The Reversal of the Hepatorenal Syndrome in Four Pediatric Patients Following Successful Orthotopic Liver Transplantation

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Four pediatric patients are presented in whom profound renal failure (hepatorenal syndrome) developed in association with severe end-stage liver disease. All four patients had successful orthotopic liver transplantation. Special emphasis is given to the preoperative and postoperative renal function in the patients, and the criteria used to establish the diagnosis of the hepatorenal syndrome are discussed. In the initial work on liver transplantation and reversal of the hepatorenal syndrome, two of the three patients recovered renal function but died in the perioperative period.[1] The four patients presented in this report have not only had reversal of the hepatorenal syndrome after successful orthotopic liver transplantation but have also survived long term. The four patients have been followed up for periods ranging from 18 months to 4.5 years. Three of the four patients have maintained near normal renal function, whereas the fourth patient (who had a left nephrectomy for obstruction and sepsis) has had a significant decline in renal function.

Case Reports

Selected clinical features of the patients presented below are shown graphically in Figures 1 and 2.

Case 1

A 12.5-year-old, 30-kg white male was referred to the University of Pittsburgh on 8/26/81 for evaluation for liver transplantation. He was first hospitalized in Chicago in May 1981 when a diagnosis of Wilson's disease was made based on elevated serum and urinary copper levels, a low serum ceruloplasm, and elevated copper in a liver biopsy. On admission to the hospital in Pittsburgh he was cachectic and deeply jaundiced with moderate ascites and hepatosplenomegaly. Admission laboratory values included a blood-urea nitrogen (BUN) of 13 mg/dL, serum creatinine of 0.5 mg/dL, total bilirubin of 35.8 mg/dL, and a urinary sodium of 26 mEq/L. During the next 2 weeks an attempt was made to control his ascites and hyponatremia. He became oliguric during this period with urinary output falling below 0.78 mL/kg/h. On 9/18/81 the BUN was 48 mg/dL, serum creatinine was 3.0 mg/dL, and total bilirubin was 26 mg/dL. Nephrology consult recommended volume expansion to rule out dehydration and prerenal azotemia. Despite expansion of the patient's intravascular volumes with both colloid and crystaloid, there was no improvement in the urinary output, the urinary sodium remained <10 mEq/L, and the fractional excretion of sodium (FEna) in the urine ranged from 0.3–0.6%. The patient required hemodialysis twice before transplantation. In addition, he had a pronounced deterioration of his neurologic status in the last several days before transplantation and he was in stage 3 hepatic coma at the time of operation. On the day preceding transplantation, laboratory values included a BUN of 80 mg/dL, serum creatinine of 4.0 mg/dL, and total bilirubin of 31.5 mg/dL, and his urinary output was 0.29 mL/kg/h. On 9/27/81 he had an 11-hour liver transplantation during which his urinary output was 0.19 mL/kg/h and his fluid balance was positive 4 L. Over the first 72 hours after operation his urinary output gradually increased from 0.18 mL/kg/h to 0.64 mL/kg/h. Over the same period his BUN rose to 102 mg/dL, whereas the serum creatinine and total bilirubin levels fell to 2.6 mg/dL and 4.5 mg/dL, respectively. By the seventh postoperative day his urinary output

ONE OF THE WELL-DOCUMENTED complications of end-stage liver disease is renal failure. The occurrence of progressive renal failure in patients with severe liver failure has been termed the hepatorenal syndrome (HRS). In 1973, Iwatsuki et al. reported three adult patients who had reversal of their renal failure after successful orthotopic liver transplantation.[1] Unfortunately, two of these patients died in the perioperative period although both had improvement in their renal function. We present four pediatric patients who not only had reversal of their renal failure after successful orthotopic liver transplantation but also have survived long term: three with stable renal function and one with progressive renal impairment.

URINE VOLUME

URINE VOLUME

cc/kg/hr

— Patient #1
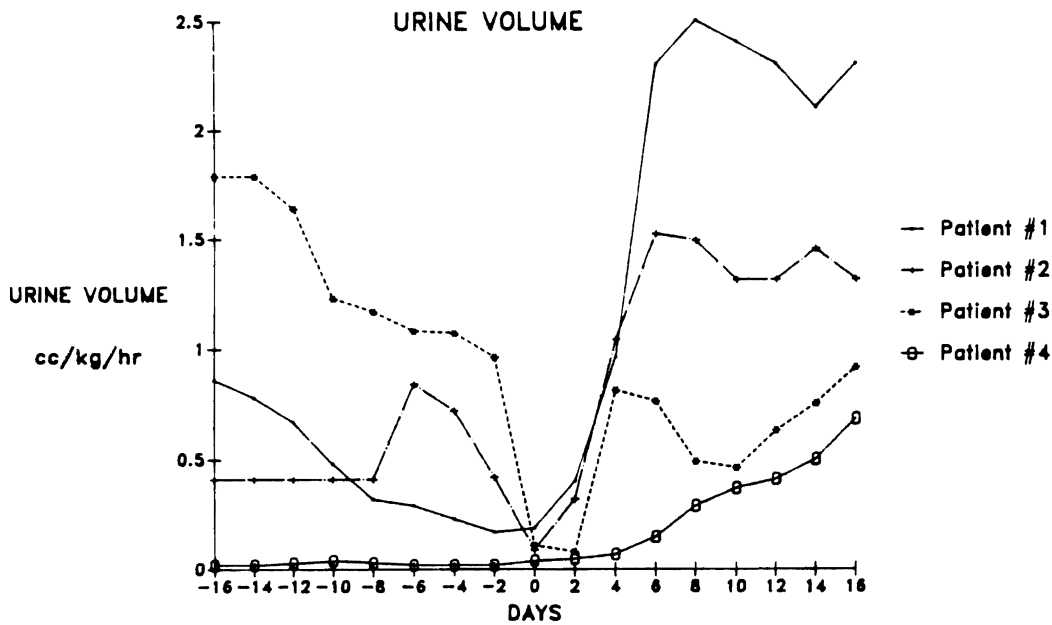—+ Patient #2
-•- Patient #3
-θ- Patient #4

DAYS

Fig. 1. The urinary output for each of the four patients is shown from pretransplantation day 16 through 16 days after transplantation. Day 0 is the day of transplantation. All four patients demonstrate oliguria in the immediate pretransplantation period with more profound oliguria in the immediate post transplantation period. All four patients demonstrated a rapid rise in their urinary output over the first 2 weeks after transplantation, indicating the recovery of renal function in all patients.

had increased to 1.99 mL/kg/h with a BUN of 74 mg/dL and serum creatinine level of 1.5 mg/dL. He did not require dialysis after operation. His general recovery was complicated by slow resolution of his neurologic dysfunction and problems with adequate oral nutrition. After 2 months he was discharged with a BUN of 24 mg/dL, serum creatinine level of 0.7 mg/dL, and total bilirubin level of 0.6 mg/dL. He has maintained stable renal and hepatic function over the 4.5 years since transplantation (Table 1).

Case 2

A 17-year-old, 90-kg white male was transferred to the University of Pittsburgh on 5/3/82 for treatment of end-stage liver failure and for possible liver transplantation. He was first diagnosed with non-A, non-B hepatitis in late 1977. After a course of corticosteroids, jaundice resolved as did a similar episode of jaundice in April 1978. In December 1981,

another episode of jaundice improved but never completely resolved following steroid therapy. In March 1982, he was admitted to a university hospital for spontaneous bacterial peritonitis and poorly controlled ascites. Laboratory values obtained on that admission included a BUN of 8 mg/dL, serum creatinine of 0.8 mg/dL, and total bilirubin of 16 mg/dL. He was treated with gentamicin and a cephalosporin, and despite persistently subtherapeutic gentamicin levels his peritonitis resolved. On 4/25/82 his BUN had increased to 59 mg/dL and his serum creatinine level increased to 2.4 mg/dL. Diuretics were stopped and his intravascular volume was expanded with colloid and crystaloid guided by his central venous pressure measurements. Despite this therapy his serum creatinine level rose to 4.5 mg/dL and his urinary sodium level fell from 55 mEq/L on 4/25/82 to 8 mEq/L on 4/27/82. Oliguria ensued and peritoneal dialysis was instituted. His mental status also deteriorated, and despite continuous peritoneal dialysis his BUN rose to 74 mg/dL and serum creatinine level rose to 5.2 mg/dL. Urinary sodium rose slightly to 26 mEq/L on 4/30/

SERUM CREATININE

— Patient #1 ■
-+ Patient #2 ▨
-•- Patient #3 ▨
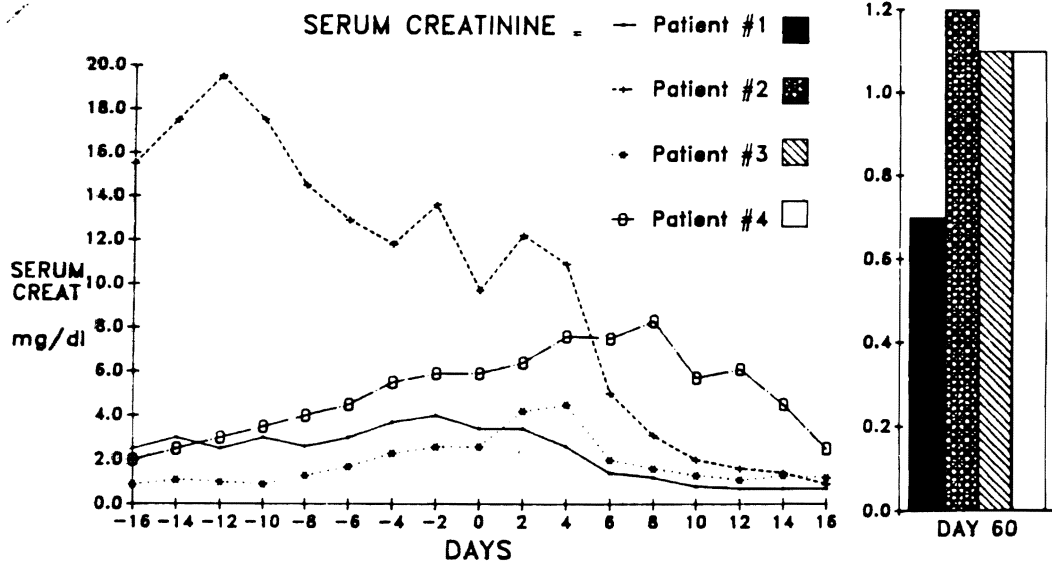-θ- Patient #4 □

SERUM CREAT mg/dl

DAYS

DAY 60

Fig. 2. The serum creatinine levels for each of the four patients is shown from pretransplantation day 16 through 16 days after transplantation. Day 0 is the day of transplantation. The four patients demonstrate varying levels of serum creatinine during the 2 weeks before transplantation as three of the four patients had dialysis during this period (see text for details). The recovery of renal function in all four patients during the first 2 weeks after transplantation is illustrated by the rapid fall in the serum creatinine level experienced by all patients during this period. The insert shows the serum creatinine level for all four patients 2 months after transplantation.

82 although oliguria persisted and FEna was persistently <1.0%. He was transferred to Pittsburgh, and laboratory values on arrival included a BUN of 102 mg/dL and serum creatinine of 15.5 mg/dL. Maximal BUN and serum creatinine levels before operation were 204 mg/dL and 19.5 mg/dL, respectively, whereas urinary output ranged from 0.4 mL/kg/h to 0.8 mL/kg/h and FEna ranged from 0.2–0.7% during the 2 weeks before transplantation. On 5/10/82 he underwent a 13.5-hour liver transplantation during which his urinary output was 0.09 mL/kg/h and he had a positive fluid balance of 6 L. One day after operation his urinary output was 0.13 mL/kg/h and urinary sodium was <10 mEq/L. He required hemodialysis twice during the first postoperative week. On postoperative day 7 his BUN and serum creatinine levels were 134 mg/dL and 3.6 mg/dL, respectively, his total bilirubin level was 15.8 mg/dL, and urinary output was >1.0 mL/kg/h. By day 14 these values had fallen to 47 mg/dL, 1.4 mg/dL, and 9.9 mg/dL, respectively. His postoperative course was complicated by a bile leak requiring an exploratory laporotomy and broad spectrum antibiotics, mild graft rejection, and a painful neuritis at the site of his dialysis shunt. These problems resolved and he was discharged on 6/24/82 with a BUN of 44 mg/dL, serum creatinine level of 1.2 mg/dL, and total bilirubin level of 2.3 mg/dL. He had rejection of his first liver and underwent a second liver transplantation on 1/6/85. He maintained normal renal function throughout the course of his second transplantation and has continued to have stable renal function over the 4 years of follow-up (Table 1).

Case 3

A 12.5-year-old, 35-kg white male was transferred on 10/25/83 to the University of Pittsburgh for evaluation for liver transplantation. He had been diagnosed at the age of 4 years as having alpha-1-antitrypsin deficiency. Since that time he had been hospitalized for a variety of complications of the liver disease including peritonitis, ascites, pleural effusions, hypersplenism, and encephalopathy. On admission in Pittsburgh physical examination was remarkable for profound jaundice, cachexia, hepatosplenomegaly, and massive ascites. Laboratory values included a BUN of 38 mg/dL, serum creatinine of 0.9 mg/dL, total bilirubin of 28 mg/dL, and urinary sodium of 30 mEq/L. After several days in the hospital, he was discharged but was readmitted on 11/14/83 for control of his ascites and again on 12/5/83 for spontaneous bacterial peritonitis. During this last hospitalization his BUN and serum creatinine levels became elevated, and by 12/14/83 they were 64 mg/dL and 1.7 mg/dL, respectively. His urinary output fell from 1.79 mL/kg/h to <1.10 mL/kg/h during this same period. Antibiotics during this period were a first-generation cephalosporin and ampicillin. Urinary sodium fell from 54 mEq/L on 12/13/83 to 24 mEq/L on 12/15/83 (no other values are available), whereas FEna ranged during the perioperative period from 0.2–0.4%. Renal consult recommended a fluid challenged to rule out dehydration and prerenal azotemia as the cause of the renal dysfunction. Despite increasing his central venous pressure to greater than 9 mmHg, his renal function did not improve. One day before operation his laboratory values included a BUN of 100 mg/dL, serum creatinine of 2.6 mg/dL, total bilirubin of 51.2 mg/dL, and his urinary output was 0.96 mL/kg/h. He underwent transplantation on 12/19/83, and during his 13-hour operation his urinary output was 0.11 mL/kg/h and he had a positive fluid balance of 5 L. By postoperative day four his BUN had risen to 166 mg/dL and serum creatinine level had risen to 4.5 mg/dL. He required dialysis five times over the first 12 postoperative days despite a urinary output that increased from 0.04 mL/kg/h to 0.75 mL/kg/h by day 12. By the end of the third postoperative week his BUN and serum creatinine levels had decreased to 86 mg/dL and 0.8 mg/dL, respectively. On postoperative day 10 he was febrile, and Candida was cultured from his urine. Work-up revealed a horseshoe kidney with a left ureteropelvic junction obstruction and hydronephrosis. After a prolonged attempt to eradicate his funguria, including the placement of a left nephrostomy tube, amphotericin irrigations through the nephrostomy tube and sys-

TABLE 1. Follow-Up Laboratory Values as of June 23, 1986

Case #	Interval from Transplant (years)	BUN (mg/dL)	Creatinine (mg/dL)	Bilirubin (mg/dL)
1	4.5	30	1.5	1.7
2	4.0	24	1.1	1.8
3	2.3	96	3.2	1.6
4	1.5	44	1.9	0.8

temic amphotericin, he underwent a resection of the left portion of the horseshoe kidney on 2/23/83. After the procedure he made a rapid recovery, and at the time of discharge on 3/7/83 his BUN was 43 mg/dL, serum creatinine level was 1.1 mg/dL, and total bilirubin level was 0.8 mg/dL. Over the past 27 months of follow-up he has remained well but has had a significant deterioration of his renal function despite continued normal liver function (Table 1).

Case 4

A 13-year-old, 80-kg white female was transferred to the University of Pittsburgh on 10/16/84 for liver transplantation. Approximately 1 month before her transfer she had a flu-like illness with nausea, vomiting, fever, malaise, and pharyngitis. Several days after the onset of symptoms she was seen by her local physician who noted right upper quadrant pain and jaundice (total bilirubin level was 20 mg/dL). The tentative diagnosis was hepatitis although serologic tests for hepatitis were negative. She was admitted to her local hospital 2 days later. Results of physical examination revealed splenomegaly, deep jaundice, and no abnormalities on neurologic examination. Laboratory values included a BUN of 58 mg/dL, serum creatinine of 4.8 mg/dL, and total bilirubin of 55.8 mg/dL. The patient was transferred to a university hospital where re-evaluation revealed that her renal failure, coagulopathy, and liver failure had all worsened and she was now in stage two hepatic coma. A diagnosis of acute Wilson's disease was confirmed by the presence of elevated serum and urinary copper levels, low serum ceruloplasm, and high copper levels on liver biopsy. Over the next 12 days her condition further deteriorated. She had two respiratory arrests requiring mechanical ventilation, dopamine, and lidocaine. She became oliguric (urinary output <0.02 mL/kg/h) and was maintained on daily hemodialysis. A liver became available for transplantation on 10/16/84 and the patient was transferred to Pittsburgh. Preoperative laboratory values included a BUN of 67 mg/dL, serum creatinine of 5.9 mg/dL, and total bilirubin of 48 mg/dL. During her 18-hour surgery her urinary output was 0.04 mL/kg/h and she had a positive fluid balance of 7 L. Over the first 7 days after operation her urinary output increased from 0.05 mL/kg/h to 0.29 mL/kg/h. She required hemodialysis four times during the first 2 postoperative weeks. Renal function steadily improved and her Bun was 80 mg/dL and serum creatinine level was 2.3 mg/dL by the end of the first postoperative month. Her total bilirubin level 1 month after operation was 3.0 mg/dL. This recovery took place in the face of a number of complications that occurred during the postoperative period. These included two episodes of cutaneous herpes requiring two 10-day courses of acyclovir, a bile leak requiring operative repair and broad spectrum antibiotics for 14 days, and moderate rejection of the hepatic allograft reversed with high-dose steroids. Two months after transplantation she was discharged with a BUN of 56 mg/dL, serum creatinine level of 1.1 mg/dL, and total bilirubin level of 1.4 mg/dL. She was readmitted approximately 3 months later for treatment of acute rejection of the hepatic allograft. At that time she had a major gastrointestinal hemorrhage as well as a severe episode of rejection. Despite these difficulties her renal function remained essentially unchanged from the time of her initial discharge and has remained stable during the 18 months of follow-up (Table 1).

TABLE 2. Criteria Used to Diagnose HRS

Criteria
Presence of severe liver disease.
Absence of primary renal disease.
Acute or subacute onset of azotemia.
Relative oliguria with urine output <500 mL/24 h.
Urinary sodium <10 mEq/L or FEna <1.0%.
Benign urinary sediment.
No response to volume expansion or correction of "prerenal" factors.

Discussion

HRS was first described by surgeons in the 1930s, and since that time it has been the subject of much research and speculation.[2] One of the major difficulties in the study of this syndrome has been the lack of universal agreement regarding the criteria needed to establish this diagnosis.[3-5] The criteria that we have used to make this diagnosis are listed in Table 2. Although not all inclusive, these criteria have served as useful guidelines to identify the presence of this syndrome in our patients awaiting liver transplantation. All of these patients had obvious severe end-stage liver failure and would have died in a relatively short time had they not undergone a liver transplantation. Three patients had deterioration of their liver function over several years, whereas Case 4 had acute hepatic failure. All four patients had profound hyperbilirubinemia at the time of their liver transplantation. However, there has been no correlation between the level of bilirubin and the onset of renal failure.[3] Our experience would tend to support this. Many of the patients awaiting liver transplantation have total bilirubin levels that are elevated to an even greater degree than the four patients presented, and yet many of these patients maintain normal renal function.

All four patients had progressive deterioration of their renal function yet, in all four, the urinalysis remained normal on repeated examinations throughout their preoperative hospital course. In Cases 1 and 3, despite long histories of progressive liver failure with multiple complications, renal failure developed acutely in less than 2 weeks. Case 2 also had chronic hepatic failure but experienced a more gradual onset of renal failure over the course of several weeks. Renal failure developed in Case 4 soon after the onset of acute hepatic failure. Neither the duration of the renal failure or length of time with hepatic failure nor the time course over which the renal failure developed seemed to influence the duration of the renal failure after transplantation.

Papper[3] noted the interesting observation that most of his 200 patients with HRS entered the hospital with normal renal function. This was also the case in three of our four patients. The question that remains unanswered is whether the HRS results from the events that precipitated the hospital admission or results from events that occur after the patient is hospitalized. The single most prominer factor in our patients appeared to be an acute depletio of the intravascular volume. In Case 4 this appeared t be secondary to severe emesis, whereas in Cases 1 and it was related to aggressive diuretic therapy to control a: cites. Cases 2 and 3 had episodes of moderately sever peritonitis, and Case 2 also had a gastrointestinal hem orrhage as another possible precipitating event. Unfor tunately no consistent precipitating event(s) has bee: identified. As stated by Papper,[3] "There are no apparen clinical, functional, renal, or hepatic laboratory charac teristics that identify those patients with cirrhosis wh will ultimately develop renal failure."

Just before transplantation, urinary output of these fou: patients averaged 0.39 mL/kg/h (range: 0.02–0.96). How ever, all patients experienced severe oliguria during op eration and during the immediate postoperative period Iwatsuki et al.[1] reported that the time for recovery of rena function in three adult patients was quite variable. In thi: series, all four patients had a significant return of rena function by the end of the second postoperative weel (Figs. 1 and 2). In all cases the recovery of renal functior was associated with continued improvement in hepati allograft function. This correlates well with the fact tha: in the isolated case reports of spontaneous recovery from the HRS reported in the literature, the single most im portant factor was improvement in the patients' live: function.[3,5-8]

All four patients received intravenous cyclosporine a: their primary immunosuppressive agent. This drug i: profoundly nephrotoxic, and it is interesting that renai function improved and normalized despite the use of this drug. The recovery of renal function also occurred in spite of the fact that three of the four patients had significant postoperative complications including, in Case 3, a left nephrectomy and the use of systemic amphotericin, an other potentially nephrotoxic agent. Three of the four pa tients have maintained stable renal function during the follow-up period, which ranges from 1.5–4.5 years. Case 3, however, has experienced a gradual deterioration of his renal function since his transplantation, possibly second ary to damage done to the remaining portion of his horse shoe kidney at the time of the partial nephrectomy or perhaps secondary to long-term cyclosporine nephrotox icity (Table 1). It is clear from the course of our patients that after recovery from the HSR there are no long-term detrimental effects on renal function. This reaffirms the concept that the renal insult in patients with the HSR is reversible and that the damaged liver is the source of the nephrotoxic "agent."

The differentiation of the HRS from prerenal azotemia or acute tubular necrosis is often quite difficult. All of the patients except Case 4 underwent a deliberate attempt to expand their intravascular volume to eliminate dehydra-

tion or prerenal azotemia as the cause of their deteriorating renal function. There was no improvement in any patient after this therapy. The attempt to expand the intravascular volume in this group of patients must be closely guided, as it was in these patients, by the central venous pressure measurements. Pulmonary edema is prone to develop in these patients even with minimal volume overload.

One finding believed by most authors to be important in the diagnosis of the HRS has been the presence of urinary sodium concentrations of <10 mEq/L. In addition, Steiner (1984) and Espinel (1976) noted that patients with the HRS had FEna of <1.0%.[9,10] All four patients had values for urinary sodium excretion within the above limits. A wide range of values was noted in all patients, and urinary sodium excretion varied with the stage of the illness. This further illustrates that no single criterion can be exclusively used to make the diagnosis of the HRS. Rather, the diagnosis is dependent on both laboratory and clinical data that are interpreted in the overall setting of the patient's illness.

The benefit of dialysis in patients with the HRS has been controversial,[11-15] and the use of dialysis in patients with the HRS has even been claimed to have an adverse effect on survival.[13] In the current series, Cases 1, 2, and 4 had dialysis before transplantation, and no patient experienced a further deterioration in their clinical status. In fact, Case 2 had an increase in urine volume after the institution of peritoneal dialysis. Three of the four patients required further dialysis treatments after operation before the return of adequate renal function. Although there is no data to support the routine use of dialysis in patients with the HRS, in our unique transplant population the use of preoperative dialysis supported three patients until a suitable donor liver could be procured, whereas postoperative dialysis provided support for three patients until there was adequate improvement in their intrinsic renal function. Therefore, in this unique group of patients with the HRS, dialysis was of unquestionable value.

It is beyond the scope of this paper to discuss the various theories that speculate as to the cause of the HRS, and the reader is referred to the excellent reviews by Papper,[3] Metz and Tompkins,[5] and Conn.[4] The major difficulty in identifying the cause of this syndrome has been high mortality associated with the syndrome, which obviously does not allow for comparisons of patients before and after recovery from the syndrome. Detailed studies of liver transplant candidates in whom HRS develops and whom subsequently undergo transplantation may provide invaluable information in the search for the cause of this syndrome.

References

1. Iwatsuki S, Popovtzer M, Corman J, et al. Recovery from "hepatorenal syndrome" after orthotopic liver transplantation. N Engl J Med 1973; 289:1155–1159.
2. Helwig F, Schutz C. A liver kidney syndrome. Clinical, pathologic, and experimental studies. Surg Gynecol Obstet 1932; 55:570–580.
3. Papper S. The hepatorenal syndrome. In Epstein M, ed. The Kidney in Liver Disease. New York: Elsevier, 1983; 87–106.
4. Conn HO. A rational approach to the hepatorenal syndrome. Gastroenterology 1973; 65:321–340.
5. Metz RJ. Tompkins RK. The hepatorenal syndrome. Surg Gynecol Obstet 1976; 143:297–304.
6. Reynolds TB. The hepatorenal syndrome. In Schaffer F, Sherlock S. Leevy C, eds. The Liver and Its Disease. New York: Intercontinental Med Book Corp, 1974; 307–313.
7. Schwartz M, Vogel S. Treatment of the hepatorenal syndrome. Am J Surg 1980; 139:370–373.
8. Baldus W, Summerskill W. Liver and kidney interrelationships. In Schiff C, ed. Diseases of the Liver. Philadelphia: JB Lippincott, 1975; 458.
9. Steiner RW. Interpreting the fractional excretion of sodium. Am J Med 1984; 77:699–702.
10. Espinel CH. The FEna test: use in the differential diagnosis of acute renal failure. JAMA 1976; 230:579–581.
11. Adler A, Feldman J, Friedman E, Berlyne G. Use of extracorporeal ascites dialysis in combined hepatic and renal failure. Nephron 1982; 30:31–35.
12. Krumlovsky F, Del Greco F, Neiderman M. Prolonged hemoperfusion and hemodialysis in the management of hepatic failure and hepatorenal syndrome. Trans Am Soc Artif Intern Organs 1978; 24:235–238.
13. Wilkinson S, Weston M, Parsons V, Williams R. Dialysis in the treatment of renal failure in patients with liver disease. Clin Nephrol 1977; 8:287–292.
14. Perez G, Oster J. A critical review of the role of dialysis in the treatment of liver disease. In Epstein M, ed. The Kidney in Liver Disease. New York: Elsevier 1978; 325–336.
15. Parsons V, Weston M, Wilkinson S. Use of dialysis in the treatment of renal failure in liver disease. Postgrad Med J 1975; 51:515–520.