MEDICAL GRAND ROUNDS

UNIVERSITY OF TEXAS SOUTHWESTERN MEDICAL SCHOOL

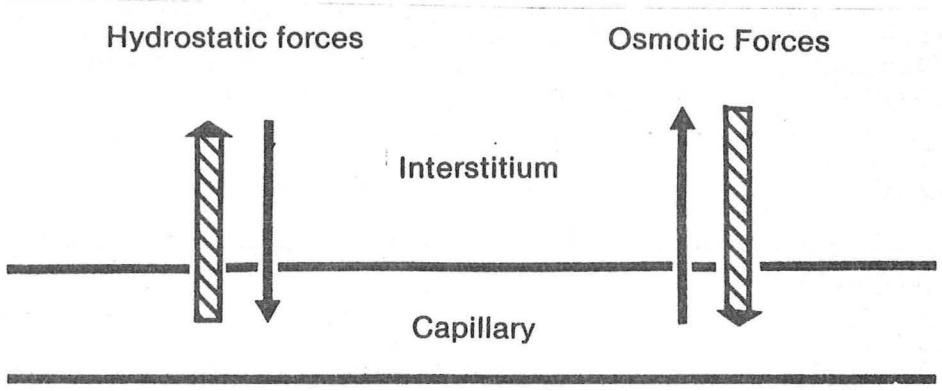
ASCITES

Athol Ware, M.D.

March 29, 1979

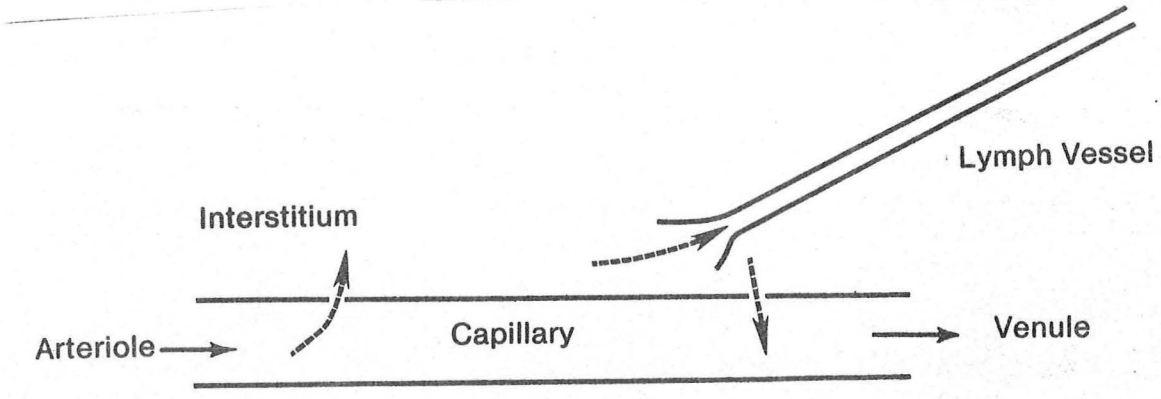
LYMPH FORMATION, CONSTITUTION AND CIRCULATION

The factors which determine the partition of fluid between plasma and the extracellular interstitium were defined in 1896 by Starling. The balance between hydrostatic and osmotic forces operating across the capillary membrane determines the movement of fluid into and out of the vascular compartment.



STARLING FORCES

The intravascular hydrostatic force is influenced by the local venous pressure and is partially offset by a tissue hydrostatic pressure. By the same token, 2 counter-balancing osmotic forces are generated by the proteins present in the fluids on either side of the capillary membrane.



NORMAL CAPILLARY FLUID CIRCULATION

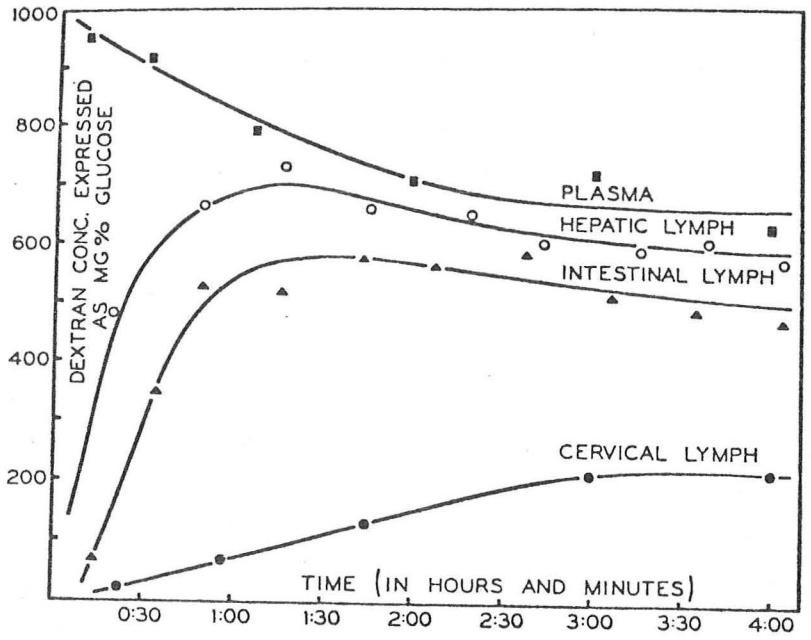
Under normal circumstances the net effect of all these forces is to allow the circulation of fluid out of the capillary into the interstitium to bathe the tissue cells. This allows the delivery of oxygen and nutritional factors to the tissues. Fluid is then returned to the plasma under the influence of the net osmotic force allowing for the removal of metabolic wastes from the tissues. A small net loss of fluid from the circulation is carried away from the interstitium by the lymph vessels. For practical purposes the characteristics of fluid obtained from draining lymph vessels (lymph) are those of the interstitial fluid. Whenever there is a disturbance in the Starling forces which promotes the movement of fluid out of the vascular compartment (increased net hydrostatic or decreased net osmotic pressure) the immediate response is an increase in lymph flow. Interstitial fluid volume does not increase and accumulate in the form of edema (or ascites) until the capacity of the draining lymph vessels to remove the extra fluid volume is exceeded. This capacity is normally quite considerable. In patients with cirrhosis, for example, the flow through the thoracic duct may increase more than 10 fold and attain rates of 15 ml/min or more before the lymph circulation becomes inadequate and fluid begins to collect as ascites.

Osmotic force is determined by the number of osmotically active particles present in solution. The most numerous osmotically active particles in body solutions are the electrolytes. Because they diffuse freely across capillaries however and because no concentration gradient is established across capillaries, no osmotic force is generated by these ions. Most capillaries are not freely permeable to proteins however and because these molecules are relatively excluded, concentration gradients are established and osmotic forces are generated. The molecular weight of albumin is approximately 69,000. Because it is a much smaller molecule than many other proteins (e.g. γ globulin, m.w. = 160,000) and because its plasma concentration is higher than any other protein, albumin becomes the most important (but not the only) determinant of the osmotic force acting across capillaries.

Osmotic Force Characteristics of Blood Constituents

	M.W.	Concentration	No. of Particles/ ml Plasma	Factor
Sodium	23	322 mg/dl	8.4×10^{19}	
				200
Albumin	69,000	4.5 gm/dl	3.9×10^{17}	
				7
Gamma globulin	160,000	1.5 gm/dl	5.6×10^{16}	

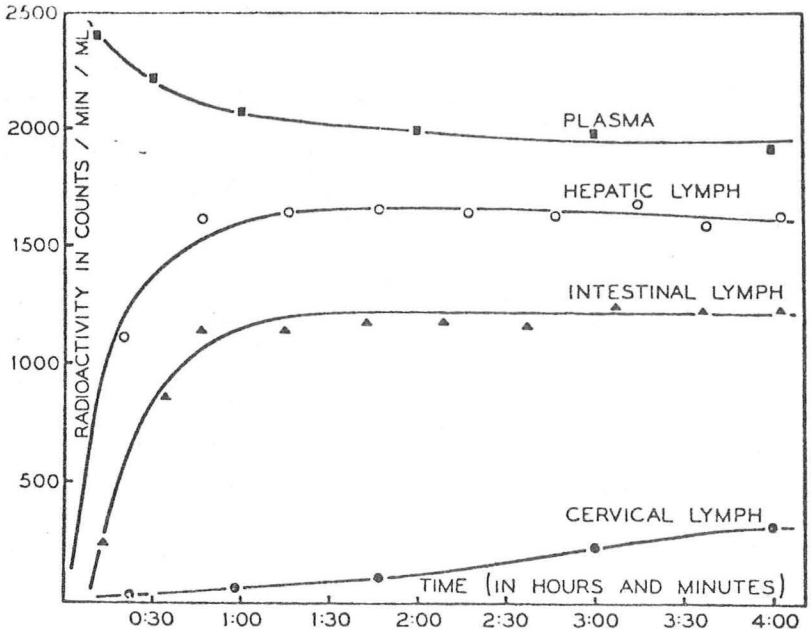
The plasma proteins exert a force which attracts fluid into the vascular compartment. Tissue fluids contain a varying concentration of protein which produce a smaller but important force attracting fluid into the interstitium. The concentration of protein in tissue fluid varies from tissue to tissue and this reflects the variation in the degree of permeability for proteins and other macromolecules exhibited by the capillaries from different parts of the body at rest.



Appearance of Dextran (MW 35000) in Lymph After I.V. Injection

(H.S. Mayerson, Handbook of Physiology, Circulation II, 1963)

This variability in vascular permeability was demonstrated in dogs by Mayerson. Figure 4 demonstrates the rate of disappearance (from plasma) of intravenously injected dextran (m.w. 35,000) and its appearance in the lymph draining various parts of the body. Dextran appeared quickly and in high concentration in hepatic lymph, less promptly and in lower but still appreciable concentrations in intestinal lymph but very slowly and in only small amounts in lymph from peripheral sites.



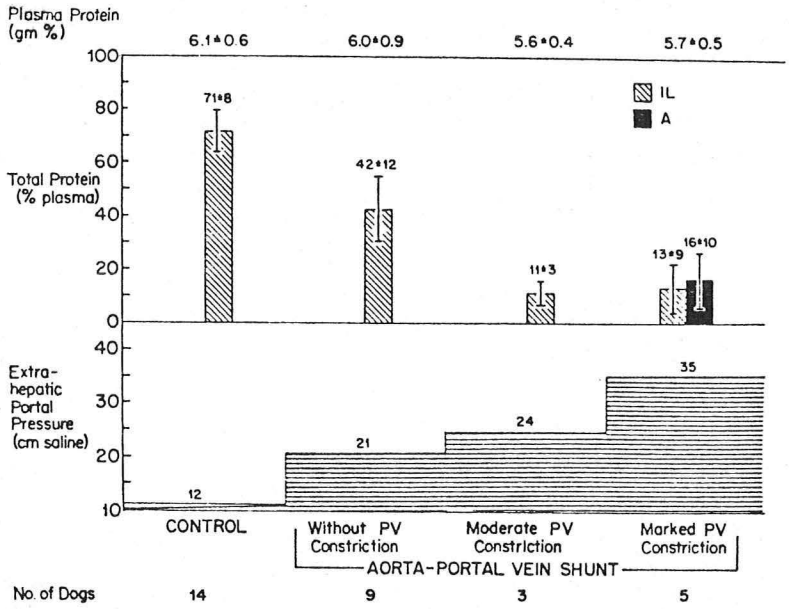
Appearance of Radioactive Albumin in Lymph
After I.V. Injection

(H.S. Mayerson, Handbook of Physiology, Circulation II, 1963)

Similar studies using radioactive albumin produced qualitatively similar findings. Albumin passed quite readily into hepatic lymph, less well into intestinal lymph and only in small amounts into peripheral lymph. It is important to note however that capillaries, even peripheral capillaries are not totally impermeable to protein.

Some of this variability in permeability can be explained on anatomical grounds. While capillaries which are found in peripheral tissues and in the splanchnic bed are "continuous" membranes with even small pores the hepatic sinusoids are "discontinuous" and are characterized by variable and often very large pores (as great as 5,000 A in diameter) which pose no barrier to the movement of proteins between plasma and the interstitial fluid in the space of Disse. What barrier does exist to protein movement in the liver probably resides in the interstitial constituents which lie between the hepatic sinusoid and the smallest hepatic lymph vessel. It is not known how far from the portal tracts and into the hepatic lobules anatomically identifiable lymph vessels extend. It is probable however that this sinusoid-lymphatic space is quite large. This sinusoidal porosity makes teleological sense when one considers the requirement of hepatic cells to have access to circulating lipid soluble protein-bound molecules.

Another determinant of vascular protein permeability is the rate at which fluid moves across the capillary wall. In capillaries such as those found in the intestine or the periphery the concentration of protein in interstitial fluid decreases as the rate of fluid movement out of the capillary increases.

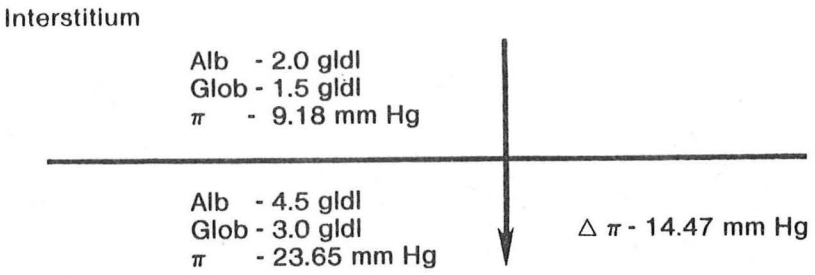


Effect of Hydrostatic Pressure on Protein Concentration in Intestinal Lymph

(Witte et al., Ann. Surg., 1969)

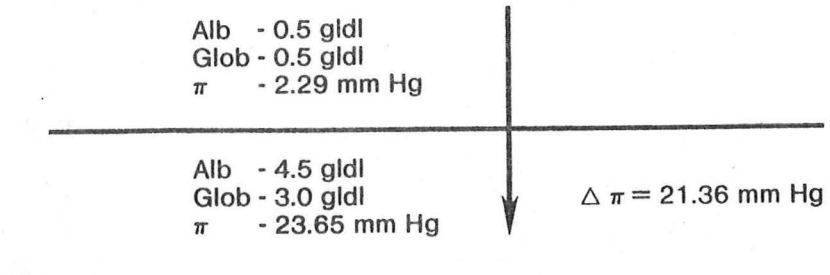
In these experiments reported by Witte et al. the hydrostatic pressure in the intestinal capillaries was progressively increased by the creation of a progressively greater portal vein constriction in animals with a previously fashioned aorto-portal vein shunt. These maneuvers resulted in a step-wise increase in portal vein pressure and a step-wise increase in the rate of intestinal lymph flow. As Fig. 6 illustrates, the concentration of protein in this lymph fluid (IL) became lower and lower as the hydrostatic pressure rose and lymph flow increased. Ultimately the capacity of the draining lymph channels was exceeded and ascites (A) developed. The protein concentration of this ascitic fluid was also low at approximately 1 g/dl.

The presence of some protein in the interstitial fluid at rest provides the system with a small but useful "buffer" to prevent wide swings in fluid movement with variations in vascular tone and hydrostatic pressure.



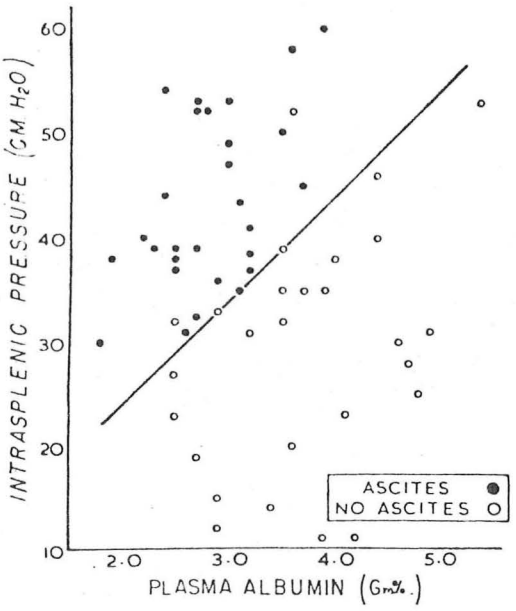
OSMOTIC FORCE ACROSS NORMAL MESENTERIC CAPILLARY

Under normal circumstances the intestinal interstitium contains approximately 3.5 g/dl total protein of which approximately half is albumin. This generates a calculated osmotic pressure of 9.18 mmHg. The calculated colloid osmotic pressure of normal plasma is 23.65 mmHg. So the net osmotic force acting across the capillary is 14.47 mmHg.



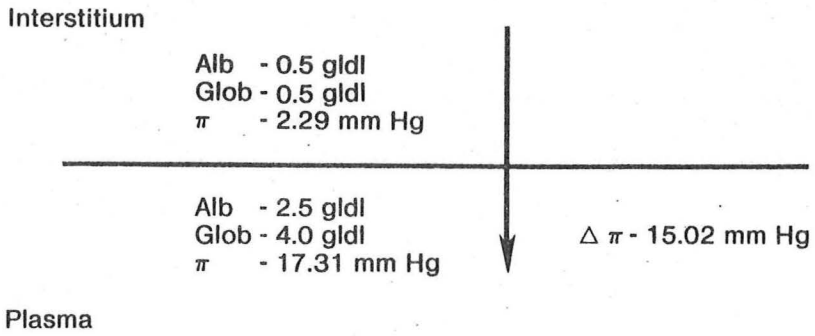
OSMOTIC FORCE WITH INCREASE IN HYDROSTATIC PRESSURE

If there is an increase in hydrostatic force and protein-poor fluid crosses into the interstitium, the concentration of protein in the interstitial fluid decreases. The interstitial osmotic pressure falls while the plasma osmotic pressure remains unchanged. The net osmotic force therefore rises and offsets the increase in hydrostatic force. The capacity of this "buffer" is approximately 7 mmHg. Ascites is a rare occurrence in patients whose only abnormality is portal hypertension (e.g. extrahepatic portal obstruction). The increase in net osmotic force associated with dilution of the interstitial protein contributes to this protection.



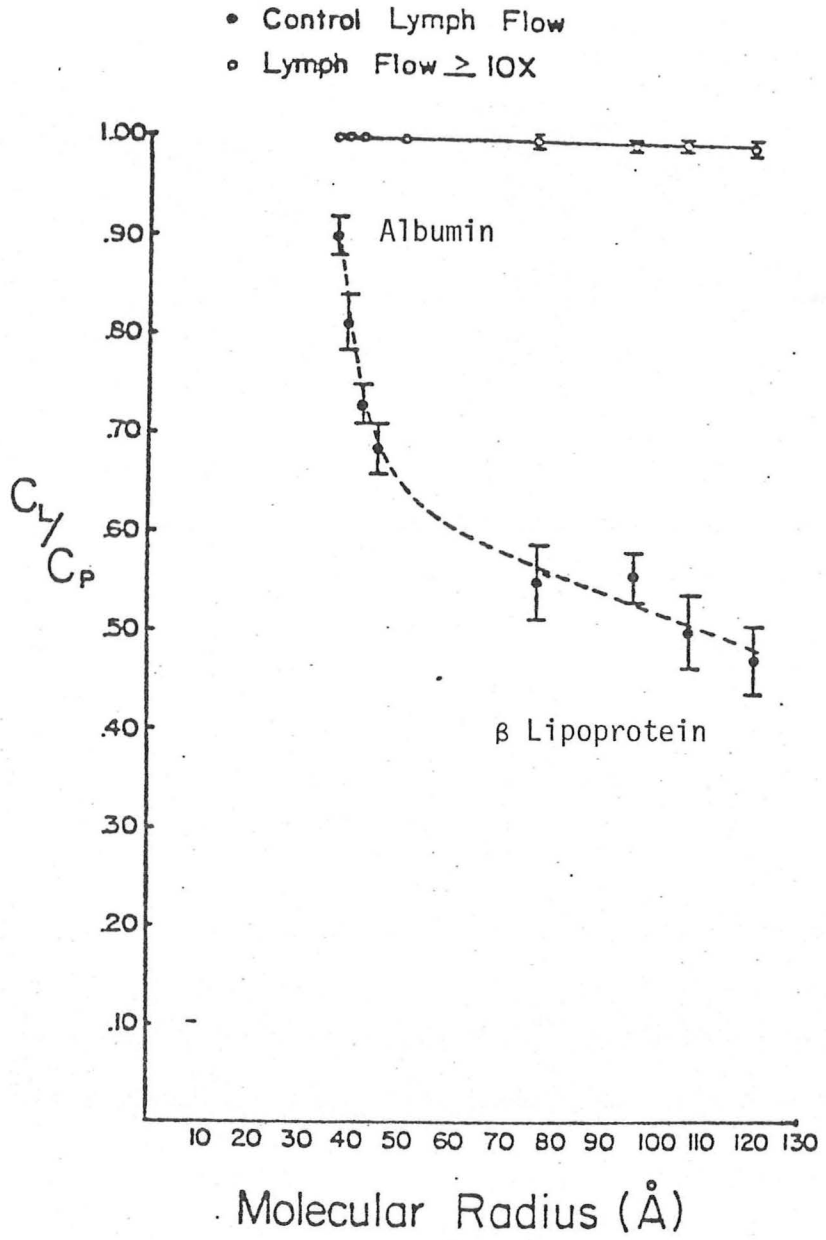
(Atkinson and Losowsky, Quart. J. Med. 1961)

Extremely high hydrostatic pressures are required to produce ascites in patients with normal plasma protein concentrations. Less and less hydrostatic pressure is required for the formation of ascites as the plasma albumin concentration decreases and the net osmotic force declines.



OSMOTIC FORCE WITH ↑ HYDROSTATIC PRESSURE AND ↓ SERUM ALBUMIN

The situation across the liver sinusoids is quite different however. Under normal circumstances macromolecules have relatively free access to hepatic lymph.

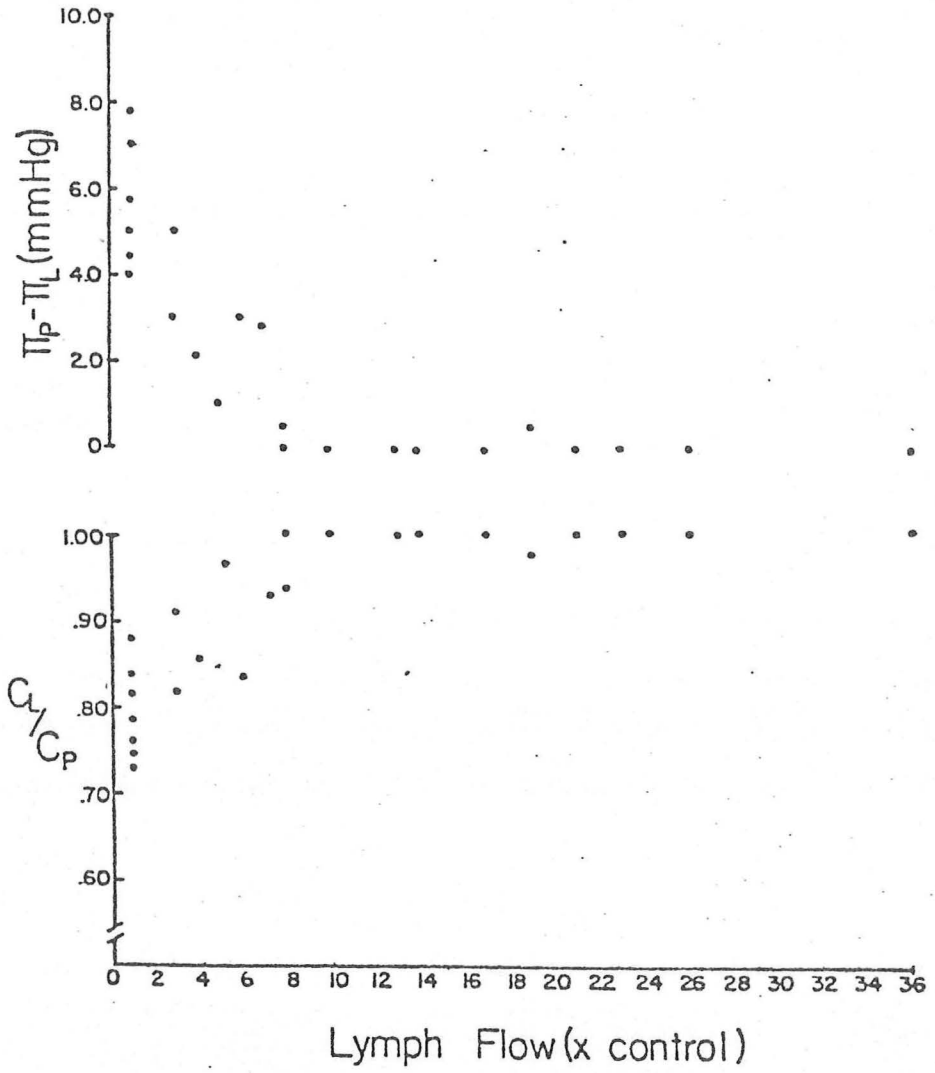


Relationship Between Molecular Size and Concentration Gradient Across Hepatic Sinusoid

(Granger et al., Gastroenterology, 1979)

Granger et al. have shown in cats that the ratio of the concentrations of various proteins in hepatic lymph and plasma varies with the molecular radius of the protein. When the hydrostatic pressure was raised however and lymph flow was increased the concentration of each of these proteins became the same in hepatic lymph as it was in plasma.

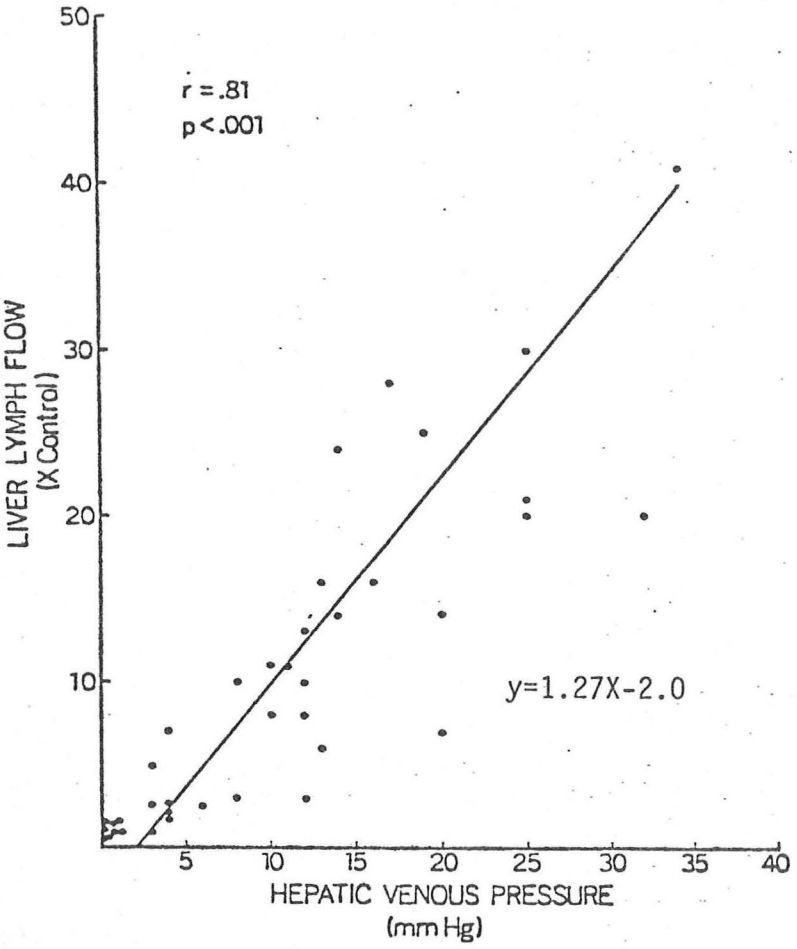
Thus the slight barrier to protein transfer present at rest diminished with increasing rates of fluid movement. It is apparent that even at rest there was very little impedence to the movement of albumin from plasma to lymph. These findings suggest that no significant osmotic forces are generated across the hepatic sinusoidal membrane.



Relationship Between Protein Concentration or Osmotic Pressure Gradients and Lymph Flow

(Granger et al., Gastroenterology, 1979)

Confirmation of this hypothesis has been provided by experiments such as these in which the measured protein concentration gradients and the calculated colloid osmotic pressure gradients have been shown to become 1 and 0 respectively with but small increments in sinusoidal hydrostatic pressure.



Relationship Between Liver Lymph Flow and Hepatic Venous Pressure.

(Granger et al., Gastroenterology, 1979)

If osmotic forces aren't operative in the liver it follows that the sole determinant of fluid movement in this organ is the sinusoidal hydrostatic pressure. The direct relationship between lymph flow and sinusoidal pressure (modified by influencing the hepatic venous pressure) has also been shown in animal experiments.

Starling, E.H.: The influence of mechanical factors on lymph production. J. Physiol. (London) 16:224, 1894.

Starling, E.H.: On the absorption of fluids from the connective tissue spaces. J. Physiol. (London) 19:312, 1896.

Mayerson, H.S.: The physiologic importance of lymph. In Handbook of Physiology, Sect. 2: Circulation, Vol. 2. Edited by W.F. Hamilton, Washington, D.C., American Physiological Society, page 1035, 1963.

Atkinson, M., Losowsky, M.S.: The mechanism of ascites formation in chronic liver disease. Quart. J. Med. 30:153, 1961.

Witte, C.L., Witte, M.H., Dumont, A.E., et al.: Lymph protein in hepatic cirrhosis and experimental hepatic and portal venous hypertension. Ann. Surg. 168:567, 1968.

Witte, C.L., Chung, Y.C., Witte, M.H., et al.: Observations on the origin of ascites from experimental extrahepatic portal congestion. Ann. Surg. 170:1002, 1969.

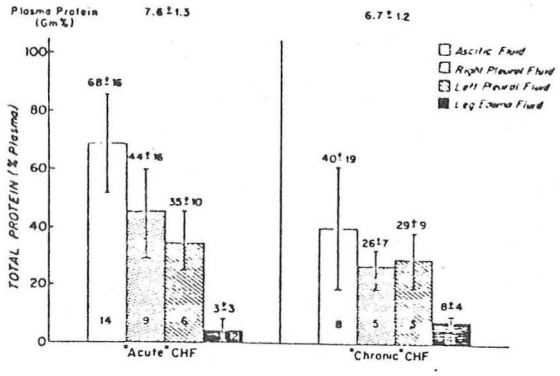
Dive, Ch.C., Nadalini, A.C., Heremans, J.F.: Origin and composition of hepatic lymph proteins in the dog. Lymphology 4:133, 1971.

Granger, D.N., Miller, T., Allen, R., et al.: Permselectivity of cat liver blood-lymph barrier to endogenous macromolecules. Gastroenterology, 1979. In press.

ASCITES IN DISEASE STATES

In circumstances where there is a marked increase in sinusoidal pressure, hepatic lymph flow will eventually exceed the capacity of the hepatic lymph vessels to return the fluid to the venous system. Fluid then accumulates locally in the interstitium of the liver. This fluid, which is rich in protein ultimately seeps through the liver capsule and forms ascites. Ascites, so derived, is characterized by a protein concentration which is very high and may even approach that of plasma.

The clinical situations where this sequence is most commonly seen are: 1) congestive heart failure and 2) Budd Chiari Syndrome.



Total protein in ascitic, pleural, and peripheral edema fluid in acute and chronic congestive heart failure (CHF). Numbers on the bottom of each bar represent number of patients studied.

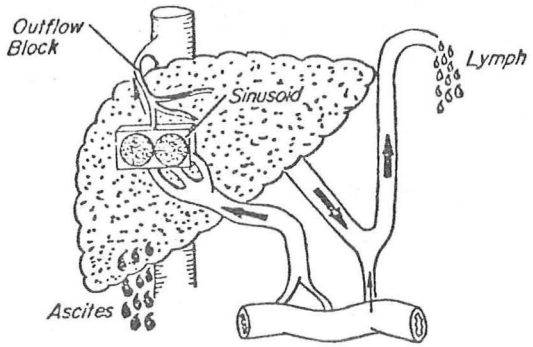
(Witte et al., Circulation, 1969)

These studies by Witte et al. in patients with acute congestive heart failure demonstrate the wide difference between protein concentrations of ascitic fluid (mean approximately 5 g/dl) and peripheral edema fluid (mean approximately 0.2 g/dl). Patients who were considered to have been in chronic congestive heart failure had a lower ascitic protein concentration (mean approximately 2.7 g/dl). Two phenomena contribute to this change in the ascitic protein concentration. If the hepatic sinusoids are subjected to an increased hydrostatic pressure for a period of time an anatomical change occurs in their structure. This modification is called "capillerization" and results in the sinusoid assuming some of the structural and therefore functional characteristics of capillaries. The large pores disappear and a more continuous membrane appears. Some exclusion of protein becomes possible and osmotic forces begin to play some role in hepatic lymph flow. The protein concentration of such lymph, while still high, becomes lower than before.

The second factor contributing to the lower ascitic protein concentration in chronic congestive heart failure is the superimposition of portal hypertension. This, coupled with a decrease in serum proteins from hemodilution, is sufficient to produce ascitic fluid from the splanchnic bed. This fluid, derived from transudation across capillaries, has a very low protein concentration. The final protein concentration measured in the peritoneal fluid is determined then by the sum of the 2 contributing pools of fluid; one relatively high in protein originating in the liver and the other, a low protein fluid filtered across splanchnic capillaries.

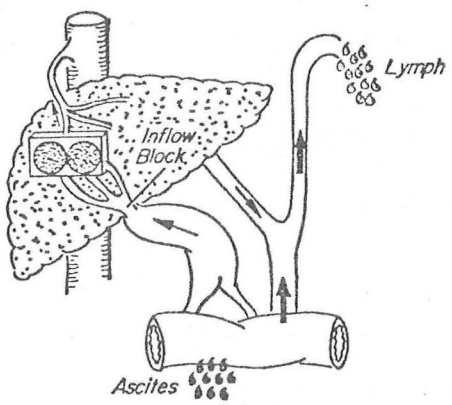
ASCITES IN CIRRHOSIS

In patients with cirrhosis this same dual origin of ascites pertains.



CIRRHOSIS

A characteristic feature of cirrhosis is the interference with hepatic venous drainage through the hepatic veins by fibrous strictures and compression caused by regenerating nodules. A large part of the sinusoidal bed also becomes obliterated by scar tissue and the consequence of this post-sinusoidal obstruction and diminished sinusoidal capacity is an increase in the hydrostatic pressure within the sinusoids and an increase in protein-rich hepatic lymph flow.

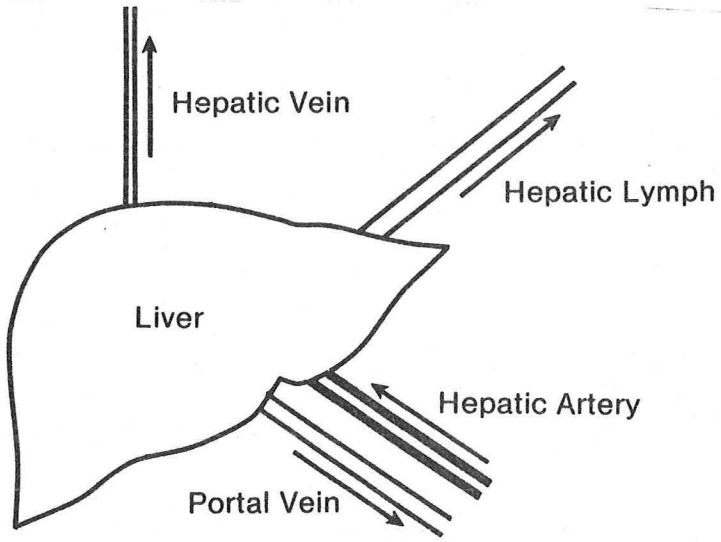


CIRRHOSIS

At the same time the portal venous pressure rises. This may simply be a reflection of the raised sinusoidal pressure but it may be compounded also by pre-sinusoidal obstruction (produced by portal fibrosis) or arterio-venous communications. The consequences of this raised portal pressure, transmitted back to the splanchnic capillaries and coupled with the usual concomitant reduction in serum albumin is the formation of excessive quantities of protein-poor intestinal lymph. Ascites develops when the production of lymph from either or both sources exceeds the transport capacity of the lymphatics. The

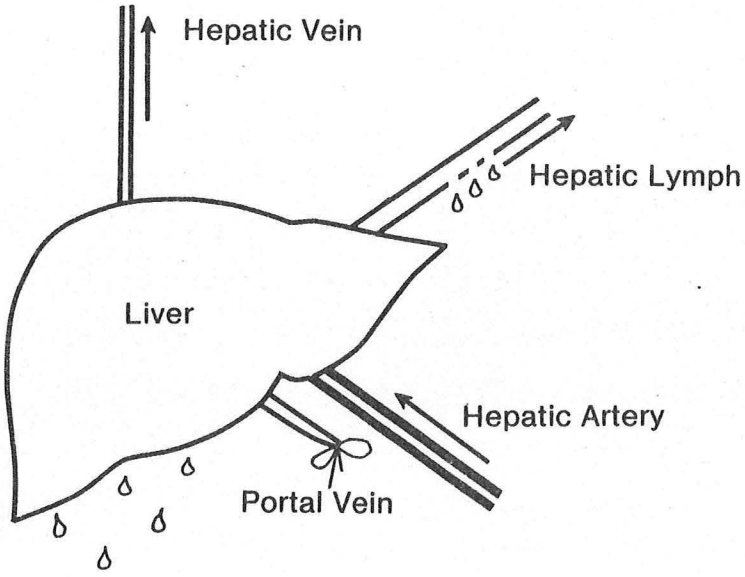
protein concentration of such fluid depends upon the relative contribution made by each source. In most instances the splanchnic pool is dominant and fluid with "typical" transudative characteristics (protein <2.5 g/dl) is found. The protein content of cirrhotic ascites is seldom as low as would be anticipated if the fluid originated solely from the splanchnic capillaries.

In some patients the hepatic venous outflow block is so severe that blood flow in the portal vein is reversed and the portal vein serves as a conduit for the removal of blood which continues to be delivered to the liver via the hepatic artery.



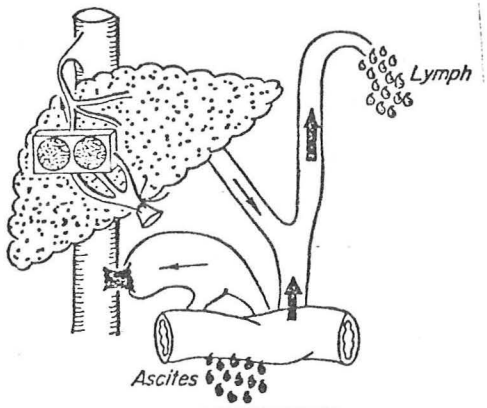
SEVERE POST SINUSOIDAL PORTAL HYPERTENSION

If these patients are treated with an end to side porto-caval shunt they are at grave risk to develop intractable high protein ascites.



AFTER END TO SIDE P-C SHUNT

The P-C shunt effectively decompresses the splanchnic bed and thereby decreases lymph formation across intestinal capillaries. The ligation and division of the portal vein however eliminates a major route of venous outflow from the liver. The sinusoidal pressure rises even further, more fluid leaves the sinusoids, the capacity of the hepatic lymphatics (some of which may be damaged at surgery) is exceeded and protein-rich fluid seeps from the liver into the peritoneum.



INEFFECTIVE
END-TO-SIDE
PORTACAVAL SHUNT

If the shunt becomes occluded portal hypertension recurs. Increased splanchnic capillary pressure increases intestinal lymph formation and contributes protein-poor fluid to the ascites pool. The measured protein concentration of the ascites becomes lower and lower as this relatively protein-free fluid dilutes the protein-rich fluid derived from the liver. Such patients vividly demonstrate the dual nature of the origin of ascites in cirrhosis.

Maddrey, W.C., Mallik, K.C.B., Iber, F.L., et al.: Extrahepatic obstruction of the portal venous system. Surg. Gynec. Obstet. 127:989, 1968.

Witte, C.L., Witte, M.H., Dumont, A.E., et al.: Protein content in lymph and edema fluids in congestive heart failure. Circulation 40:623, 1969.

Cherrick, G.R., Kerr, D.N.S., Read, A.E., et al.: Colloid osmotic pressure and hydrostatic pressure relationships in the formation of ascites in hepatic cirrhosis. Clin. Sci. 19:361, 1960.

Witte, C.L., Witte, M.H., Cole, W.R., et al.: Dual origin of ascites in hepatic cirrhosis. Surg. Gynec. Obstet. 168:1027, 1968.

Witte, M.H., Witte, C.L., Cole, W.R., et al.: Contrasting patterns of ascites formation in hepatic cirrhosis. J.A.M.A. 208:1661, 1969.

Witte, M.H., Dumont, A.E., Cole, W.R., et al.: Lymph circulation in hepatic cirrhosis: Effect of portacaval shunt. Ann. Int. Med. 70:303, 1969.

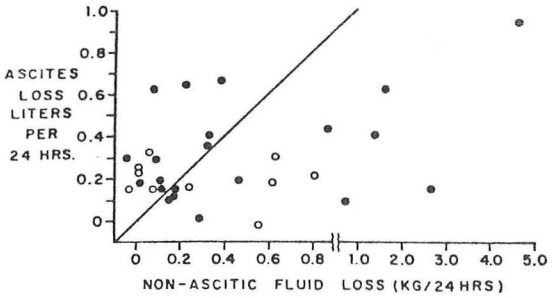
Witte, M.H., Witte, C.L., Dumont, A.E.: Physiological factors involved in the causation of cirrhotic ascites. Gastroenterology 61:742, 1971.

Witte, C.L., Witte, M.H., Kintner, K., et al.: Colloid osmotic pressure in hepatic cirrhosis and experimental ascites. Surg. Gynec. Obstet. 133:65, 1971.

Witte, M.H.: "Ascitic, Thy Lymph Runneth Over". Gastroenterology, 1979. In press.

COMPARTMENTALIZATION OF ASCITES

In classical studies reported in 1970 Shear, Ching and Gabuzda demonstrated that fluid present in the form of ascites was not readily available for return to the vascular compartment. Patients with cirrhosis and ascites were studied under standardized conditions and the volume of ascites was measured repeatedly during the course of spontaneous or diuretic driven diuresis.



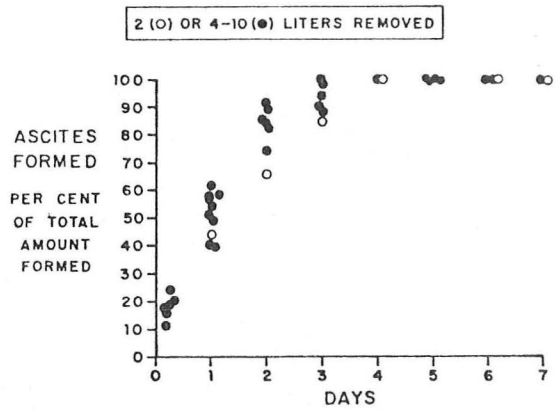
Absorption of Ascitic and Nonascitic Fluid during Spontaneous Diuresis (○) *and Administration of Diuretic Agents* (●).

(Shear et al., N. Engl. J. Med., 1970)

During spontaneous diuresis the ascitic volume in no patient decreased by more than 300 ml per day. Even under the influence of diuretics only one patient mobilized more than 700 ml of ascitic fluid per day. This patient lost 930 ml of ascites but, at the same time, he cleared 5 Kg of nonascitic fluid (i.e. edema). These studies clearly showed a wide disparity between the availability of edema fluid and of ascites fluid for mobilization during diuresis. This phenomenon is probably explicable on the grounds that much of the ascitic volume is not exposed to an absorptive surface but is, in effect, a bag of fluid whose outer perimeter alone is in contact with the peritoneal

lymphatics and capillaries. There is evidence, too, that even this access to absorption is limited in patients with cirrhotic ascites. Buhac and his colleagues have presented histological data which suggests that patients with cirrhosis and ascites have a thickened fibrous peritoneum. Furthermore they have shown in rats that abrasion of the diaphragm with subsequent fibrous obliteration of the major lymphatic vessels draining the peritoneum markedly decreases the rate of resorption of various fluids instilled in the peritoneum. This peritoneal fibrosis in patients with cirrhotics might help explain why the maximum volume of fluid that could be mobilized from the ascites in cirrhotics during effective diuresis was often lower than the measured maximum rate at which intraperitoneally injected saline can be resorbed in normal people (700 to 900 ml/day).

Shear et al. also measured the rate of ascites re-formation after paracentesis.

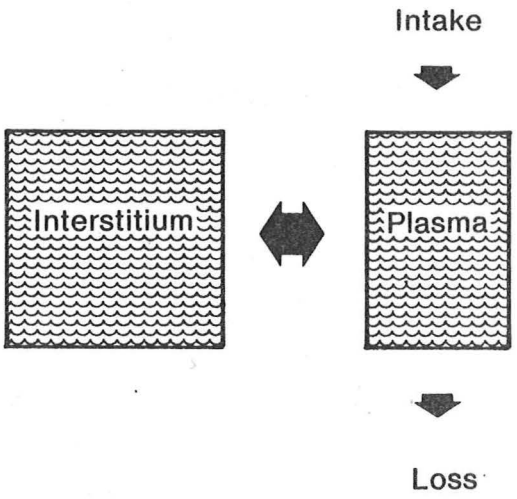


Ascites Formation after Paracentesis Plotted on a Percentage Rather than a Volume Scale.

(Shear et al., N. Engl. J. Med., 1970)

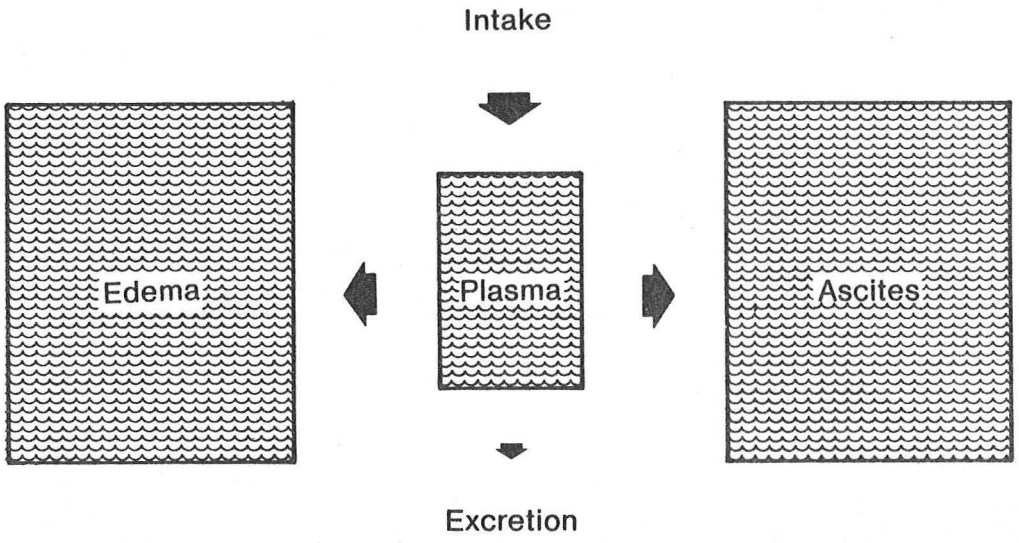
They demonstrated that irrespective of the volume of fluid removed (from 2 to 10 liters) ascites reformed at a rapid and relatively standard rate. Approximately ½ of the new ascites which formed did so within 24 hours of paracentesis and the process of reformation was virtually complete in 2 days. The rate of ascites re-accumulation in these patients was many times greater than their maximum rate of ascites resorption.

This compartmentalization and relative sequestration of ascitic fluid has therapeutic implications and consequences.



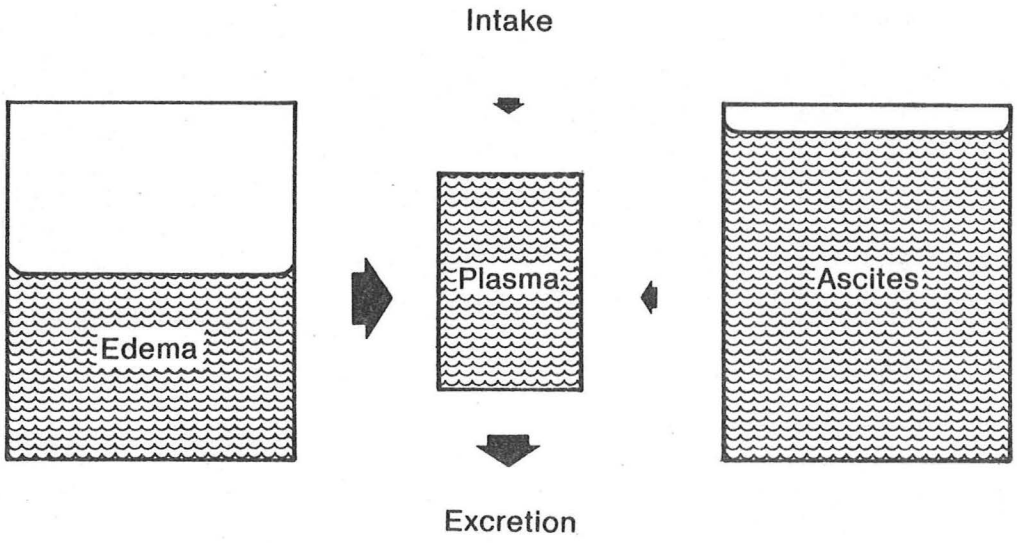
NORMAL FLUID COMPARTMENTS

In a normal person fluid intake equals fluid loss and the plasma volume is normal and in equilibrium with the interstitium.



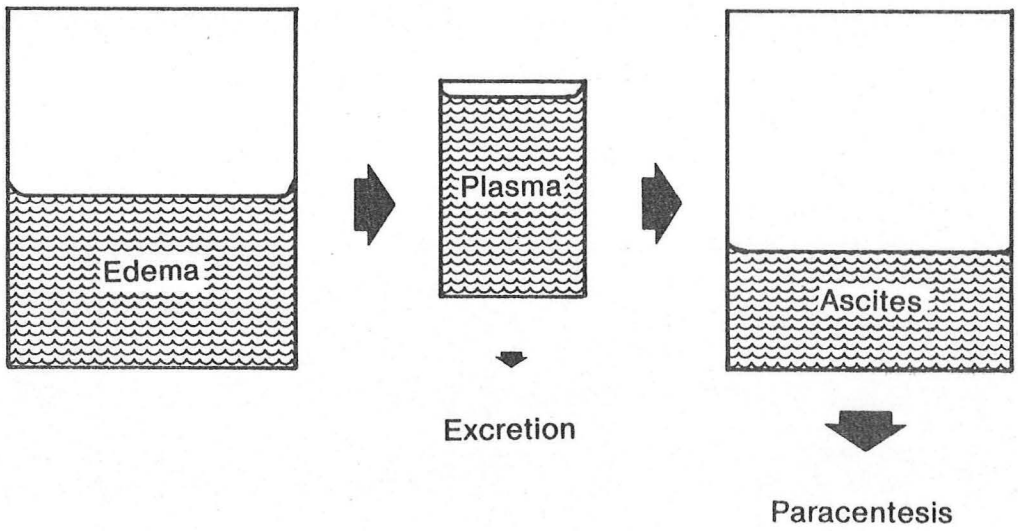
FLUID COMPARTMENTS IN CIRRHOSIS

In a patient with cirrhosis who is forming edema and ascites intake of fluid exceeds output, the plasma volume is normal or increased and the excess fluid is distributed as edema fluid or ascites depending on which of the Starling forces is most severely disturbed.



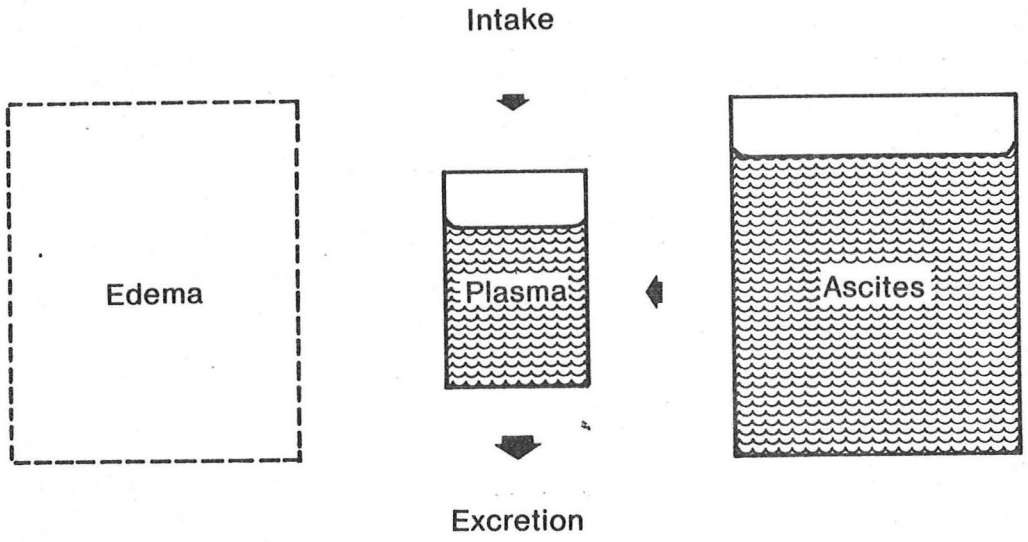
FLUID COMPARTMENTS IN CIRRHOSIS AFTER THERAPY

Therapy of such a patient is aimed at increasing the renal excretion of fluid which is derived from the vascular compartment. This decrease in vascular volume, decreases hydrostatic force and because the kidneys excrete a protein-free fluid the colloid osmotic force also tends to rise. These changes in Starling's forces reverse the movement of fluid across the capillaries and tend to restore plasma volume. Edema fluid is more readily available for this process than ascitic fluid. The intake of salt and water is restricted to prevent the restoration of plasma volume by exogenous fluid and to promote renal losses.



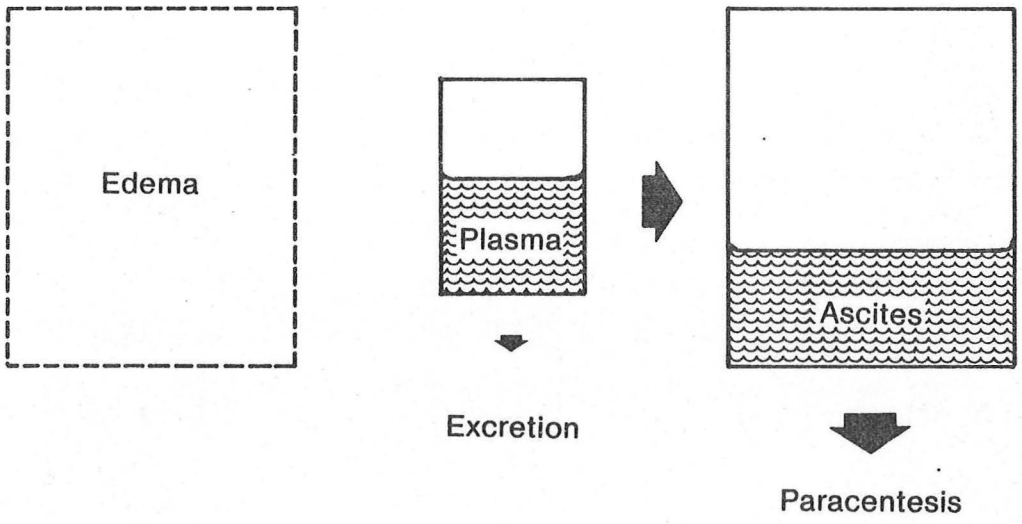
FLUID COMPARTMENTS
AFTER PARACENTESIS IN PATIENT C EDEMA

If a large paracentesis is performed in such a patient, ascites re-accumulation occurs rapidly at the expense of the plasma volume. This limits renal excretion of fluid and encourages a major resorption of edema fluid to maintain the blood volume. In these therapeutic circumstances the ready availability of edema fluid allows a quite vigorous therapeutic approach.



FLUID COMPARTMENTS IN PATIENTS
WITH ASCITES ALONE AFTER THERAPY

In the patient who has ascites without edema therapy must be much more circumspect. The limited rate at which ascitic fluid returns to the vascular space means that potent and effective diuretics coupled with restricted fluid intake are likely to decrease the vascular volume to the point of pre-renal azotemia.



FLUID COMPARTMENTS AFTER PARACENTESIS
IN PATIENT WITHOUT EDEMA

A generous paracentesis in such a patient is also a hazard to blood volume and renal function. Therapy in patients with ascites alone must be cautious and should be adjusted to produce no more than 0.5 Kg loss of body weight per day. If the forces acting to produce ascites are sufficiently strong, ascites may form at a rate exceeding its resorption rate even when the vascular volume has been reduced to the point where azotemia supervenes. Such patients are said to have intractable ascites and they pose major problems in management. More and more potent diuretics are not of avail because the problem is not one of renal refractoriness but one of redistribution of fluid from ascites to the vascular compartment. Because this is a mechanical problem it requires a mechanical solution and a variety of approaches have been tried in the past.

SURGICAL APPROACHES TO ASCITES

Year	Procedure
Forever	Multiple Paracentesis
1898-1943	Omentopexy
1943	Peritoneo-Ureterostomy
1946	Subcutaneous Drainage
1955	Ileal Entectropy
1959	Side to Side P-C Shunt
1962-1968	Peritoneo-Caval Shunt with Holter Valve
1961-1974	Ascites Reinfusion
1974	Peritoneo-Venous (LeVeen) Shunt

All of these various maneuvers aimed at achieving one of three effects:

a) Simplex removal of fluid (paracentesis, peritoneo-ureterostomy).
b) Transformation of ascites into edema fluid.
c) Direct transfer of ascites into the vascular compartment.

Shear, L., Ching, S., Gabuzda, G.I.: Compartmentalization of ascites and edema in patients with hepatic cirrhosis. N. Engl. J. Med. 282:1391, 1970.

Buhac, I., Jarmolych, J.: Histology of the intestinal peritoneum in patients with cirrhosis of the liver. Amer. J. Dig. Dis. 23: 417, 1978.

Lill, S.R., Parsons, R.H., Buhac, I.: Permeability of the diaphragm and fluid resorption from the peritoneal cavity in the rat. Gastroenterology, 1979. In press.

Zink, J., Greenway, C.V.: Control of ascites absorption in anesthetized cats: Effects of intraperitoneal pressure, protein and furosemide diuresis. Gastroenterology 73:1119, 1977.

Luttwak, E.M., Fabian, R.P., Mordochovich, D.: Role of peritoneal absorption in ascites. Surg. Gynec. Obstet. 141:693, 1975.

Shear, L., Swartz, C., Shinaberger, J.A., et al.: Kinetics of peritoneal fluid absorption in adult man. New Engl. J. Med. 272:123, 1965.

Crosby, R., Cooney, E.A.: Surgical treatment of ascites. New Engl. J. Med. 235:581, 1946.

Welch, C.S., Welch, H.F., Carter, J.H.: Treatment of ascites by side to side portocaval shunt. Ann. Surg. 150:428, 1959.

Smith, A.N.: Peritoneo-caval shunts with a Holter valve in the treatment of ascites. Lancet I:671, 1962.

Hyde, G.L., Eiseman, B.: Peritoneal atrial shunt for intractable ascites. Arch. Surg. 95:369, 1967.

Mortenson, R.A., Lawton, R.L.: Surgical treatment for intractable ascites. Amer. J. Surg. 116:929, 1968.

REINFUSION OF ASCITES

The first infusion of ascitic fluid into a human was performed in 1911. The occasional early use of this form of therapy was predicated on preserving the protein contained in ascitic fluid in patients who required repeated paracenteses. The potential for this approach as a means of treating patients with intractable ascites and the investigation of its effects on vascular and renal function have been addressed only over the last 20 years. The experience of all investigators has been that while sometimes quite dramatic acute benefits followed ascites reinfusion no long term benefit followed the use of this form of therapy and the survival of patients so treated was not prolonged. It was a very cumbersome form of therapy and the general consensus was reached that the short term gains did not warrant the effort involved because no long term benefit ensued. Apart from an occasional infection and the suggestion that variceal hemorrhage was sometimes provoked no serious complications were noted to follow the procedure although almost all patients developed a febrile response to the infusion.

Studies performed on patients undergoing ascites re-infusion has provided important insights into the hemodynamic performance and control of patients with cirrhosis and ascites and especially into the pathophysiology of the hepatorenal syndrome. This information has been extended and confirmed subsequently by studies in patients receiving LeVeen peritoneo-venous shunts.

The hepatorenal syndrome remains an ill-defined, nebulous entity whose salient features are the presence of oliguric renal failure in the setting of severe liver disease. The kidneys are anatomically normal and function perfectly well if they are transplanted to another host. Studies by multiple techniques have shown a marked decrease in renal perfusion and a redistribution of renal blood flow from the cortex to the medulla in patients with this syndrome. At a clinical level there is marked oliguria with a normal urinary sediment, an extremely low urinary (Na^+) and a concentrated urine with a high osmolality. Other functional disturbances are listed below.

FINDINGS IN "HEPATORENAL" SYNDROME

1.	Cardiac Output	N or ↑
2.	Serum Aldosterone	↑↑
3.	Serum Renin	↑
4.	Renal Vasc. Resistance	↑
5.	Renal Blood Flow	↓
6.	G.F.R.	↓
7.	Urine Volume	↓↓
8.	Urine (Na^+)	↓↓
9.	Urine Osmolarity	↑
10.	Plasma Volume	N or ↑

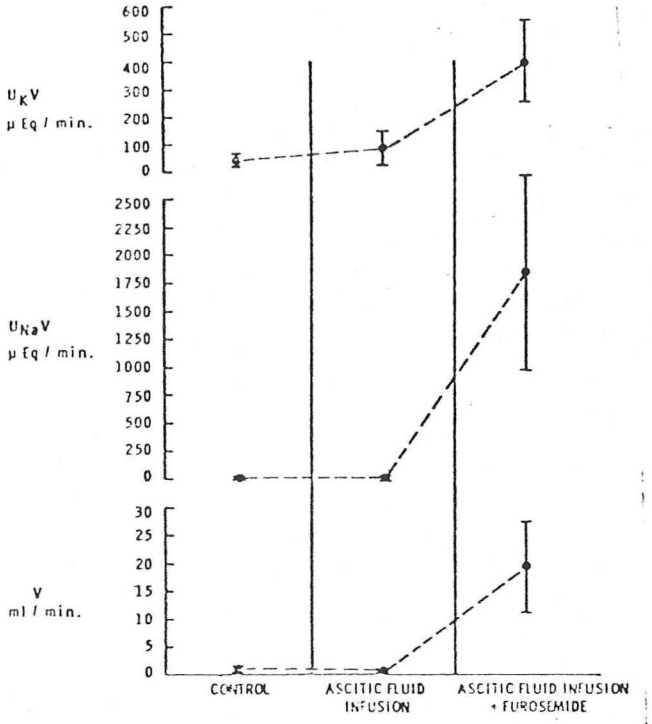
The clinical and functional picture presented by a patient with the hepatorenal syndrome is virtually identical to that of a dehydrated patient with pre-renal azotemia and a constricted plasma volume. The problem has always been that the plasma volume in these patients has usually been found to be normal or increased. This has led to the speculation that an unidentified humoral factor is released or perhaps not destroyed and this inappropriately provokes the hemodynamic effects which would be appropriate for a patient with a contracted blood

volume. Much experimental effort has been expended trying to identify or reverse this presumed humoral (or neural) effect. A difficulty arises however in determining what the "normal" plasma volume should be in patients with severe liver disease who have portal hypertension, are often anemic and may have multiple arterio-venous communications. Age-matched normal controls would seem to be inappropriate and even patients with cirrhosis but without ascites or functional renal failure may be inappropriate because of the milder disease they manifest. If one adds the well recognized observation that the hepatorenal syndrome may be precipitated by the use of diuretics, paracentesis or just hospitalization with salt and water restriction to the clinical fact that this syndrome only develops in patients with ascites and ascites moreover that is, or has been, refractory to therapy one can arrive at the conclusion that the blood volume of these patients is in fact less than they need. The hemodynamic changes become then appropriate responses to a less than adequate blood volume for that particular patient. Strong support has come for this notion of a reversible decrease in "effective" blood volume by studies performed in the 1960's by Tristiani and Cohn, by Vlahcevic et al. and by Ecknoyan et al. in 1970.

EFFECT OF PLASMA EXPANSION

1.	Cardiac Output	↑
2.	Serum Aldosterone	↓
3.	Serum Renin	↓
4.	Renal Vasc. Resistance	↓
5.	Renal Blood Flow	↑
6.	G.F.R.	↑
7.	Urine Volume	-or ↑
8.	Urine (Na^+)	-or sl ↑
9.	Urine Osmolarity	↓
10.	Plasma Volume	↑

Most of the physiological derangements present in patients with intractable ascites with or without renal failure were reversed by the re-infusion of large volumes of ascitic fluid or by the infusion of an equivalent solution of albumin and saline. The interesting observation was made however, that while renal plasma flow and glomerular filtration increased remarkably, and while the aldosterone and renin levels plummetted, diuresis and especially urinary sodium excretion were either not attained at all or else were only modest.



Effect of Ascitic-Fluid Infusion and the Superimposition of Furosemide Injection on Urine Volume, Sodium and Potassium Excretion.

(Eknoyan et al., NEJM, 1970)

In some patients this was associated with a rising central venous pressure. The addition of diuretics (especially furosemide) was followed however by massive diuresis and natriuresis. This observation suggested the possibility that volume deficit was not the sole factor operating in these patients.

It is difficult to determine from the literature how frequently patients with what is considered to be the hepatorenal syndrome fail to respond to volume challenge and furosemide therapy. There are suggestions that this does occur and is more likely to be seen in patients with associated severe acute liver disease. It is possible that the mechanisms producing functional renal failure in these patients are different from those in the relatively stable cirrhotic with intractable ascites. In this latter group the evidence is overwhelming that the major factor leading to the hepatorenal syndrome is a reversible decrease in "effective" plasma volume.

Yamahiro, H.C., Reynolds, T.B.: Effect of ascitic fluid infusion on sodium excretion, blood volume and creatinine clearance in cirrhosis. Gastroenterology 40:497, 1961.

Kaiser, G.C., Lempke, R.E., King, R.D., et al.: Intravenous infusion of ascitic fluid. Arch. Surg. 85:763, 1962.

Vlahcevic, Z.R., Adham, N.F., Jick, H., et al.: Renal effects of acute expansion of plasma volume in cirrhosis. New Engl. J. Med. 272:387, 1965.

Reynolds, T.B., Lieberman, F.L., Redeker, A.G.: Functional renal failure with cirrhosis. The effect of plasma expansion therapy. Medicine 46:191, 1967.

Tristani, F.E., Cohn, J.N.: Systemic and renal hemodynamics in oliguric hepatic failure: Effect of volume expansion. J. Clin. Invest. 46:1894, 1967.

Clermont, R., Vlahcevic, Z.R., Chalmers, T.C., et al.: Intravenous therapy of massive ascites in patients with cirrhosis. II. Long term effects on survival and frequency of renal failure. Gastroenterology 53:220, 1967.

Vlahcevic, A.R., Adham, N.F., Chalmers, T.C., et al.: Intravenous therapy of massive ascites in patients with cirrhosis. I. Short term comparison with diuretic treatment. Gastroenterology 53:211, 1967.

McCloy, R.M., Baldus, W.P., Maher, F.T., et al.: Effects of changing plasma volume, serum albumin concentration and plasma osmolality on renal function in cirrhosis. Gastroenterology 53:229, 1967.

Eknoyan, G., Martinez-Macdonado, M., Yium, J.J., Suki, W.: Combined ascitic-fluid and furosemide infusion in the management of ascites. New Engl. J. Med. 282:713, 1970.

Hacker, L.C., Reinhardt, G.F., Brettschneider, L., Stanley, M.: Intractable ascites: Treatment by continuous autogenous ascitic infusion. Rev. Surg. 31:449, 1974.

Rosoff, L., Zia, P., Reynolds, T. et al.: Studies of renin and aldosterone in cirrhotic patients with ascites. Gastroenterology 69:698, 1975.

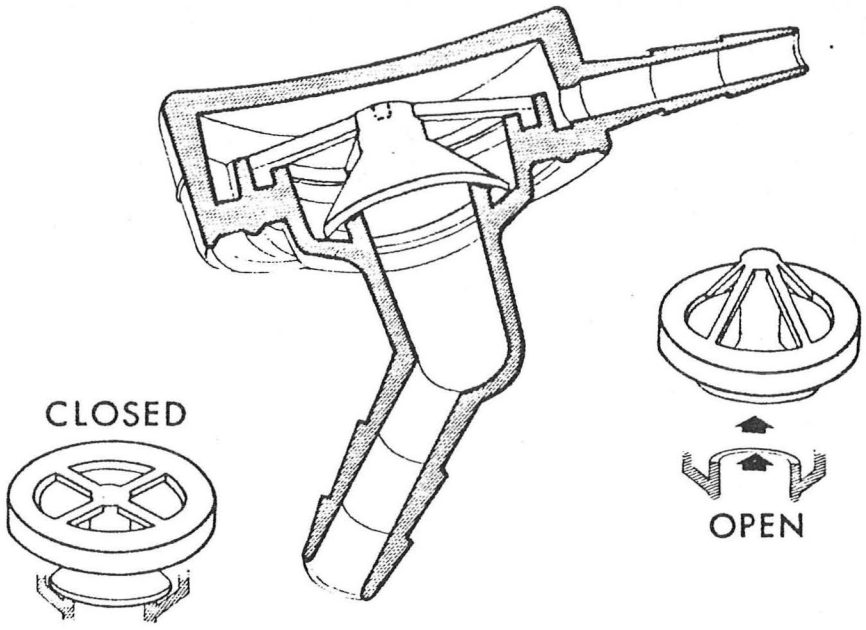
Graziano, J.C., Reinhardt, G.F., Howell, H.S., et al.: Clinical experience with autogenous ascitic fluid infusion for cirrhotic ascites. Amer. Surg. 43:520, 1977.

LEVEEN SHUNT

TECHNIQUE

Autogenous reinfusion of ascites was much too cumbersome a technique ever to become a useful form of therapy. Previous attempts to establish permanent peritoneo-venous shunts using flow activated valves like the Holter valve had been unsuccessful mainly because of the problem of keeping the shunt patent. In 1974 LeVeen reported the first

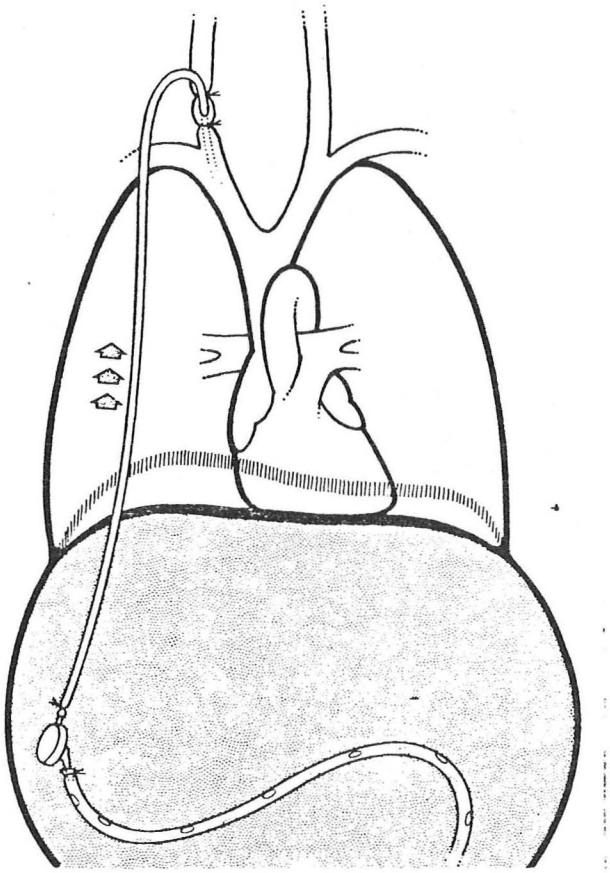
results using a new mechanism designed to function as a one way valve and to be activated by a pressure gradient.



The Pressure Activated Valve—The diaphragm and struts are made of silicone rubber and remain in the closed position unless a force of greater than 3–4 cm of water opens it.

(LeVeen et al., Ann. Surg. 1976)

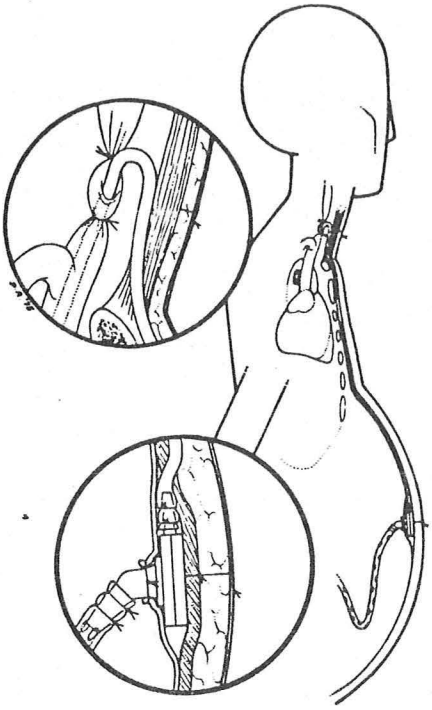
The valve is kept closed by the tensile force exerted by the silicone struts. A pressure of 3-5 cm of H_2O is required to overcome this force and to elevate the diaphragm and allow flow through the valve.



Schematic Drawing Showing Placement of LeVeen Shunt

(H.H. LeVeen, Practical Gastro-enterology, 1978)

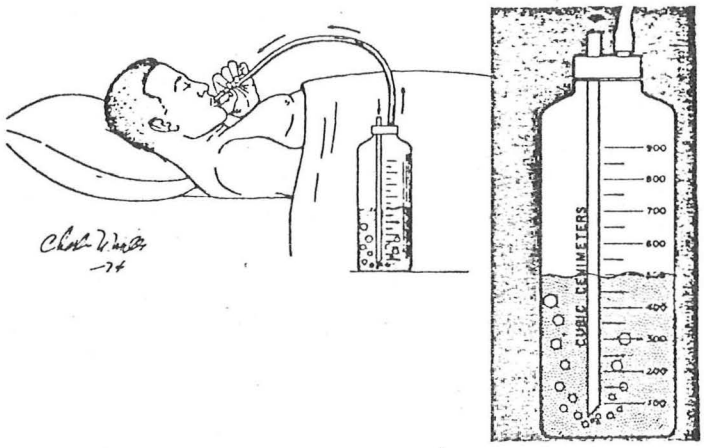
One limb of the shunt lies free in the peritoneal space and is connected to the valve which is placed extraperitoneally but beneath the abdominal wall muscles.



(LeVeen et al., Ann. Surg. 1976)

The venous limb is burrowed subcutaneously up the chest wall and inserted into one of the jugular veins (usually the internal jugular) and positioned to lie in the superior vena cava near the opening into the right atrium. While ever a pressure gradient of 5 cm H_2O exists between the peritoneal cavity and the superior vena cava the valve will stay open and ascitic fluid will flow into the vein. If this pressure gradient is lost, the valve will close. Blood is prevented from refluxing back into the venous limb of the shunt and clotting thereby the standing column of ascitic fluid that remains undisplaced when the valve closes.

The operation is technically simple and can be performed under local anesthesia. Post operatively it is important that the pressure gradient be maintained to keep the valve open. Most patients with chronic ascites have stretched and thinned abdominal walls. When only a small volume of fluid is removed from the peritoneal cavity the intra-abdominal pressure falls to low levels because of the lax abdominal musculature. The normal abdomino-thoracic pressure gradient induced by inspiration may not develop adequately in such patients. Two maneuvers are employed to assist in maintaining the valve open. One is the use of an abdominal binder which raises the intra-abdominal pressure by compression. The degree of pressure generated can be varied with the tightness with which the binder is applied. This has particular application for patients who have large abdominal hernias which vitiate other means of increasing intra-abdominal pressure. The second technique involves exercises which require inspiration against resistance.



The patient inspires against resistance of about 5 cm of water to increase the differential pressure between the superior vena cava and the peritoneum.

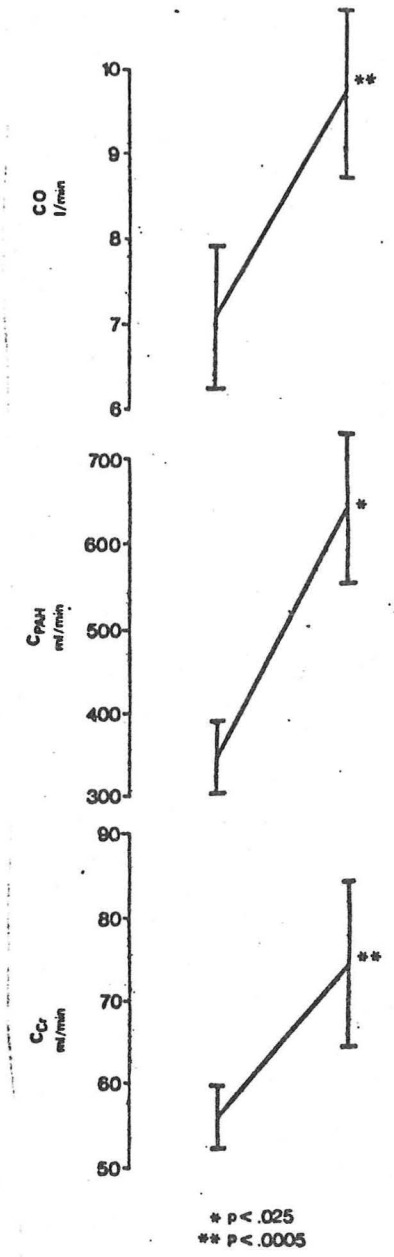
(LeVeen et al., Ann. Surg. 1974)

Lying supine, the patient sucks on the tubing to draw air through a 5 cm column of water. This exercise increases the negative intrathoracic pressure and increases intra-abdominal pressure. Patients are instructed to repeat these 10-20 minute exercises three to six times each day.

RESULTS

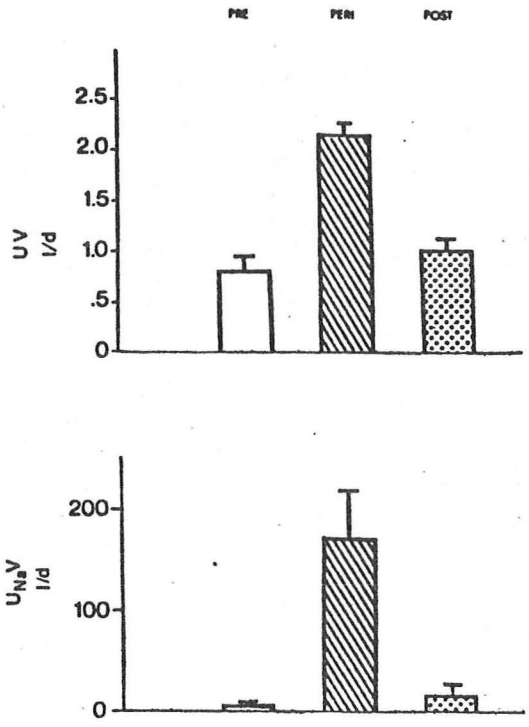
More than 2,000 LeVeen shunts have been placed in patients with ascites. Very few of these patients have been studied effectively however. Nor have the clinical results been described in a way which allows an adequate quantitative assessment of benefits and risks in various population subgroups.

Blendis et al. have reported careful physiological measurements on 15 patients who were studied pre-shunt (immediate 6 days before operation) peri-shunt (the first 3 days following the procedure) and post-shunt (the next 2 week period).



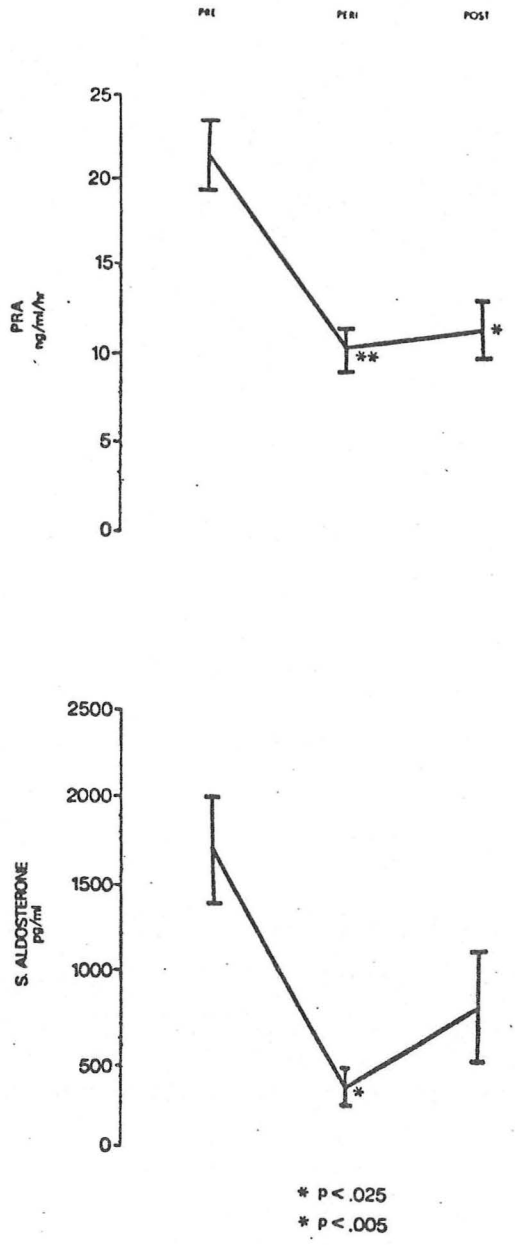
(Blendis et al., Gastroenterology, 1979)

Immediate and dramatic increases in cardiac output were accompanied by marked increases in renal blood flow and GFR.



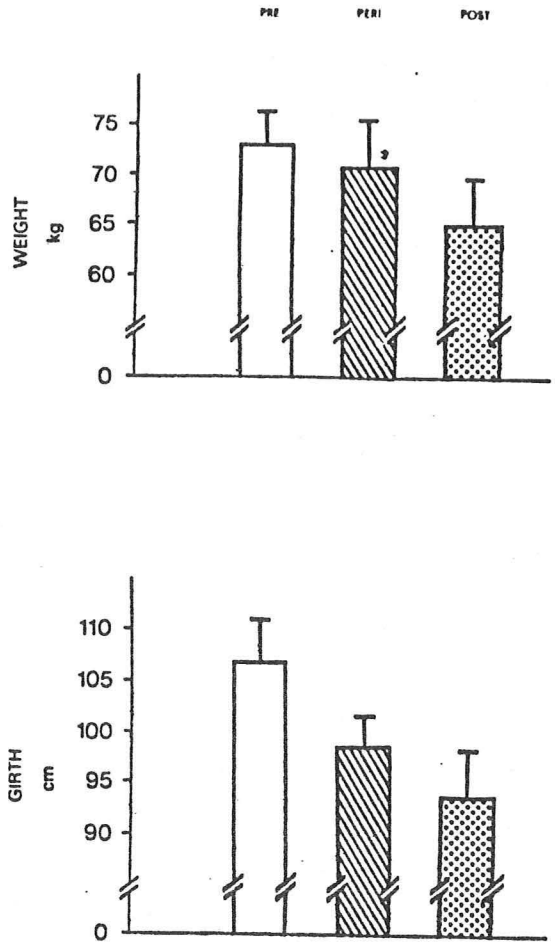
(Blendis et al., Gastroenterology, 1979)

Natriuresis and diuresis were immediate accompaniments although these authors stressed the requirement for coincidental therapy with furosemide to achieve these results. Almost all authors have routinely incorporated the use of furosemide into their protocol for the immediate post-operative management of patients with LeVeen shunts. Some reports document even more dramatic initial diureses with urine volumes as high as 8 to 12 liters per day. To a great extent this unnecessarily rapid rate of diuresis can be modified by the judicious use of furosemide, the avoidance of abdominal binders in the early post operative period, and, if necessary, the discarding of large volumes of ascites at the time of surgery.

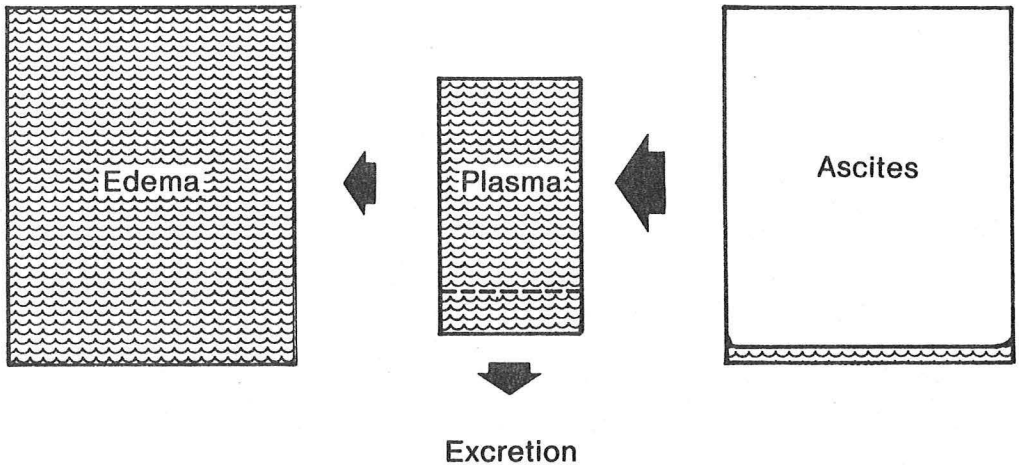


(Blendis et al., Gastroenterology, 1979)

Immediate dramatic reductions in both plasma renin and plasma aldosterone levels are achieved and essentially maintained even when the ascites has been cleared.



(Blendis et al., Gastroenterology, 1979)



FLUID COMPARTMENTS AFTER LEVEEN SHUNT

There is no question that the insertion of this shunt can lead to absolutely dramatic clinical responses in patients who have been crippled by intractable ascites and who have faced imminent death from one of the many serious complications associated with the presence of a large quantity of ascites.

COMPLICATIONS OF ASCITES

Inanition

Spontaneous bacterial peritonitis

Hernias (umbilical, ventral incisional)

Ruptured abdomen

Respiratory embarrassment and infections

Reflux esophagitis

? Precipitation of variceal hemorrhage

Therapy associated catastrophes

Ascites is not just a cosmetic problem as this list of serious problems indicates.

The problems and complications associated with the use of the LeVeen shunt are not inconsiderable either.

COMPLICATIONS OF LEVEEN SHUNT

Common	Less Common
Fever	Pulmonary Edema
D.I.C.	Variceal Hemorrhage
Shunt Occlusion	Bowel Obstruction
Hypokalemia	Air Embolism
Infection	Trauma to Rec. Lar. N.
Ascites Leak	Pneumothorax

Fever and laboratory indications of D.I.C. are very common. Symptomatic D.I.C. and infections are much less common. The cause of the fever is unknown but is presumed to be a pyrogen in the ascitic fluid. The trigger for D.I.C. is also unknown, is also considered to be present in the ascitic fluid and has been linked with an activated tissue thromboplastin and with bacterial endotoxin. D.I.C. may be serious or even fatal. The occurrence of symptomatic D.I.C. probably requires interruption of the shunt but the best method of dealing with the asymptomatic patient with laboratory evidence of consumption has not been established. It may be simple observation.

The development of a documented bacterial infection in the peritoneal fluid or blood stream also poses major therapeutic problems. One is reluctant to remove the shunt and yet concerned that the foreign body may serve as a nidus for continued or recurrent sepsis. If an attempt is made to treat such infection with prolonged antibiotics, recurrence of the same infection demands removal of the shunt.

Laparotomy may become necessary for unrelated or related causes. (Bowel obstruction from incarcerated hernias or strictures is not rare.) Before the abdomen is opened the shunt must be tied off else air embolism may result. A ligature around the subcutaneous tubing on the chest wall is sufficient. The ligature may subsequently be removed after the abdomen is closed and all air is excluded.

The frequency with which these complications develop and the possible association of complications with predictable pre-operative clinical findings has not been adequately assessed yet despite the widespread and growing use of the procedure. It is very difficult therefore to define specifically the use and the contraindications for using this innovative therapy. The following are personal opinions derived from what literature is available and a limited experience with the procedure at Parkland Memorial Hospital.

INDICATIONS FOR LEVEEN SHUNT

Ascites which is:

1. Intractable to adequate medical therapy.
2. Present in a compliant patient.
3. A major determinant of the patient's prognosis.
4. Not likely to become responsive with resolution of associated acute liver disease.

It is important not to expect more from the LeVeen shunt than it is capable of giving. It will, if successful, remove ascites and will reverse functional renal failure if such renal failure is the consequence of ascites formation. It will not cure the underlying liver disease; it will not cure renal failure due to other causes; it will not reverse encephalopathy unless the precipitant for encephalopathy is the uremia associated with functional renal failure; and it will not cure renal failure that is caused by severe hypoalbuminemia with sequestration and non mobilization of edema fluid. If renal failure forms part of the indication for inserting the shunt it is important to demonstrate beforehand that a large volume challenge coupled with I.V. furosemide will promote a diuresis and increase GFR. This volume challenge is given preferably but not necessarily in the form of an ascites re-infusion.

RELATIVE CONTRAINDICATIONS TO LEVEEN SHUNT

1. An element of acute and potentially reversible liver disease.
2. Functional renal failure in presence of edema and marked hypoalbuminemia.
3. Severe acute liver disease.
4. Encephalopathy.
5. Infected ascites.
6. Recent U.G.I. bleeding.
7. Elevated right sided heart pressures.
8. Non-compliance with medical regimen.

The experience of most centers appears to have been the same in that the patients who are most likely to develop serious complications such as symptomatic D.I.C. and sepsis are those patients who have had associated acute liver disease with jaundice, or patients who have been encephalopathic. Some of these patients have also failed to respond with a diuresis suggesting that in patients with severe acute liver disease the genesis of the hepatorenal syndrome might be different from those patients with relatively stable or inactive cirrhosis. The patient's cooperation and compliance is very necessary in the post operative period. A patient whose ascites is intractable because of his non-compliance will not be benefited by a LeVeen shunt but is very likely to have recurrent "intractable" ascites compounded by the added complication of an intraperitoneal and intravenous foreign body. Diuretics and dietary restrictions continue to be a necessary part of therapy

for some months in most patients. The respiratory exercises may have to be continued even after the patients abdominal muscles regain their tone. An abdominal binder may be necessary for a prolonged period. Failure to comply with these facets of the regimen is a common cause of recurrent ascites.

CAUSES OF PERSISTENT OR RECURRENT ASCITES

1. Non-compliance
2. Occluded shunt
3. Mal-placed venous tip
4. CHF

The major concern of course in such a patient is that the shunt has become occluded. This, if it occurs, appears to occur within the first month of insertion and to be more common if the ascites has a high protein content. The venous limb is the more common site of obstruction. Occasionally the venous limb will be inadequately anchored and may migrate into the I.V.C. within the abdomen or into a more peripheral vein in the arm or neck. Kinking of the tube can lead to obstruction; or placement in the I.V.C. within the abdomen can totally prevent the development of a pressure gradient. If the right sided filling pressures become elevated because of congestive heart failure (or as in one of our patients, from anemia) the pressure gradient may be lost too and ascites may recur.

METHODS TO EVALUATE PATENCY OF SHUNT

1. Isotopic
2. Doppler
3. Contrast radiology

Shunt patency can be checked by any of these techniques. The contrast radiological approach is direct and distinguishes between obstruction and malfunction. The isotope and doppler methods should be performed in association with inspiratory exercises.

The isotopic method involves the instillation of sulphur colloid technetium^{99} into the peritoneal cavity. If the shunt is patent the isotope reaches the blood stream and is taken up by the reticuloendothelial system of the liver and spleen (a liver-spleen scan). If the shunt is not working the isotope remains in the peritoneal cavity and there is no uptake over the liver or spleen. An occluded or malpositioned shunt requires replacement or repositioning.

In summary the LeVeen peritoneo-venous shunt offers a great deal to appropriately selected patients. It has some serious complications however and should not be used indiscriminantly. The frequency and severity of the risks demand that the procedure be reserved for those patients whose major problems will be addressed by relief of ascites and in whom more conservative forms of therapy have been found wanting after an adequate trial.

Leveen, H.H., Christoudias, G., Moon, I.P., et al.: Peritoneo-venous shunting for ascites. Ann. Surg. 180:580, 1974.

Leveen, H.H., Wapnick, S., Grosberg, S., et al.: Further experience with peritoneo-venous shunt for ascites. Ann. Surg. 184:574, 1976.

Fullen, W.D.: Hepatorenal syndrome: Reversal by peritoneo-venous shunt. Surgery 82:337, 1977.

Wapnick, S. Grosberg, S., Kinney, M., LeVeen, H.H.: LeVeen continuous peritoneal-jugular shunt. J.A.M.A. 237:131, 1977.

Pladson, R.T., Parrish, R.M.: Hepatorenal syndrome: Recovery after peritoneo-venous shunt. Arch. Int. Med. 137:1248, 1977.

Berkowitz, H.D., Mullen, J.L., Miller, L.D., et al.: Improved renal function and inhibition of renin and aldosterone secretion following peritoneo-venous (LeVeen) shunt. Surgery 84:120, 1978.

Mateshe, J.W., Beart, R.W., Bartholomew, L.G., et al.: Fatal disseminated intravascular coagulation after peritoneo-venous shunt for intractable ascites. Mayo Clin. Proc. 53:526, 1978.

Dupas, J.L., Remond, A., Vermynck, J.P., et al.: Superior vena cava thrombosis as a complication of peritoneo-venous shunt. Gastroenterology 75:899, 1978.

Reinhardt, G.F., Stanley, M.M.: Peritoneo-venous shunting for ascites. Surg. Gynec. Obstet. 143:419, 1977.

Ansley, J.D., Bethel, R.D., Bowen, P.A., et al.: Effect of peritoneo-venous shunting with the LeVeen valve on ascites, renal function, and coagulation in 6 patients with intractable ascites. Surgery 83:181, 1978.

Witte, M.H., Witte, C.L., Jacobs, S., et al.: Peritoneo-venous (LeVeen) shunt. Control of renin-aldosterone system in cirrhotic ascites. J.A.M.A. 239:31, 1978.

Wapnick, S., Grosberg, S., Kinney, M., et al.: Renal failure in ascites secondary to hepatic, renal and pancreatic disease. Treatment with a LeVeen peritoneo-venous shunt. Arch. Surg. 113:581, 1978.

Stein, S.F., Fulenwider, J.T., Ansley, J.D.: Accelerated fibrinogen and platelet destruction after peritoneo-venous shunting. Gastroenterology 74:1161, 1978.

Zarchy, T.M., Chan, C.H., DiBiancho, R., et al.: Peritoneo-venous shunt for intractable ascites: Complications. Gastro-enterology 74:1169, 1978.

LeVeen, H.H., Wapnick, S., Diaz, C., et al.: Ascites: Its correction by peritoneo-venous shunting. Curr. Prob. Surg., Vol. XVI, No. 2, Feb. 1979.

Puig, J.G., Antón, F.M., Gonzales, J.M., et al.: Peritoneo-venous shunt and bacterial endotoxin. Mayo Clin. Proc. 54:733, 1979.

Blendis, L.M., Greig, P.D., Langer, B., et al.: The renal and hemo-dynamic effects of the peritoneo-venous shunt for intractable hepatic ascites. Gastroenterology, 1979. In press.