My Cup Runneth Over

Controversy and feud have been woven into the fabric of human relationships since the beginning of recorded history, and probably before that too, although no one bothered to document it. It seems likely that even the Big Bang, which began it all, was itself no more than a cosmic row, like the disputes that raged between the gods on Mt. Olympus. Controversy has touched all aspects of human endeavor: politics, business, exploration, inheritance, ownership, romance, and ideology. But, of these, the strife that flares between and within religions has unhappily been the most pernicious and dangerous, as a glance at trouble spots around the world, now and throughout history, will readily confirm. Science and medicine have not been without controversy and feud either, and when these were played out there was frequently embellishment with vitriol and recrimination. In some cases, altercations dwelt on questions of priority or ownership of a discovery or an invention, as exemplified by the arguments between Newton and Liebniz over The Calculus, and Robert Gallo and Luc Montagnier over HIV. In other cases, science came into conflict with religion, as Galileo and Darwin experienced to their great distress, and as stem-cell research unfortunately faces today. Some disputes focused specifically on the veracity and appropriateness of hypotheses or methods—Wit-ness the battle in the 17th century between Thomas Hobbes (his geometry) and John Wallis (his algebra) to square the circle, yet even here the debate was often laced with secondary gain for ego and reputation. Hepatology, which is usually intellectually rarified, free of materialism, and temperamentally genteel, has had its controversies, some of which were clearly liver disease and ascites. Yet even here the debate was often laced with secondary gain for ego and reputation. Hepatology, which is usually intellectually rarified, free of materialism, and temperamentally genteel, has had its controversies, some of which were clearly liver disease and ascites. But the most graphic timeworn portrayal of ascites that survives to this day was found among the excavations of pre-Hispanic Mesoamerica, from the Classic period (300–900 CE) of the Mayan civilization. Among the famous delicate sophisticated ceramic figurines unearthed at Jaina, a small limestone island just off the coast of Campeche, Mexico, that was used as a necropolis, was the depiction of a young man with massive ascites and an everted umbilicus (Fig. 1). Skeletons of a young woman found at the same archeological site and a young man buried at Ticoman in Central Mexico (from the Formative or Pre-Classic Mayan period that began 4000 years ago), respectively, showed changes of digital clubbing and hypertrophic osteoarthropathy that tie in well with ascites, as all three are well-known complications of cirrhosis.

Of course, in the 4th century BCE, Hippocrates also recognized the dropsy, or askiTes (askoITê), as he would have known it in Greek by the word derived from the ancient term askos (askoÊ), meaning a leather bag or sheepskin used to carry wine, water, or oil. Parenthetically, it should be noted that even though the word ascites derives from the same root, this term does not refer to a patient with ascites but rather to members of a heretical Christian sect of the 2nd century, who were so named because of the practice of dancing around an inflated wineskin at their meetings, according to their interpretation of the Gospel of St. Matthew (NIV IX:17). The word “dropsy,” which appeared in English in the late 13th century (shortened from the Middle English/Old French hydropsy), referred to any accumulation of watery fluid in the serous cavities or connective tissues of the body, whereas “ascites,” which entered the language a century later, referred specifically to abdominal dropsy. Hippocrates realized that not only did abdominal dropsy derive directly from the diseased liver but also that it was a fatal complication, for in his aphorisms (VII:55) he states that “When
the liver is filled with water and bursts into the epiploëon (the omentum), in this case the belly is filled with water and the patient dies."9 Now, inasmuch as Hippocrates realized that ascites springs from the diseased liver, he certainly deserved kudos for his observation, although he left the task of uncovering the mechanism to his successors. Into this breach, a century later, stepped Erasistratos of Chios, who, like his elder contemporary Herophilus of Chalcedon, had migrated from the Greek coastal cities of Asia Minor to Alexandria. There, at the Museum and Library established by the Ptolomies, together they founded a school of anatomy that was destined for renown. Erasistratos, who may be called the first scientific physiologist, proposed a pathophysiological explanation for hepatic ascites that is not too far from the truth, even today. Much ridiculed by Galen, whose writings in 2nd-century CE Rome some 400 years later reported the work, Erasistratos ascribed ascites to a rock-hard liver, “. . . as water cannot accumulate . . . in any other way than from narrowness of the blood vessels going through the liver."10 For Erasistratos, congestion (hyperemia) or plethora, as he named it, “. . . which causes blood to pass from the veins to the arteries . . . ” was a chief cause of disease, and for ascites “a chronic and scirrhous inflammation of the liver or spleen, which prevents the assimilation of the food in the bowels and its distribution through the body, but changes it into water, which being refrigerated, is deposited between the intestine and the peritoneum."11 Although Galen mocked this assessment, his alternative view that ascites is caused by too many humors,10 notably the cold and the moist ones, was not more plausible. Aretæus of Cappadocia, Galen’s near contemporary, whose other considerable contributions included coining the term asthma, classifying headaches, and giving the first accurate description of diabetes, did not do so well with ascites, as he considered dropsy to result from “a copious cold draft, . . . where much water is swallowed and the fluid transferred to the peritoneum.”12

After a promising start, the physicians of old seemed to lose interest in ascites from the mechanistic perspective and investigation of its wellhead dried up, so to speak, for 1,500 years. Instead, efforts focused on getting rid of ascites by paracentesis,13 purgation, diaphoresis, and the use of hydragogues, and to a limited extent by restricting sodium in the diet.14 In those days, life without salt seemed unimaginable, as salt had been essential and ubiquitous in medicine, culture, and history for thousands of years,15 although the 12th century Regimen of Health from the School of Salerno did warn a little against excess salination.16 Then, in Oxford in the late 17th century, motivated by Harvey’s discovery of the circulation of the blood a few decades earlier, Cornishman Richard Lower, who among other achievements was the first to show that venous blood was oxygenated in the lungs and the first to perform a blood transfusion, tied off the thoracic portion of the inferior vena cava in a dog. He found that not only did the animal succumb quickly but also passive venous congestion of the liver caused the “. . . dropsy known as ascites.”17 Thus was reborn the notion that the formation of hepatic ascites was due to hemodynamic compromise in the liver. Hepatic venous outflow obstruction later became a standard experimental technique to induce ascites18–21 and is a cardinal finding in the Budd-Chiari syndrome22 and nowadays an uncommon but troublesome problem for liver transplant recipients in whom the inferior caval anastomosis causes significant obstruction to graft venous drainage.23 Once the principle was established that hepatic ascites might be caused by venous obstruction of the liver, it was no leap of faith to realize that
obstruction could affect the portal venous radicals within the liver too, and for this cirrhosis was likely to be the prime cause. In a painstaking morphological and functional analysis, using vascular injection with gelatin and India ink and perfusion techniques on normal livers and livers from cirrhotic patients with and without ascites, McIndoe confirmed an association between progressive portalhepatic venous disruption and portal hypertension, and the subsequent evolution of ascites and portosystemic collaterals (including gastroesophageal varices).24 During the 19th century, clinical guidelines had already been established for distinguishing hepatic ascites from conditions that simulate it, including tuberculous and malignant peritonitis and other forms of peritoneal fluid accumulation,25 some of which were quaintly referred to as “encysted abdominal dropsy”26 (i.e., ovarian cysts, renal cysts, and hydatid tumors).

By the first third of the 20th century, it seemed that the conundrum of cirrhotic ascites had been solved and was explicable on the basis of portal venous hypertension that led to fluid extravasation from the capillary circulation,27 according to the celebrated mechanism that Ernest Starling had elucidated some 30 years earlier,28–30 with hypoalbuminemia31 and a little lymphatic insufficiency32,33 thrown in for good measure. Renal sodium conservation by antidiuretic activity, after all, was only a compensatory response to “underfilling” of the circulation due to fluid “losses”27,30 into the abdominal cavity. But if that conventional explanation were true, how could the volume of ascites often be so enormous, sometimes exceeding the plasma volume many fold over, unless somehow sodium and water retention were the cause and not the consequence of cirrhotic ascites? That such an unconventional thought should have occurred to the late Telfer Barclay Reynolds, then and for 30 years Chief of the Hepatology Service at the University of Southern California Medical Center, should come as no surprise, as the hallmark of his illustrious 60-year career in medicine in Southern California was to question conventional wisdom and debunk it. “Pete,” as he was known to all except his wife, Kit—for, as he said, with a first name like Telfer, any nickname would do—began in hepatology in 1952 at the Royal Postgraduate Medical School in London, on a coveted Bank of America-Giannini fellowship. Instead of joining the throng, Pete gravitated toward the rising star of British medicine, a young faculty member named Sheila Sherlock, and became a vanguard of the international multitude of fellows whom she trained. Committed to hepatology, and armed with an interest in circulatory physiology and the technique of hepatic vein catheterization, Pete returned to Los Angeles to pursue a lifelong career in liver disease that overflowed with the highest level of traditional clinical practice, a love of physical signs, masterful teaching, insightful and inspired clinical investigation, and scholarly writings. His daunting teaching and high expectations, combined with his jet-black hair, won him, with respect and trepidation, the fellows’ and residents’ appellation of “Black Pete.” For those who knew him only with jet-white hair, that nickname will come as a surprise. Memorable too were the animated clinical debates conducted in the presence of the patient, sometimes obliviously and often in “semi-Spanish,” at the Monday noon clinical conference, the Wednesday evening meetings at his celebrity country club (where he rubbed shoulders with Bob Hope and pursued his passion for golf), and the hospitality and generosity of the temporary accommodation for new fellows and visitors at the little house he built behind his home.

Reynolds’s scientific contributions will doubtless be recounted in numerous obituaries, following his passing a few weeks ago at the age of 82. Some of his work has been cited already, several times, in previous Landmarks articles; the more one digs, the more one discovers his gifts, for which he self-effacingly rarely sought praise or recognition. Reynolds discovered new syndromes34–37 and new physical signs38; he extended our understanding of autoimmune hepatitis,39 alcoholic liver disease40,41 and its dubious treatment,42 portal hypertension,40,42,43 shunt surgery,44 drug hepatotoxicity,45 and other hepatological entities. Like the psalmist,45 Reynolds might have said of his professional and personal life, “My cup runneth over,” which incidentally was a concept he applied to the problem of sodium retention in patients with cirrhosis and ascites. It had been argued that the high plasma volumes that had been found in patients with cirrhosis were artifacts of measurement, because distention of the splanchnic bed and hepatic lymphatics obscured a decrease in the nonportal or “effective” plasma volume.46 Reynolds and colleagues showed that measurement of plasma volume using 131I-labeled albumin and 51Cr-labeled red cells was reliable and not invalidated by 131I-albumin leakage from the circulation.47 Next, in their landmark articles,48,49 they showed that in patients with cirrhosis who had spontaneous loss of ascites there was consistency of portal pressure despite both a natiuresis and a rise in glomerular filtration rate, whereas in other patients with cirrhosis following paracentesis there was no fall in plasma volume nor an increase in the rate of ascites formation. In fact, ascites can be made to reform in patients with cirrhosis by administering a sodium-retaining hormone. In other words, it is possible for ascites to form as a result of plasma-volume expansion in cirrhosis. Thus was cast the “overflow theory” of ascites formation,49 and for the patient with cirrhosis with ascites it seems that “his cup truly
runneth over too.” The schism between the underfill protagonists and the overflow antagonists was bridged only 18 years later, when Schrier and colleagues proposed the now well-accepted peripheral arterial vasodilatation hypothesis that allows for “underfilling” by expansion of the vascular space, leading to reduction in the effective blood volume, which is then remedied by sodium and water retention that “overflows” the plasma volume and spills into the peritoneal cavity. In its context, it seems that the patient’s cup is both half full and half empty at the same time.

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