Hepatorenal syndrome: a historical appraisal of its origins and conceptual evolution

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The hepatorenal syndrome (HRS), a progressive but potentially reversible deterioration of kidney function, constitutes a serious complication of hepatic decompensation. Coexistence of liver/kidney damage, mentioned in the dropsy literature, was highlighted by Richard Bright in 1827 and confirmed in 1840 by his contemporary nephrology pioneer Pierre Rayer. Cholemic nephrosis was described in 1861 by Friedrich Frerichs, and the renal tubular lesions of HRS by Austin Flint in 1863. The term "acute hepato-nephritis" was introduced in 1916 by Paul Merklen, and its chronic form was designated HRS by Marcel Dérot in 1930s. HRS then was applied to renal failure in biliary tract surgery and to cases of coexistent renal and hepatic failure of diverse etiology. The pathogenesis of HRS was elucidated during the 1950 studies of renal physiology. Notably, studies of salt retention in edema and its relation to regulating the circulating plasma volume by John Peters and subsequently Otto Gauer defined the concept of "effective blood volume" and the consequent elucidation of ascites formation in liver failure. Parallel studies of intrarenal hemodynamics demonstrated severe renal vasoconstriction and preferential cortical ischemia to account for the functional renal dysfunction of HRS. Dialysis and liver or combined liver-kidney transplantation transformed the fatal HRS of old into a treatable disorder by the 1970s. Elucidation of the pathogenetic mechanisms of renal injury and refinements in definition, classification, and diagnosis of HRS since then have allowed for earlier therapeutic intervention with combined i.v. albumin and vasoconstrictor therapy, enabling the continued improvement of patient outcomes.

Kidney International (2021) **99,** 1321–1330; https://doi.org/10.1016/j.kint.2021.02.037

KEYWORDS: acute kidney injury; ascites; bile nephrosis; hepatorenal syndrome; liver failure

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Received 29 August 2020; revised 12 February 2021; accepted 17 February 2021; published online 27 March 2021

The origin of medical concepts can hardly be determined precisely, but insight into their emergence and conceptual evolution can be gleaned from a historical appraisal of their adoption into the nosography of medicine. The course followed by the time-honored evolutionary process of generating medical knowledge is a product of the interplay between observation, experience, and analytical thought that is effectively articulated; then transmitted, investigated, verified; and ultimately integrated into the parlance of medicine.[1] This painfully slow process accelerated in the 19th century and has literally exploded since World War II. It is within this general framework of knowledge accrual that the progressive renal dysfunction that complicates hepatic decompensation came to be identified as the hepatorenal syndrome (HRS). This review explores the origins and the conceptual evolution of the HRS, a serious life-threatening complication of liver failure that went unrecognized until the 19th century.[2–4]

Ancient origins

It was within the broad scheme of chance accrual of ancient medical knowledge that movement, body heat, and blood were first recognized as determinants of life. The vitality of blood was reinforced by the experience of early hunters and gatherers. Their daily quest for food clearly displayed the largest organ of their kill flush with vital blood was the liver, which began to be considered a crucial organ. Over time, the liver came to be perceived as an organ of divination in the mysticism of Mesopotamia, a seat of feelings and emotions in the holy scriptures, and the site of the immortal soul in the mythology of Greece.[5,6]

These cultural determinants of "hepatocentrism" notwithstanding, it was Greek medicine that established the primacy of the liver in medical thought. Beginning with the Hippocratic doctrine (ca. 5th–4th centuries BC) of the 4 humors (yellow bile, black bile, phlegm, and blood), the liver was destined to prominence as the generator of 2 of the humors, blood and yellow bile. The importance of bile was further magnified by the Platonic view of bile as a morbid secretion that causes inflammation.[7] Actually, it was Galen (130–210) who in his formulation of physiology established the centrality of the liver as the essential nutritive organ that produced blood and secreted bile, a cleansing excretory function in which it was assisted by the spleen for eliminating black bile and the kidneys for eliminating excess fluids. These distorted Galenic concepts would dominate medical

scholarship until the discovery of the circulation in 1628 by William Harvey (1578–1657), when the liver was dethroned as the body's principal organ but maintained its central role as a glandular organ essential to nutrition. Still, although Harvey did clarify the physical dynamics of the circulation, blood continued to be considered a homogeneous red fluid formed in the liver, which Harvey said was then "*imbued with spirits*."[6] It is in the 19th century that the bone marrow was established as the seedbed of blood cell formation.[8] More important, even after the functions of the bone marrow, liver, and spleen were also elucidated, the kidney continued to be considered a parenchymatous secretory organ subservient to the nutritional needs of the body well into the 20th century.[9]

Early inklings

It was when the kidney began to be studied as an independent site of disease that its potential link to liver disease, in what would become the HRS, began to be perceived but not established. The coexistence of liver and kidney disease is mentioned in scattered reports throughout medical texts, particularly in the literature on dropsy, whose study by Richard Bright (1789–1858) would lead to the emergence of nephrology. In his original 1827 "*Report of Medical Cases*," Bright also records his observations on 7 cases of dropsy due to liver disease.[10] In his introductory remarks to this section, he states that the liver in cases of dropsy due to kidney disease was ". . . *seldom perfectly healthy, though deviation from the natural structure has been often slight but showed a tendency to granulation.*" In his case reports of dropsy cases due to liver disease, their urine is variably reported as "*scanty*," diminishing before death, "*high coloured*," or loaded with "*pink sediment*" that did not coagulate on heating, except in one case. The kidneys of case 26 of dropsy attributed to liver disease are described as "*rather pale, with irregular vascularity but in structure normal*," whereas those of case 29 are said to be "large, unhealthy."[10]

By the same token, another eminent founder of nephrology, Pierre Rayer (1793–1867), reports on the occurrence of liver cirrhosis in subjects with kidney disease. In the section of "albuminous nephritis" of his 3-volume magisterial "*Traité des Maladies des Reins*," Rayer refers to Bright's remarks and states that the liver was abnormal in a third of his cases of albuminous nephritis, small in some and nodular in others.[11] Also, Jean Martin Charcot (1825–1893) in his 1877 book on liver and kidney diseases reports on the occurrence of Bright's disease in 14%–6% of cases of alcoholic liver cirrhosis.[12,13] The finding of concurrent hepatic and renal lesions at postmortem examination soon began to be reported by other investigators.[14,15] As a result, by the mid-1870s, "*uræmia in afflictions of the liver*" became a topic of discussion, with "*uræmic poisoning*" as a "*functional derangement*" reported as a "*first symptom of structural liver disease . . . in the absence of structural kidney disease.*"[16,17]

It is evident then that when kidney disease began to be recognized in the 19th century, it was noted to coexist in some cases with liver abnormalities. Could any of these cases be considered early inklings of the HRS? Possibly, but who can be sure?

Clinical beginnings

The recognition of what would become the HRS came from the convergence of 2 intertwined paths to its nosography. The first was from studies of liver disease, notably by the German pathologist Friedrich Frerichs (1819–1885), well known for his contributions to Bright's disease but equally famous for his contributions to diseases of the liver. In his classic "*A Clinical Treatise on Diseases of the Liver*," published in 1858, Frerichs describes the oliguria of liver failure in the absence of significant changes in renal pathology.[18] In the *Atlas* accompanying his book, Frerichs clearly identifies what is termed cholemic nephropathy (Figure 1).[19] It was a trainee of Frerichs, Adolf Weil (1848–1916), who in 1886 reported an "*acute infectious disease with splenomegaly, icterus and nephritis*" that would become his eponymous disease due to leptospirosis.[20] Actually, cases of Weil disease were some of the first to highlight the coexistence of liver and kidney injury and the introduction of the term "*hepatonéphrite*" in the French literature.[20,21]

Renal lesions in liver cirrhosis and their essential clinical features were documented in 1863 by the US physician Austin Flint (1812–1886).[22] In his report of 46 cases of ascites due to liver cirrhosis that was fatal in 24 and autopsied in 11, Flint noted that at postmortem the most common extrahepatic organ involved was the kidney in 6 of 11 autopsied cases. As the renal lesions were degenerative rather than inflammatory, they came to be classified as "*nephrosis*," a term introduced in 1905 to differentiate renal tubular degenerative lesions from the glomerular inflammatory lesions of "*nephritis*."[23] Thus, by the closing decades of the 19th century, hepatologists were becoming increasingly aware of the occurrence of renal damage in some of their patients with cirrhosis.

The second path to the recognition of the HRS was from a renal perspective prompted by the general interest in nephritis that followed Bright's description of his eponymous disease. One of the initial reports to highlight it was by the French physician Prosper Jean Merklen (1874–1939), who in 1916 described 15 patients with acute hepatic failure, jaundice, and ascites who developed an "*acute nephritis*" evidenced by an oliguria that rapidly progressed to anuria, which he termed "*hépato-néphrite aigue*" (acute hepatonephritis).[24] Nine of his cases died with uremia, whereas 6 developed polyuria and recovered. The entity was studied and exposed in greater detail by a pioneer of French nephrology, Maurice Dérot (1901–1985). In his 1937 monograph "*Les Hépatonéphrites*," Dérot describes what he termed "*hépatonéphrite simple*" (simple hepatonephritis) with a rapidly progressive deteriorating course that corresponds to what came to be classified in the mid-1990s as HRS type 1 and that of "*hépatonéphrite chronique*" (chronic hepatonephritis) or "*syndrome hépatorenaux*" (hepatorenal syndrome) with a slower indolent chronic course that corresponds to that of HRS type 2 classification.[25]

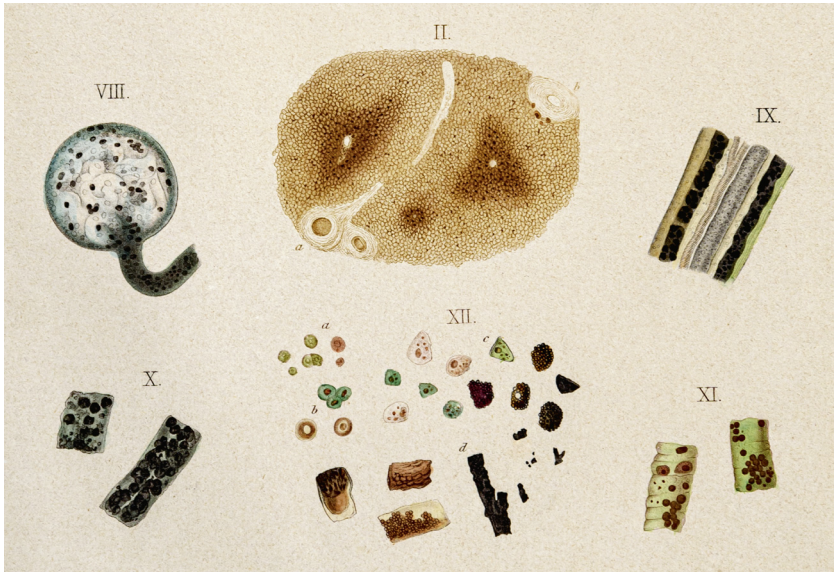

Figure 1 | Jaundice of the kidneys in a 55-year-old man with cancer of the head of the pancreas. Plate I is reproduced from Frerichs FT. *Atlas of Pathological Anatomy Illustrative of a Clinical Treatise on Diseases of the Liver: Part 1*. Murchison C, ed. Brunswick, Germany: Frederick Vieweg and Son; 1861. [Murchison C, Trans],[19] courtesy of the Royal College of Physicians of Edinburgh Library. Author's legend: "Fig. 2 Hepatic lobule; Fig. 8 Malpighian capsule and commencement of a uriniferous tube; Fig. 9 A group of uriniferous tubes from the pyramids of the same kidney; Fig. 10 Two fragments of uriniferous tubes from the cortical portion of the kidney; Fig. 11 Two other pieces of uriniferous tubes from same kidney; Fig. 12 Glandular epithelium cells from the same kidney."

It is in this setting that a link of liver and kidney disease received attention in the surgical literature of the 1920s, specifically as acute renal failure noted in jaundiced patients undergoing surgery for gallstones, biliary tract disease, or liver trauma.[2,26] Thus, it was as a surgical complication of "*liver death*" that the term "*hepatorenal syndrome*" entered the English surgical literature in the early 1930s, and soon began to be reported in nonsurgical cases of jaundice and liver failure (Figure 2).[26–30] As a result, a diagnosis of HRS came to be applied to a wide array of clinical conditions with coexistent kidney and liver dysfunction, resulting in an expanding list of confounding terms (urohepatic syndrome, hepatourologic syndrome, hepatic nephropathy, jaundice-related nephropathy, bile nephrosis, and cholemic nephropathy). The expanding list of diverse and varied entities considered as HRS led to expressed concern over its indiscriminate application to disparate conditions other than the unexplained renal failure observed in alcoholic cirrhosis and the proposal that they collectively be termed "*pseudo-hepatorenal syndromes*."[31] It was only after studies of kidney function in liver cirrhosis clarified the pathogenesis of the HRS that the condition would be elucidated and properly classified in the 1990s and further clarified thereafter.[32]

Initial functional studies

Medical interest in renal function in general and in liver disease in particular attracted increasing attention after World War II when the proliferating studies of kidney function in health and disease were compiled and analyzed by a founding father of nephrology, Homer Smith (1895–1962).[33] In his classic 1951 book, "*The Kidney. Structure and Function in Health and Disease*," Smith summarized the then available information on HRS as one due to diverse conditions wherein a failure of the detoxifying function of the diseased liver leads to the accumulation of potentially nephrotoxic agents that,

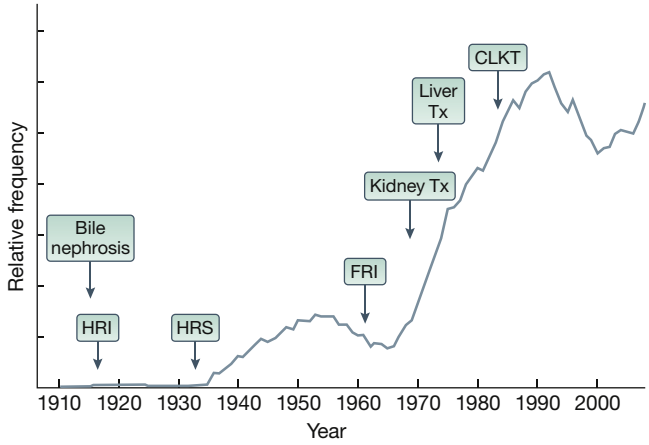

Figure 2 | Graphic display of the relative frequency of the term "hepatorenal syndrome (HRS)" used in a corpus of books (vertical axis) over time (horizontal axis). The boxes indicate the principal events in the conceptual evolution of HRS since 1910. The dramatic increase seen after 1969 corresponds to the period when liver or combined liver-kidney transplant made the once fatal disease that HRS had been a potentially curable disease. (Source: Google Ngram viewer.) CLKT, combined liver and kidney transplant in cases of HRS; FRI, functional renal insufficiency; HRI, hepatorenal insufficiency; Kidney Tx, kidney of HRS case transplanted into a kidney failure patient; Liver Tx, normal liver transplanted into patient with HRS; Osm, osmolality.

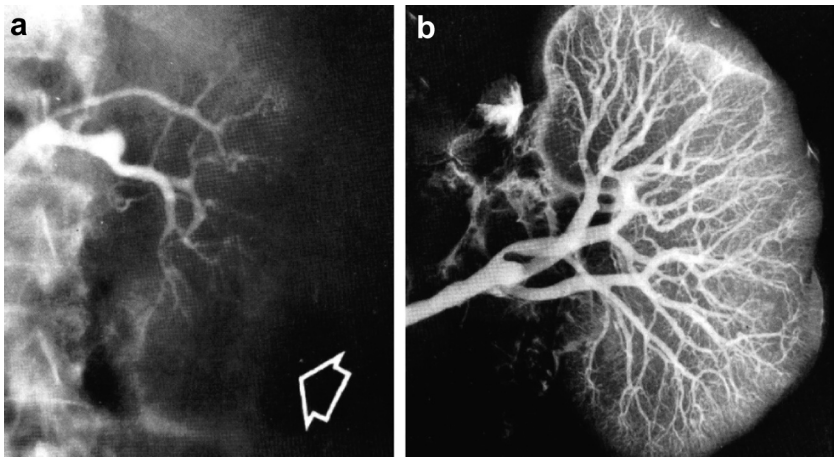

Figure 3 | The renal vasculature in the hepatorenal syndrome. (**a**) Selective renal arteriogram of a patient with oliguric kidney failure and liver cirrhosis while alive. Note the extreme abnormality of the intrarenal vessels. The arcuate and cortical arterial system are not recognizable, nor is there a distinct nephrogram present. The arrow indicates the edge of the kidney. (**b**) Renal arteriogram of the same kidney at postmortem. Note the filling and clear demarcation of the arterial vascular bed to the periphery of the cortex, which had not been visualized *in vivo*. The vascular attenuation and tortuosity seen in (**a**) are no longer present. Reproduced from *The American Journal of Medicine*, Volume 49, Epstein M, Berk DP, Hollenberg NK, Adams DF, Chalmers TC, Abrams HL, Merrill JP. Renal failure in the patient with cirrhosis: the role of active vasoconstriction, Pages 175–185, Copyright © 1970, with permission from Elsevier.[66]

with an added contributory role of jaundice, result in reduced renal filtration rate and plasma flow.[34,35]

It was in the period after 1950, when bench research began to be integrated into clinical research in earnest, that a series of investigations actually began to successfully delineate the pathogenesis of HRS. These were part of the ongoing seminal studies of that formative period that revolutionized renal physiology and were instrumental to the nascence of nephrology as an investigative scientific discipline that ushered the founding of the International Society of Nephrology in 1961.[36] As they pertain to HRS, these consisted principally of (i) studies on sodium retention in edematous disorders particularly as it relates to the regulation of circulating plasma volume; (ii) studies on changes of intrarenal blood flow in the acute renal failure of shock that had emerged as a medical concern during World War II; (iii) expanded evidence for a role of jaundice in causing renal injury[37,38]; and (iv) an increasing understanding of kidney disease and failure as clinical entities that can be treated by renal replacement therapy.[3,4] Parallel studies of hepatic function revealed the liver as a complex organ with major detoxifying, synthetic, and immunologic functions. Collectively, these conceptual changes eventuated in a progressively clearer understanding of the pathophysiology of the HRS and provided a sound basis for the improved management of patients afflicted with a potentially fatal disease that had been first recognized from its structural features.

Sodium retention. Credit for highlighting the deranged functional link between liver and kidney failure has been given to the British hepatologist Dame Sheila Sherlock (1918–2001) for reporting in 1956 on sodium retention, hyponatremia, progressive oliguria, and increasing azotemia in 9 patients with liver failure.[39] Actually, the electrolyte complications of edema were then receiving increased attention in general.[40–42]

It was when sodium retention began to be investigated in the context of the distribution of body fluid compartments that the role of the kidney began to be appreciated. This was initially examined as it concerned total body water in the mid-1930s and expanded to that of edema in general in 1948 by one of the founders of renal physiology, John P. Peters (1887–1955).[43,44] In his summary statement about renal function in water and salt retention, Peters states that the kidney, "*responds to some function of the volume of the circulating blood but is indifferent to changes in the volume of body fluids at large.*" This was the concept that would ultimately come to be termed "effective blood volume," a fundamental notion for the understanding of salt balance in varied causes of edema formation.

It was within this conceptual setting then that the avid sodium retention of patients with cirrhosis as a hallmark of ascites formation and a principal feature of HRS faced the enigma of the increased levels of measured plasma volume of these patients. This issue was addressed in the 1960s by investigators at the storied Thorndike Laboratories of the Boston City Hospital, notably by Solomon Papper (1922–1984), who actively contributed to the elucidation of HRS for the following 2 decades.[45,46]

The discrepancy between plasma volume and salt retention had been noted as early as the 1940s from clinical observations that in congestive heart failure, weight gain, decreased hematocrit, and increased measured plasma volume precede the rise of venous pressure that had been considered the cause of edema theretofore. This was the concept of "forward failure" in cardiac decompensation, then promoted by the US cardiologist Eugene Stead (1908–2005)

and his associates.[47,48] Subsequent studies by the cardiovascular physiologist Arthur Guyton (1919–2003) elucidated the interrelationship of kidney function and circulatory filling pressures observed in varied clinical derangements.[49] Coupled with the studies of the German physiologist Otto Gauer (1909–1979) on the regulation of blood volume,[50,51] the concept of reduced "effective plasma volume" emerged as the explanation of continued sodium retention in the presence of increased plasma volume seen in patients with liver cirrhosis.[52–54] These were soon confirmed in elegant studies of experimental portal cirrhosis in dogs.[55] Consequently, it was the explanation of "forward failure" of the decompensated heart that informed and helped replace in the 1970s the previous "underfill" theory by the newly defined "overflow" theory of ascites formation in decompensated liver cirrhosis. The "overflow theory" clearly demonstrated that the primary abnormality of ascites formation is attributable to inappropriate sodium and water retention despite the absence of volume depletion.[52,56] This was progressively refined and updated by the meticulous studies of Robert W. Schrier (1936–2021) and his associates. As a result, by the 1980s, it was replaced by the current concept that the reduced effective circulating volume in the context of an expanded volume of patients with cirrhosis is principally caused by a splanchnic vasodilatation, with the consequent compensatory activation of vasoconstrictor mechanisms (sympathetic nervous system, renin-angiotensin axis, and arginine vasopressin) promoting avid salt retention and reduced renal blood flow and glomerular filtration.[57–60] Coupled with increased cardiac output, the hemodynamic effect of vascular underfilling is initially compensated and a new steady state is achieved. However, with progressive decompensation of liver cirrhosis, these compensatory mechanisms gradually fail to restore the arterial circulation, resulting in a functional renal failure and the onset of HRS.[3,4]

That these adaptive changes were a result of altered renal hemodynamics due to peripheral vasodilatation was demonstrated in 1962 by Solomon Papper and his associates.[45] In studies of patients with Laennec cirrhosis, the infusion of metaraminol, a synthetic α-adrenergic vasoconstrictor, resulted in increased water, sodium, potassium, and total solute excretion; this was a forerunner of things to come when another vasoconstrictor, terlipressin, would be introduced in the effective management of HRS some 40 years later.[3,4]

In his studies of volume control, Otto Gauer had used head-out water immersion, whose effects were first noted by a Philadelphia physician, Henry Hartshorne (1823–1897) in his 1845 medical thesis on hydrotherapy.[61] To quote Hartshorne's insightful explanation of the sequence of events that follow water immersion, "*If the blood be thus driven from the external and internal parts, what becomes of blood? The heart and great vessels, it would seem, must be burdened. Such is to a degree the case; and it is perhaps the stimulus of this fullness and distension or its action on the elasticity of those great vessels and the heart that constitutes the reaction which leads forth the urine in abundant effusion. Such overloading of the heart and great organs would be dangerous in every case if the volume of blood remained the same.*"[61]

This was a prescient inductive analysis that was validated in patients with cirrhosis in the 1970s, when with the encouragement and mentoring of Otto Gauer, one of the authors (ME) expanded the model of water immersion beyond its original focus on the renal handling of water to that of solute excretion and mediators of volume homeostasis.[62] In a series of studies, subjects with decompensated liver cirrhosis undergoing 4–6 hours of head-out water immersion were shown to reverse their avid antinatriuresis to a significant natriuresis that was associated with suppressed levels of renin and aldosterone, enhanced urinary prostagladin E excretion, augmented atrial natriuretic factor, and a concomittant increase in creatinine clearance.[62,63] This was a direct demonstration that a contracted effective circulating volume of cirrhotics was a principal determinant in mediating the abnormalities of renal function in individuals with decompensated liver cirrhosis. This was the pathophysiologic basis for what would evolve into the treatment of HRS with albumin administration and vasoconstrictor infusion.[3,4]

Intrarenal blood flow. Another conceptual change that laid the groundwork for elucidating the pathogenesis of HRS came from studies that challenged the prevailing homogeneity of intrarenal blood flow in a kidney composed of identical nephrons. The initial evidence for a role of redistribution of intrarenal blood flow as the cause of the renal ischemia of acute renal failure was presented by Josep Trueta (1897–1977) in the mid-1940s.[64] Technological improvements in the study of intrarenal blood flow, such as radioactive xenon washout and selective renal arteriography, were instrumental in clarifying further the role of intrarenal blood flow in kidney function in general.[65] Their application to the study of HRS validated a significant reduction in mean renal blood flow that had been noted from clearance studies but now demonstrated for the first time a preferential reduction in cortical perfusion.[66] Simultaneous renal arteriography disclosed an absence of distinct cortical nephrograms and of vascular filling of the cortical vessels of these subjects (Figure 3, left panel[66]). Postmortem angiography on the kidney of 5 of these same patients revealed a striking normalization throughout the arborization of the renal arterial tree (Figure 3, right panel).

With increasing interest in HRS, variable abnormalities in renal function began to be reported in virtually all acute and chronic liver diseases of varied etiology, albeit principally in those with liver failure due cirrhosis who had ascites and were jaundiced. The principal defect that emerged was a potentially reversible functional renal failure due to severe renal vasoconstriction.[3,4] That death was not due to renal failure was documented when kidneys from HRS cases were transplanted to patients with kidney failure but normal liver and the transplanted kidney resumed normal function.[67] More convincing proof derived from liver transplantation into

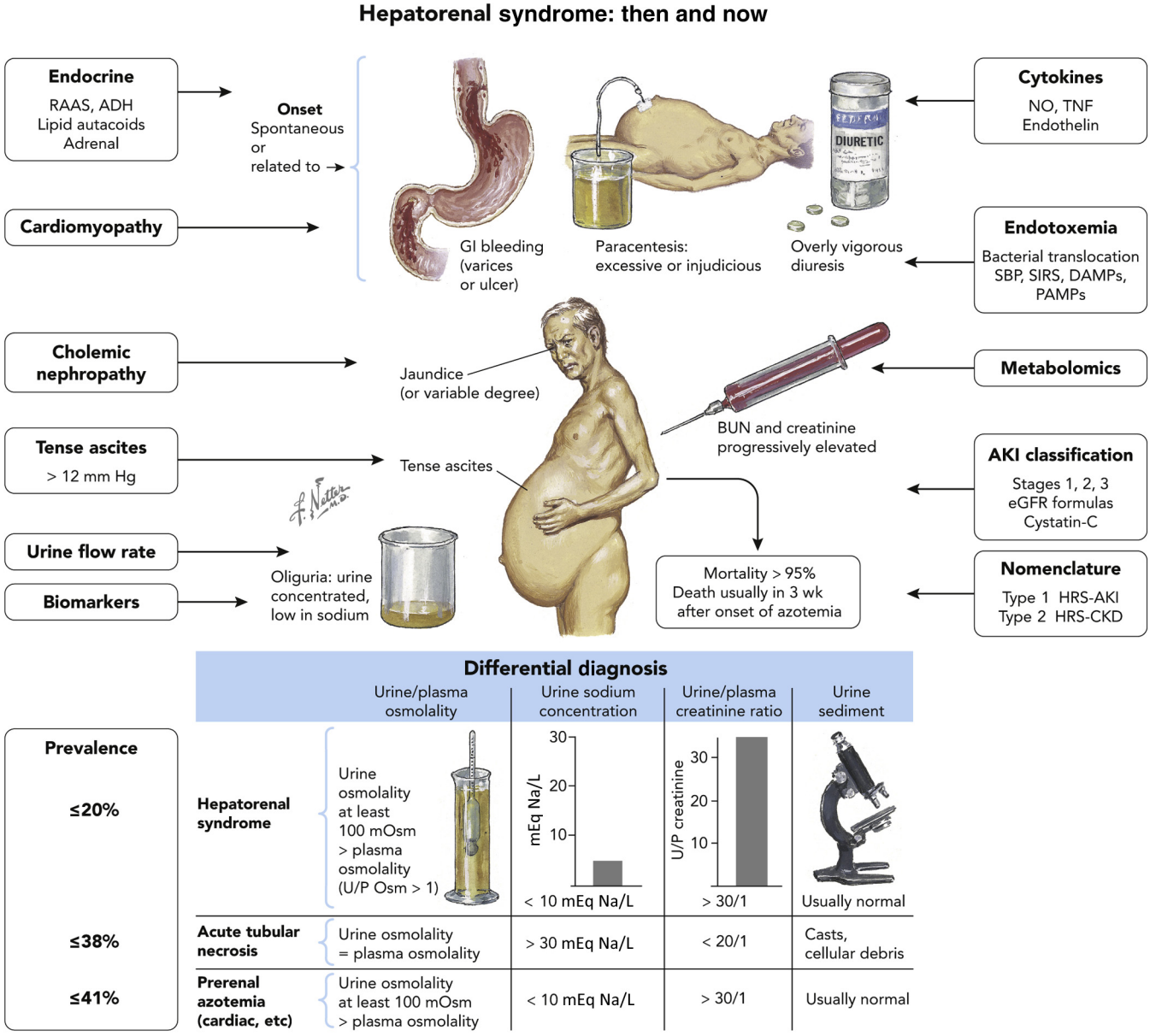

Figure 4 | Hepatorenal syndrome (HRS), THEN and NOW. THEN is 1985, when the original colored figure in the center was painted by Frank Netter. NOW represents the status in 2020, entailing the more recent studies of liver and kidney function (shown in the surrounding boxes in black lettering, based on several studies[3,4,69–72]) that subsequently elucidated the HRS and consequently improved the outcome of this otherwise fatal disease. Modified and updated from the central colored figure, which highlights a summary of common physical findings, some of the precipitating events, and the characteristic urinary excretory pattern (bottom of figure). Figure reproduced with permission from *Clinical Symposia Volume 37, Number 5, 1985*. Netter illustration from www.netterimages.com. © Elsevier Inc. All rights reserved. ADH, antidiuretic hormone; AKI, acute kidney injury; BUN, blood urea nitrogen; CKD, chronic kidney disease; DAMP, damage-associated molecular pattern; eGFR, estimated glomerular filtration rate; GI, gastrointestinal; NO, nitric oxide; PAMP, pathogen-associated molecular pattern; RAAS, renin-angiotensin-aldosterone system; SBP, spontaneous bacterial peritonitis; SIRS, systemic inflammatory response syndrome; TNF, tumor necrosis factor; U/P, urine/plasma.

patients with HRS that restored normal function to their otherwise failing native kidneys (Figure 2).[68]

As a result, by the mid-1970s, it was evident that the renal failure of HRS was a reversible hemodynamic functional abnormality attributed to circulating agents accrued in liver failure that had been postulated some 50 years earlier by Merklen and Dérot, and of the hemodynamic changes of shifting blood volume foreseen a century earlier by Hartshorne.[24,25,61]

Elucidation of mediating mechanisms

It was on this general framework that studies that followed elucidated the mechanisms involved in the pathogenesis of renal dysfunction in patients with liver cirrhosis

(Figure 4[3,4,69–76]). These have been the subject of metanalysis,[73,74] consensus conferences,[75,76] and several recent excellent reviews,[3,4,69–72] They will not be detailed herein other than to highlight their principal contribution to the conceptual evolution of the current approach to detecting, diagnosing, classifying, and treating the HRS.

Kidney failure. Increasing blood urea nitrogen and creatinine levels were an integral component of the definition of HRS from the outset.[24,30,39] Concern with their utility in assessing the severity of renal dysfunction derived from evidence of potential confounders, including reduced urea synthesis and creatinine production of patients with cirrhosis, magnified by their reduced muscle mass, restricted protein intake, and likely renal tubular secretory dysfunction.[69–72] The definition and classification of chronic kidney disease and acute kidney injury (AKI) by the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines proved instrumental in the resolution of these limitations, as well as in improving the evaluation, classification, and nomenclature of HRS.[77,78]

Notable among those was the adoption of the 2012 KDIGO guideline for the definition and classification of AKI into 3 stages as a dynamic progression of renal dysfunction in HRS rather than the binomial yes or no diagnosis based on a creatinine cutoff level that had been used for HRS theretofore. Equally important were the concerted efforts of KDIGO at validation of the estimated glomerular filtration rate formula and the standardization of creatinine measurement in clinical laboratories. Studies in their application to the evaluation of kidney function in liver failure have documented the merits of 2 estimated glomerular filtration rate formulas for use in liver disease, one integrating cystatin C and the other the Modification of Diet in Renal Disease–6 formula that, in addition to creatinine, age, gender, and ethnicity, integrates the level of albumin and blood urea nitrogen in estimating the glomerular filtration rate.[70–72] In addition, the KDIGO definitions of AKI and chronic kidney disease have contributed to a refinement of the nomenclature of HRS of the rapidly progressive type 1 into HRS-AKI and of the chronic type 2 into HRS–chronic kidney disease (Figure 4). These have added a granularity and specificity to the terminology and classification of HRS that had been missing previously and enabled an earlier diagnosis and treatment with consequent improved morbidity and mortality outcomes.[3,4,69–72]

It has also become increasingly documented that HRS does not represent the only cause of AKI in cirrhotics or occurs only in isolation (Figure 4). In fact, HRS often develops in conjunction with other causes of AKI, especially of acute tubular necrosis, that may prove to be irreversible.[79–81] This is clinically evident in individuals with HRS whose kidney function fails to recover, and they become dependent on dialysis, necessitating their treatment with joint kidney and liver transplantation. It has been proposed that nonreversible cases of AKI in patients with cirrhosis (type 1 HRS, HRS-AKI) which persist over a period of >3 months be termed HRS–non-AKI.[4]

Renal biomarkers in liver cirrhosis. An active quest for renal tubular biomarkers that could detect renal insults earlier than actual tubular injury has been going on for the past 2 decades. The most promising biomarkers that have been identified are as follows: neutrophil gelatinase-associated lipocalin, interleukin 18, kidney injury molecule 1, tissue inhibitor of metalloproteinases 2, insulin-like growth factor binding protein 7, and liver type fatty acid–binding protein. Biomarkers are of special utility in patients with cirrhosis because of their reduced blood urea nitrogen and creatinine synthesis, magnified by their reduced muscle mass, restricted protein intake, and likely tubular secretory dysfunction, which collectively limit the reliability of blood urea nitrogen and creatinine in their clinical evaluation. Apart from their inherent value in the diagnosis and prognosis of renal tubular injury, the additional value of biomarkers in HRS is in the differentiation of acute tubular necrosis from the hemodynamically mediated potentially reversible cases of HRS-AKI. Results indicate neutrophil gelatinase-associated lipocalin as being of greatest utility in this regard. The available data on these as well as on metabolomics, although promising, remain inconclusive, and their clinical applicability awaits validation and broader availability.[4,82–84]

Systemic mediators of injury. A relatively recent concept implicated in the pathogenesis of HRS is that of the exaggerated defense response of the body to an infectious or noninfectious insult, termed the systemic inflammatory response syndrome (SIRS).[3,4,85] To provide context, alcoholic hepatitis frequently progresses to multiple organ failure and death in liver disease. At the time of admission, patients with alcoholic hepatitis frequently manifest criteria of SIRS even in the absence of an infection. That the presence of SIRS may predispose to multiple organ failure and death in alcoholic hepatitis was demonstrated from studies in which SIRS was a major predictor of multiple organ failure (odds ratio, 2.69; $P = 0.025$) and strongly correlated with mortality (36% in SIRS vs. 14.9% in controls; $P = 0.002$).[86]

Inflammation in liver cirrhosis is promoted by 2 groups of molecules: pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs). PAMPs represent bacterial products, such as lipopolysaccharide, flagellin, and nigericin, which result from translocation of gut bacteria or bacterial infections in general and spontaneous bacterial peritonitis in particular (Figure 4). In contrast, DAMPs represent intracellular components released from injured hepatocytes, including high-mobility group protein B1, heat shock protein, adenosine triphosphate, and double-stranded genomic DNA.

Even in the absence of overt bacterial infection, such as spontaneous bacterial peritonitis, both PAMPs and DAMPs may promote inflammation and release of proinflammatory cytokines through activation of pattern recognition receptors, such as toll-like receptors. This systemic proinflammatory response, in turn, may exacerbate the development of HRS acting by 2 complementary mechanisms: a systemic pathway and a direct effect on the kidney.[3,4,70,72]

SIRS also enhances the arterial production of vasodilators (nitric oxide and prostanoids), leading to a further reduction in systemic vascular resistance and consequently diminished effective arterial blood volume, whereas DAMPs and PAMPs may act directly on the kidneys. Patients with cirrhosis and renal dysfunction manifest increased expression of toll-like receptor 4 receptors and caspase-3 in tubular renal cells, both important components of the innate immune system.[87] Of interest, in animal models of liver cirrhosis, gut decontamination has been shown to reduce renal expression of toll-like receptor 4 and prevent renal dysfunction and tubular damage, suggesting that increased toll-like receptor 4 expression in the kidneys may be attributable to exposure to PAMPs.[87]

As a result, inflammation is now considered to play an important role in the pathogenesis of HRS. One could posit that these newly identified factors represent an unraveling of past mysterious nephrotoxic agents postulated as a cause of the HRS.

Treatment of HRS. Given the convincing evidence that HRS is attributable primarily to an extreme underfilling of the arterial circulation secondary to widespread arterial vasodilation, especially in the splanchnic circulation, treatment with volume expansion (albumin infusion) coupled with systemic vasoconstrictors (noradrenaline and vasopressin analogues) has been used in the management of HRS. Vasopressin analogues with a predominant V1 receptor effect have a preferential effect on the splanchnic circulation and are effective in improving renal function in most cases and in reversal of the HRS in about half of them.[3,4,70–72]

Terlipressin is one such synthetic vasopressin analogue that selectively possesses greater affinity for V1 receptors predominantly located in the smooth muscle cells of the arterial circulation of the splanchnic vasculature. It reduces splanchnic blood inflow and therefore portal pressure, and redistributes part of the otherwise sequestered intravascular volume to the central circulation with consequent improved kidney function.[87]

The recently reported CONFIRM study, a North American randomized controlled trial of terlipressin plus albumin for the treatment of HRS-1 (HRS-AKI), demonstrated that terlipressin + albumin was significantly better than albumin alone in achieving documented HRS-1 reversal.[88] The response was durable and associated with a reduced need for dialysis both before and after liver transplant.

Clinical practice guidelines of the European Association for the Study of the Liver recommend terlipressin in combination with albumin as a first-line intervention for HRS-AKI, with the aim of decreasing serum creatinine to <1.5 mg/dL.[70,72,87] Although this approach is not curative of the underlying liver disease that drives the development of HRS-AKI, it has become increasingly accepted in Europe that its early use in treatment leads to reversal of AKI and that such patients may recover sufficiently to proceed to subsequent liver transplantation without the need for dialysis. Thus, in many ways, it is considered as a bridge to liver transplantation. In the United States, the Food and Drug Administration issued a Complete Response Letter rejecting the new drug application for terlipressin on September 16, 2020 and requested additional data. The CONFIRM study was never powered to assess survival, but rather to allow time to either recover from liver failure (as in alcoholic hepatitis) or as a bridge to liver transplantation.

Conclusion

For the centuries of medical history that the liver was considered a vital organ, the kidney was viewed as a subservient excretory organ for the elimination of fluidities. The 1827 report of Richard Bright that differentiated the dropsy of kidney disease from that due to liver disease also noted the coexistence of injury to both organs in several cases of dropsy, a finding documented by many of Bright's contemporaries. The actual identification of a link derived initially from studies of liver disease that identified cholemic nephrosis in the 1850s; and later from renal studies that revealed a functional renal insufficiency in patients with liver failure that was spontaneously reversible in some. The functional nature of kidney failure of the HRS was clinically documented in the late 1960s from reports of the resumption of normal function of transplanted HRS kidneys and in the early 1970s from liver transplantation that reversed the renal insufficiency of HRS patients. Since then, the elucidation of several mechanisms of injury (Figure 4) has resulted in various preventive and bridging treatments of HRS until liver or combined liver and kidney transplantation becomes available (Figures 2 and 4).[3,4,89,90] More important, the modified definition and classification of HRS have enabled an earlier therapeutic intervention with combined albumin and terlipressin therapy with improved outcomes of HRS. The wide array of factors and mediators incriminated in the causation of HRS continues to expand without a single culprit yet identified as the primary cause. Additional studies are required to extend most of these provocative findings to more specifically identify and elucidate the mechanisms that promote HRS to further enhance its future detection, diagnosis, classification, and treatment.[3,4,69–72]

DISCLOSURE

All the authors declared no competing interests.

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