ing no more than 5 or 10 counts per minute per ml, in other words, not significantly greater than background. In view of the studies of Feldman *et al.*(10) using the same type of apparatus, it is certain that the failure to find beryllium in the ultrafiltrate represents a true non-diffusibility and is not an artifact resulting from the apparatus employed. While it is not considered that the cellophane ultrafilter resembles in all regards the glomerular filtration mechanism of the kidney, such *in vitro* studies often lead to significant suggestions. Taken together with the clearance data, the ultrafiltration studies point toward the involvement of tubular activity in beryllium excretion. The clearance of a non-filtrable substance seems unusual, but there is insufficient data to discuss it further. Studies on the state of beryllium in the blood, now in progress, and further work on the renal mechanisms involved, will be required for elucidation of the problem.

As shown in the table, an attempt to demonstrate an inhibitory effect of p-aminohippuric acid and carinamide on possible tubular excretion of beryllium was not successful, but because of the variety of tubular secretory systems, negative findings in such an experiment prove little.

Summary. Carrier-free Be^7 injected in an insoluble form has a very low clearance as compared with the simultaneous inulin clearance. When citrate, a potent complexer of beryllium, is added to insure that the injected beryllium is in an insoluble form, the clearance is much greater, despite the fact that ultrafiltration studies indicate the soluble beryllium to assume a non-diffusible form after mixing with the blood. The addition of carrier does not markedly alter the beryllium clearance. The clearance ratio, *i.e.*, C_{Be}/C_{inulin}, varies widely enough to suggest that the two substances are not excreted by the same mechanism, and the possibility of tubular activity in beryllium excretion comes to mind. This idea is supported by ultrafiltration studies which show that beryllium exists in the plasma in a non-diffusible form. Complete clarification of the problem must await further work on the state of beryllium in the blood.

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Differential Rates of Diffusion of Mannitol from Phases of Extracellular Compartment in Edematous States.*† (19286)

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The development of a simple and accurate

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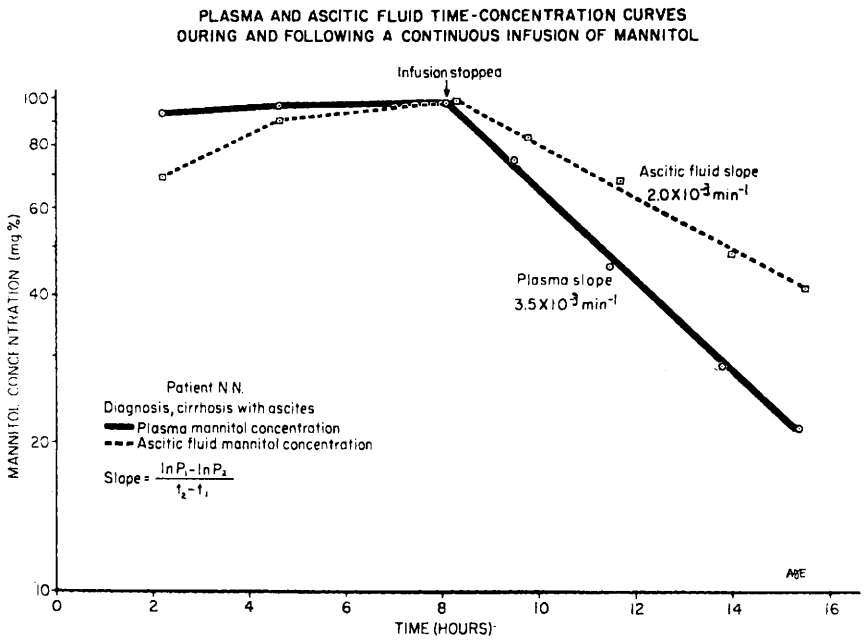

FIG. 1. Example of plasma and ascitic fluid time-concentration curves during and following a continuous infusion of mannitol.

method for measuring extracellular fluid volume has been the subject of much investigation. Recently a series of three carbohydrates, sucrose(1,2), mannitol(3-5), and inulin(6,7) have been used to estimate extracellular volumes. These substances obviate the disadvantage of variable entrance into cells, diffuse into a smaller space of distribution and presumably more accurately estimate the extracellular volume(8). A procedure for determining the mannitol space has been reported that was independent of route of removal of mannitol and corrected automatically for any extrarenal disposal(9). The procedure (infusion-slope method) has the added advantage in that it obviates urine collections. Close correspondence has been observed between the inulin space as measured by the infusion-recovery method and the mannitol space measured by the infusion-slope method (10). These data would seem to establish the validity of both methods for measuring the extracellular fluid volume. It should be noted that these studies were carried out in normal subjects.

An important requirement in the determination of the mannitol space by the infusion-slope method is that the clearance rate of mannitol from plasma water and from all other recesses of the extracellular phase be comparable after the mannitol infusion is stopped. The purpose of this study was to test the validity of this assumption by simultaneously measuring the comparative rates of diffusion of mannitol from plasma and ascitic fluid in patients with cirrhosis and from plasma and peripheral edema fluid in patients with congestive heart failure.

Methods. Three groups of male subjects were employed, 1) normal individuals admitted for minor surgery, 2) cases of cirrhosis with ascites, and 3) patients with congestive heart failure and peripheral edema. The subjects were allowed food and water *ad libitum* but were kept recumbent in bed throughout the experimental procedure. No preliminary hydration was employed. A priming injection of mannitol was followed by a constant sustaining infusion for 8 hours. Mannitol plasma levels were maintained between 100 and 200 mg %. All solutions were made up in 0.45% saline solution. A Bowman constant injection pump was used for the intravenous infusion at a rate of 1.9 cc/min. with a mean variation of 3.6 $\pm$ 2.5% in the volume flow per minute. Ascitic fluid was obtained by

means of an indwelling nylon catheter introduced into the peritoneal cavity through a 17 gauge needle(11). In patients with congestive heart failure, peripheral edema fluid was obtained by the subcutaneous insertion of a special 16 gauge needle prepared with additional holes along the barrel. Blood and interstitial fluid samples were drawn simultaneously at 2, 4, and 8 hours during the infusion and at hourly intervals for 3 hours after the infusion was stopped. Mannitol was determined by the method of Corcoran and Page(12). Mannitol recovery from plasma averaged 100.1 ± 6.5%. Plasma and edema fluid blanks were run routinely. Plasma concentrations of mannitol were corrected for plasma water content according to the concentration of protein present.

Results. When the mannitol infusion was stopped, the concentration of mannitol in body fluids fell rapidly as mannitol was excreted. The logarithms of mannitol concentrations plotted against time proved to be a linear function. (Fig. 1). Taking any 2 points on the regression line, one can calculate the slope as follows:

$$S = \frac{{}_{n}P_1 - {}_{n}P_2}{t_2 - t_1}$$

where S = slope (min^{-1}), P_1 = a regression plasma concentration at t_1, P_2 = a regression plasma concentration at t_2. The magnitude of the slope value is a direct measure of the rate of removal or clearance of mannitol.

Table I summarizes the slope values for mannitol obtained in normal subjects, cases of cirrhosis, and patients with congestive heart failure. The mean plasma slope in normal subjects was 5.0 ± 1.13 × 10^{-3} min^{-1}. This was significantly higher than the mean plasma slope obtained in cirrhotic patients 3.5 ± 0.82 × 10^{-3} min^{-1} P = .05) and that obtained in patients with congestive heart failure 2.7 ± 0.67 × 10^{-3} min^{-1} (P < .01).

From Fig. 1 it can be seen that mannitol diffused more rapidly from the circulating plasma than from ascitic fluid. A summary of differential rates of mannitol diffusion from various recesses of the extracellular compartment is shown in Table I. When analyzed by the method of paired comparisons, the mean differences between plasma and ascitic fluid

TABLE I. Comparative Rates of Diffusion of Mannitol from Various Phases of the Extracellular Compartment.

Normal subjects: Plasma slopes (1×10^{-3} min^{-1})		Cases of cirrhosis with ascites: Time-concentration slopes (1×10^{-3} min^{-1})				Cases of congestive failure with peripheral edema: Time-concentration slopes (1×10^{-3} min^{-1})				
Subject	Patient	Plasma	Ascitic fluid	Diff.*	% diff.†	Patient	Plasma	Edema fluid	Diff.*	% diff.†
1. J.M.	1. J.S.	2.5	2	.5	20	1. A.L.	3.5	0	3.5	100
2. R.N.	2. V.G.	4.6	4	.6	13.1	2. G.F.	2	.4	1.6	80
3. K.G.	3. N.N.	3.5	2	1.5	42.8	3. R.O.	3	.6	2.4	80
4. V.S.	4. J.K.	4	2	2	50	4. P.G.	2	.7	1.3	65
5. H.B.	5. C.R.	3	1.2	1.8	60	5. A.A.	3	2.5	.5	16.7
Mean	—	3.5	2.2	1.3	37.2	—	2.7	.8	1.9	68.3
Stand. dev.	—	.82	1.04	.69	19.9	—	.67	.97	1.14	31.4
—	P	.05		.03	—	P	<.01	—	.04	—

* Diff. = Plasma slope − ascitic fluid slope.

† % diff. = $\frac{\text{Diff.}}{\text{Plasma slope}} \times 100$.

slopes (1.3×19^{-3} min^{-1}) and between plasma and edema fluid slopes (1.9×10^{-3} min^{-1}) were both statistically significant.

Discussion. The impairment of daytime glomerular filtration rates in this series of cases of cirrhosis and congestive heart failure was evident in the decreased rate of plasma clearance of mannitol. In the measurement of the mannitol space by the infusion-slope method, a basic requirement is that mannitol be uniformly cleared from all recesses of the extracellular compartment. The differences in slope values between plasma vs. ascitic fluid, and plasma vs. interstitial edema fluid, indicated that this requirement was not met in the edematous states studied.

It was of particular interest to note that the mannitol was cleared at a more rapid rate from ascitic fluid than from peripheral edema fluid. Other data indicate that mannitol and inulin equilibrate at a faster rate in ascitic fluid than in peripheral edema fluid(13). This conflicts with any *a priori* concept that ascitic fluid is relatively adynamic in contrast to peripheral edema fluid, and is in agreement with recent findings on the rapid exchange of labelled protein in experimental ascites(14).

Conclusions. 1. The plasma clearance of mannitol observed during morning hours was significantly decreased in this series of cases of cirrhosis with ascites and congestive heart failure with edema. 2. Rates of diffusion of mannitol from various recesses of the extracellular compartment were not uniform in two edematous states, namely, cirrhosis with ascites and congestive heart failure with edema. 3. The mannitol method as determined by the infusion-slope procedure cannot be applied to the measurement of the extracellular fluid compartment in certain edematous states.

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Plasma Protein. IV. Results with Generally Labeled Plasma Protein.* (19287)

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We have reported(1,2) on the metabolism of plasma protein labeled by feeding donor rats serine-β-C^{14} and administering the C^{14}-

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