Hepatorenal syndrome (HRS) is defined by the presence of acute or chronic liver failure with advanced liver failure and renal dysfunction. HRS can occur in up to 40% of cirrhotic patients and the primary mechanism is centered around the concept that severe systemic/splanchnic vasodilatation results in severe renal vasoconstriction. However, this paradigm ignored the potent toxic effects of bile acids and bilirubin, which has been termed cholemic nephrosis. The earliest report that I could find was by Haessler et al\textsuperscript{1} that recounts a description by Quincke\textsuperscript{2} from 1899, who states, “At an early stage the cortex is diffusely stained with bilirubin. As time passes the pigment accumulates in granular form in the cells of the convoluted tubules and more markedly in those of the loop of Henle, and in the lumen of the latter many free granules may be seen, together with yellow, green, or brown casts. It is noteworthy that the glomeruli remain practically unstained. There is cloudy swelling of the tubular epithelium, with loss of the brush border, and even necrosis here and there. In Quincke’s opinion, these severe changes cannot but result in a lessened renal activity, and thus may have serious consequences for the organism as a whole.” Haessler et al ironically states, “The mode of escape through the kidneys of circulating blood and bile pigment has received but scanty attention in the past as compared with that of foreign dyestuffs,” which continues to be the case even today. This entity has been well described with most studies occurring between 1920-1970.\textsuperscript{1-8} However, this entity has been mostly forgotten in the modern literature. Additional synonyms include bile nephrosis, jaundice-related renal insufficiency, or jaundice-associated acute kidney injury. We recently used the term bile cast nephropathy (BCN) to describe the presence of bile/bilirubin casts in patients with severe liver and renal dysfunction. More recent case reports have introduced bile acid nephropathy\textsuperscript{18} and bile nephropathy\textsuperscript{23} into the literature.

The pathologic findings of BCN are characterized primarily by extensive acute tubular injury with bile-stained tubular casts.\textsuperscript{1,10,11} Macroscopic findings at autopsy include yellowish discoloration of the kidneys in jaundiced patients which can become dark green in color after formalin fixation, which oxidizes bilirubin and coverts it to biliverdin. The tubular casts in bile cast nephropathy can be quite distinct with a greenish-yellow color as in our biopsy. These tubular casts may contain variable degrees of cellular debris consistent with a significant component of tubular injury. Many casts appear acellular and most are located in distal nephron segments, but casts in proximal tubules may be seen in severe cases. In many cases, the bile casts can have a dark red color, which resemble myoglobin or red blood cell casts, and can be as dark or granular in texture. The Hall’s (or Fouchet) stain can be used to confirm the presence of bile or bilirubin. However, this histochemical stain is insensitive, so in the setting of severe liver dysfunction and jaundice reddish tubular casts most likely represent bile casts. An immunohistochemical study for myoglobin can be used to exclude the diagnosis of rhabdomyolysis-associated acute tubular injury. Red blood cell casts as observed in the recently described entity of warfarin-related nephropathy are generally identifiable by light microscopy with hematoxylin and eosin staining. A hemoglobin immunohistochemistry study or Prussian blue iron stain can exclude hemoglobin or hemosiderin, respectively. Therefore, the finding of pigmented casts should always raise the differential diagnosis of myoglobin casts, bile casts, or hemoglobin casts and generally the clinical data can easily help distinguish between these possibilities. These casts do not resemble “myeloma” casts,
which often have a fractured or sharp-edged appearance and may be surrounded by giant cells, but “myeloma” cast nephropathy might also be considered in the differential diagnosis. Immunofluorescence microscopy would demonstrate that these casts are monoclonal in nature. The clinical setting of severe liver dysfunction or a jaundiced patient should trigger one to consider the diagnosis of BCN / cholemic nephrosis. Surprisingly, the clinical information regarding liver failure or jaundice is not always provided by the nephrologist and sometimes a directed question is necessary.

Given the large void of information on the topic of BCN / cholemic nephrosis, we recently conducted our own clinicopathologic study based on 41 autopsy cases of jaundiced patients and 3 renal biopsies from our pathology archives at the University of Chicago. The underlying liver diseases that caused the jaundice could be classified into the following 4 categories: 1) cirrhosis due to viral hepatitis, alcohol abuse, non-alcoholic steatohepatitis, chronic TPN hepatotoxicity, cardiac cirrhosis, or cryptogenic causes (n=23); 2) obstructive/cholestatic category due to primary sclerosing cholangitis, obstructive masses in the liver or pancreas, cholangitis lenta, or sinusoidal obstructive syndrome (n=14); 3) hepatocellular category includes severe acute liver damage including shock liver, giant cell hepatitis and fulminant autoimmune hepatitis (n=5); or 4) hemolytic category due to elevation of indirect bilirubin from hemolytic anemia (n=2). Our patients ranged from 4 weeks to 89 years of age with 25 males and 19 females. We found intrarenal bile casts in ~50% of jaundiced patients with severe liver dysfunction at autopsy, but 12% of the autopsy cases had extensive involvement of both proximal and distal tubules. Gross (macroscopic) evidence of bilirubin staining as seen by yellowish discoloration of the renal cortex and medulla was identified in seven (17%) of the 41 autopsy cases and all seven cases contained numerous bile casts. Of 13 patients that satisfied the criteria for hepatorenal syndrome (ascites, cirrhosis, and renal dysfunction), 11 (85%) had intrarenal bile casts. Bile cast formation involves the distal nephron segments in mild cases and extends to the proximal tubules in severe cases. Bile casts are observed in all categories of jaundice/liver failure, except for the hemolytic group, but there were only two such cases in our study. Of interest, bile casts were present in all 8 (100%) patients with alcoholic cirrhosis and 2 of our renal biopsies were also from such patients.

Therefore, bile casts were commonly observed but not limited to patients with hepatorenal syndrome. Extensive and severe acute liver dysfunction could also result in the formation of intratubular bile casts. Our finding that alcoholic cirrhosis may predispose to bile cast formation is of interest and requires additional studies for validation. Heymann and colleagues have provided an opposing view about the significance of bile casts, but we maintain that the current data suggest that bile casts are by themselves an important contributor of renal dysfunction in the setting of liver failure. Perhaps, the most compelling data regarding the toxic effects of bile acids has been recently presented in an animal study by Fickert and colleagues. Several additional case reports also advance the discussion on the topic.

The clinical significance of bile casts remains unknown due to the large absence of data in our medical literature. Currently, most patients in this clinical setting may not undergo biopsy. To better understand the clinical significance of bile cast nephropathy, more kidney biopsies should be performed. In particular, the presence of bile casts may be useful to determine whether liver failure patients should undergo a simultaneous liver-kidney versus liver alone transplantation. We hope that attention is redirected to this important entity and revives the conversation between nephrologists, hepatologists, transplant surgeons, and pathologists to embark on additional studies to better understand the importance of bile casts.

Cholemic nephrosis represents a spectrum of kidney injury that ranges from proximal tubulopathy due to intracellular accumulation of bilirubin/bile acids, which may interfere with mitochondrial function and possibly other cellular functions, to the presence of intrarenal bile casts, which both obstruct and have direct toxic effects on epithelial cells. Bile casts represent the most severe spectrum of cholemic nephrosis, and we propose that BCN is an appropriate term for this pathologic entity.
References: