# Preface

Chronic liver failure is a frequent event in clinical practice. For people aged between 18 and 55 years, it ranks eighth as the cause of death and is the most common reason for hospital admission in gastroenterology or liver units and the main indication for liver transplantation. Chronic liver failure is probably the most complex clinical syndrome in human pathology. In addition to problems associated with the impairment of hepatic function, there are complications related to portal hypertension and to the strategic situation of the liver between the intestine and the systemic circulation.

Encephalopathy, due to impaired hepatic metabolism of ammonium and other neurotransmission inhibitory substances produced in the intestines, is the most important event directly associated with hepatic failure. Patients may even progress to deep coma. Mortality associated with hepatic encephalopathy is however low, and most patients recover. Only when hepatic encephalopathy develops in association with other organ failure, particularly renal failure, the prognosis is poor. Coagulopathy, due to reduced hepatic synthesis of procoagulant factors, is also a remarkable feature of chronic liver failure, but the clinical relevance of this problem is also low due to the simultaneous decrease in the synthesis of anticoagulant factors by the liver. Finally, hypoalbuminemia, due to reduced hepatic synthesis of albumin, is another characteristic feature of chronic liver failure. Our concept of the relevance of hypoalbuminemia in liver failure has changed over time. At the beginning, it was considered essential in the pathogenesis of circulatory failure and ascites. Subsequently, these problems were related to splanchnic arterial vasodilatation rather than to low albumin synthesis, and our focus on the importance of albumin in liver failure has shifted. Finally, recent studies suggest that reduced serum albumin concentration and particularly impairment of albumin function could be relevant as a mechanism of chronic liver failure. Albumin is an essential transporter of hormones and other important endogenous substances for organ function. It is also a fundamental transporter of endogenous toxic substances from tissues to excretory organs such as the liver or the kidneys and of therapeutic agents to their target cells. Finally, albumin has specific biological functions, the most important being its antioxidant properties. The albumin binding and transport capacity in chronic

liver failure is almost totally absent due to saturation of the molecular binding sites and also due to profound alterations in the molecular structure.

Although the most characteristic complication of portal hypertension in chronic liver failure is gastrointestinal hemorrhage due to esophageal varices, the most relevant event associated with the increased portal pressure is without doubt the development of a cardiovascular dysfunction due to reduced splanchnic arterial vascular resistance and impaired cardiac inotropic and chronotropic functions and cardiac output. Splanchnic reduction in vascular resistance is due to both arterial vasodilation and increased angiogenesis. The mechanisms of the impaired cardiac function are still not well understood. Both disorders are progressive during the course of the disease, compromising arterial pressure and leading to homeostatic activation of the renin–angiotensin system, sympathetic nervous system, and vasopressin. These systems are powerful vasoconstrictors and impair the renal ability to excrete sodium and free water, leading to ascites, water retention and dilutional hyponatremia, and extrasplanchnic vasoconstriction. Vasoconstriction within the liver increases portal pressure and reduces hepatic blood flow. Vasoconstriction within the kidney is the mechanism of hepatorenal syndrome. Finally, there is vasoconstriction in other territories such as the muscles and brain. Recent studies indicate that reduction in cerebral blood flow and brain edema related to dilutional hyponatremia are important features in the predisposition of patients with advanced chronic liver failure to develop encephalopathy linking circulatory and cerebral dysfunction in chronic liver failure.

The liver contains most of the cells of the reticuloendothelial system (Kupffer cells) and this particular allocation of the phagocytic activity is an essential mechanism for preventing the translocation of viable bacteria and bacterial products from the intestinal lumen to the systemic circulation. Intestinal motility is markedly reduced in advanced cirrhosis, probably as a consequence of the sympathetic nervous system overactivity, and this leads to intestinal bacterial overgrowth. Portal hypertension produces anatomic changes in the intestinal mucosa and increases intestinal permeability. Finally, the phagocytic activity of hepatic reticuloendothelial system is markedly reduced in patients with advanced cirrhosis. The combination of these three features is one of the most important pathological events in chronic liver failure. It makes the patients vulnerable to endogenous bacterial infections, mainly from intestinal origin. On the other hand, it also determines the continuous passage of bacterial products (endotoxin, bacterial DNA) into the systemic circulation, leading to a chronic inflammatory state with persistent activation of the innate immune system and cytokine synthesis.

Malnutrition and cardiocirculatory dysfunction associated with chronic liver failure may be related to this feature.

The development of an acute liver failure over a chronic liver failure (a condition known as acute-on-chronic liver failure) is another common complication in patients with advanced cirrhosis. It usually occurs in close chronological relationship to a precipitating event, commonly an infection. In addition to a deterioration of liver function, as manifested by increased bilirubin and INR, these patients present an acute and severe deterioration in the function of many other organs including the brain, kidneys, heart, peripheral circulation, lungs, and adrenal glands. Acute-on-chronic liver failure is one of the main causes of death of cirrhosis. Mortality relates to the number of organ failures, being greater than 90% in those with more than three organ failures. The incidence of acute-on-chronic liver failure is particularly high in patients with advanced chronic liver failure in the waiting list for liver transplantation. Prevention of bacterial infection, improvement in the intensive care management of multiorgan failure, and development of effective artificial liver support systems are essential features to improve survival in these patients.

Chronic liver failure is, therefore, the consequence of not only a decreased hepatic function but also the impairment in the function of many other organs. It is a difficult field to study. Investigators in chronic liver failure should ideally be physicians expert in clinical hepatology and intensive care, with a profound knowledge of cardiovascular and renal pathophysiology and bacterial infections. This type of investigator is infrequent and probably explains why the percentage of papers dealing with chronic liver failure published in the main hepatology journals represents less than 5% of the total number of articles despite being the most frequent cause of hospital admission and the main cause of death in patients admitted to gastroenterology or hepatology units. The aim of this book is not only to review the current state of the art in the pathophysiology and treatment of chronic liver failure but also to stimulate young investigators to enter into this complex research area.

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