstrated (11, 12) that

TABLE V

Conservation of albumin with low sodium diet

	E. G.		C. M.	
	Unrestricted salt intake	Low sodium intake	Unrestricted salt intake	Low sodium intake
Interval between paracenteses (*days*)	23	75	29	39
Total albumin given intravenously (*grams*)	525	1125	975	525
Average albumin given intravenously daily (*grams*)	22.8	15.0	33.6	13.5
Protein removed in ascitic fluid (*grams*)	300 (T.P. 3.0 grams %) (10.0 liters)	258 (T.P. 3.0 grams %) (8.6 liters)	444 (T.P. 3.7 grams %) (12.0 liters)	468 (T.P. 3.1 grams %) (15.1 liters)

TABLE VI

*Liver function tests before and after albumin administration**

Patient	Interval between determinations *months*	Total serum bilirubin *mgm./100 cc.*		Thymol turbidity *cc. $BaSO_4$*		Bromsulphalein retention %	
		Before therapy	After therapy	Before therapy	After therapy	Before therapy	After therapy
Immediate improvement							
S. P.	1	7.0	2.7	1.1	2.2		25
F. F.	1	3.9	2.4	2.5	1.8		
J. G.	1	16.2	8.3	3.3	3.0	31	
Slow improvement							
G. D.	3	6.5	4.0	3.1	2.1		
P. B.	2	3.8	1.2	4.4	3.7		42
J. M.	2	0.4	0.8	1.3	2.6	16	16
A. D.	2	2.8	4.3	4.2	1.6	42	
H. H.	1	6.0	3.8	3.0	2.4		
Delayed improvement							
J. S.	6	0.3	1.4	1.5	1.7	32	32
W. M.	8	0.4	1.1	2.4	2.3	24	18
Improved only with low sodium diet							
E. G.	8	1.4	2.7	1.2	1.8	43	36
V. L.	2	0.4	0.5	2.5	2.5		
C. M.	7	1.0	1.5	4.7	1.7		
Failure							
M. C.	4	0.6	1.2	2.1	0.6	36	48
P. W.	5	3.7	1.9	3.6	1.8	36	52

* Normal values: B.S.P.—Less than 5% retention (5 mgm. dye per kilogram body weight). Bilirubin—Less than 1.0 mgm./100 cc. Thymol Turbidity—Less than 1.7 cc. $BaSO_4$

serum albumin will alter the thymol turbidity. Therefore, the apparent improvement in this test shown by some patients is not reliable nor indicative of the true state of liver function. There was a tendency, however, for the serum bilirubin concentration to decrease in those patients who had a prompt diuresis with loss of ascites and edema. It can also be seen that some patients with nearly normal bilirubin before treatment did not show improvement in fluid retention. In the patients on whom bromsulphalein tests were done before and after treatment no significant change appeared even though loss of edema and ascites was effected by treatment in some.

DISCUSSION

The use of concentrated albumin in the treatment of edema and ascites associated with hypoalbuminemia has been viewed with optimism on theoretical grounds. Encouraging results were obtained by Kunkel (3) early in the study of its use in cirrhosis of the liver but the results of Thorn *et al.* (2), and Patek *et al.* (13) have borne out the original conservative estimate of its value made by Janeway and his co-workers (1). The series reported here reveals that a wide range of results may be obtained even when patients are treated over long periods of time. Although striking improvement was seen in a few patients, the relatively poor effect in 11 out of 20 patients studied (not including nine patients in whom the effect of albumin could not be satisfactorily evaluated) leads to a similar conservative estimate of the efficacy of albumin therapy in chronic liver disease. The fact that some patients in our series improved after the prolonged administration of

albumin suggests that such improvement may have been the result of dietary treatment alone. Furthermore, since it has been shown that albumin administered intravenously can be utilized as a protein nutrient (14), some benefit was undoubtedly derived from this nutrient effect of albumin. However, albumin is neither a specific for the treatment of the fluid retention nor the underlying liver disease.

The most economical use of albumin is obtained when the diet is low in sodium, since the formation of ascitic fluid and loss of protein is greatly reduced by this means. This is in disagreement with Armstrong (15) who has minimized the importance of a low sodium intake in the treatment of liver disease. As the data presented here indicate, the removal of ascitic fluid containing 300 grams of protein may involve the waste of between 100 and 200 grams of albumin. A high intake of salt and water increases the formation of ascites. If ascitic fluid is present in large quantities or is rapidly forming, the entry of albumin into the fluid drains protein from the serum in larger quantities than would be the case were ascitic fluid present in small quantities or its formation diminished by measures such as sodium restriction. Furthermore, to maintain a given serum albumin concentration, less albumin is required when its loss into ascitic fluid is minimized by reducing the rate of formation of ascites. A low sodium diet is of most benefit to those patients who require repeated paracenteses. However, when albumin therapy is being initiated in a case of anasarca, a diet low in sodium should yield the most efficient use of albumin, regardless of the final response.

The mechanism by which concentrated albumin induces a diuresis is not clear. Albumin administration undoubtedly increases the serum osmotic pressure. Evidence suggesting that this is an important factor is the observation of Thorn *et al.* (2) and substantiated here, that peripheral edema is most easily mobilized when therapy is begun. The importance of the osmotic factor is minimized, however, by the finding of increased concentrations of protein in the edema and ascitic fluid when albumin is given intravenously. The increase in ascitic fluid protein thus produced would appear to emphasize the importance of portal hypertension as a causative factor in ascites formation. It should be pointed out, however, that the passage of protein into ascitic fluid following intravenous albumin took place even in patients undergoing a rapid diuresis. It seems likely that factors in addition to lowered serum osmotic pressure and portal hypertension are operative in the retention of fluid in cirrhosis of the liver. Patek has shown in a limited series of studies that there is increased renal blood flow and glomerular filtration when albumin is administered (13), presumably resulting from the increased plasma volume. This may hasten salt and water excretion by the kidney. Further studies of renal function in cirrhosis both before and during albumin therapy are clearly indicated.

The occurrence of harmful effects from albumin therapy must be emphasized. Since a majority of patients with cirrhosis are over the age of 45, and are therefore subject to possible degenerative heart disease, it may be expected that a rapid increase in plasma volume such as is produced by albumin may result in cardiac complications.

Finally, the augmented plasma volume following albumin administration may increase the burden upon esophageal varices and precipitate rupture and hemorrhage. Such an occurrence may have been the cause of death in three patients in this series. In view of such incidents albumin should be administered cautiously and heroic efforts to raise serum albumin levels above normal are to be avoided.

SUMMARY AND CONCLUSIONS

1. Concentrated salt-poor human serum albumin was administered intravenously to 29 patients with cirrhosis of the liver who had fluid retention. The albumin was administered over periods varying from four days to eight months. The data were considered suitable for analysis in 20 of the patients. Of these, four patients had an immediate diuresis with loss of ascites and edema, five had a slow response in from one to three months, and two recovered from ascites and edema after prolonged treatment of six and eight months, respectively. Nine patients must be considered failures although the fluid retention was partially controlled in three by the use of a low sodium diet. The four patients who underwent immediate improvement had not required paracentesis before albumin therapy and had massive edema. Diuresis might have occurred subsequently in these pa-

tients from a nutritious diet alone. Nevertheless, albumin administration was effective by inducing an immediate, rapid diuresis, beginning before the serum albumin concentration reached normal. The slow response in seven patients cannot be definitely attributed to the albumin administered as the other therapeutic measures used concomitantly might have given as satisfactory results.

2. Fatal hemorrhage from esophageal varices was coincident with, or shortly followed, albumin administration in three patients. Severe epistaxis and bleeding from a duodenal ulcer may have been induced by this therapeutic measure. Pulmonary edema and pleural effusions were observed as untoward effects, presumably attributable to albumin therapy. The use of this form of therapy, especially in elderly or cardiac patients, or in the presence of known esophageal varices, is dangerous and caution should be exercised.

3. Albumin entered the ascitic and edema fluid following its intravenous infusion whether diuresis occurred or not. The total protein content of the ascitic fluid rose in approximately parallel fashion with the rise in serum albumin. During a given period between paracenteses in five patients the protein lost in the ascitic fluid approximated the amount of albumin administered intravenously.

4. Ascitic fluid formation was found to be retarded by a low sodium diet in three patients, and thus the loss of albumin by paracentesis was reduced. Sodium restriction allowed the maintenance of normal serum albumin concentrations more economically than did a diet unrestricted in sodium.

5. Serial serum bilirubin, thymol turbidity and bromsulphalein tests showed no consistent change during or after treatment with albumin. Recovery from ascites and edema was seen to precede the return of liver function tests to normal values.

6. It is concluded that concentrated salt-poor human serum albumin, under the conditions of this study, is neither specific for the relief of ascites nor markedly beneficial in the treatment of the underlying liver disease. In view of the variety of results obtained with concentrated human serum albumin in patients with cirrhosis of the liver, it is concluded that other factors in addition to a reduced serum osmotic pressure, as represented by decreased serum albumin concentrations, are active in the retention of fluid.

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