Introduction

Regeneration of the liver is a remarkable phenomenon of fundamental biological significance. The normal adult hepatocyte is a stable cell with a life span similar to the life of the organism. Destruction of part of the liver sets in motion an explosive burst of mitotic activity that will restore the liver mass in a matter of days or weeks, depending on the species. Cell replication will stop when the deficit has been restored. Liver regeneration has been demonstrated in every species in which it was investigated, including man, but most studies have been done in rats. Following a 67% hepatectomy in the rat, DNA synthesis requires 5–8 h to begin and 24 h to peak, and declines progressively thereafter. Mitotic activity follows the same course with a time lag of 8–12 h. The initial response involves only the hepatocytes but, beginning a day later, the bile ducts and littoral cells share in the response (Bucher and Malt 1971). The magnitude of the response is proportional to the amount of liver mass excised. Hepatocytes throughout the liver participate in the process, not just those at the margin of resection. In rats, after a 67% hepatectomy the organ is restored in 7–10 days (Karran et al. 1974). In man it is well advanced after a few weeks (Blumgart et al. 1971). The architecture of the regenerated liver is indistinguishable from the normal.

It now appears that the complex process involved in regulating proliferation of hepatocytes is largely controlled by humoral factors. The hormones of the pituitary, adrenal, parathyroid, and thyroid have been shown to influence the regenerative response (Hays 1974; Shulte-Herman 1974). The release by the liver itself of humoral substances that inhibit or stimulate liver regeneration has been implicated (Labrecque and Pesch 1975; Makowka et al. 1983). There is solid evidence that the splanchnic organs, especially the pancreas, are involved in releasing factors that preserve the integrity of the hepatocyte (Starzl and Terblanche 1979) and promote its proliferation (Duguay and Orloff 1976; Bucher and Swaffield 1975). The exact nature of the regulatory system remains to be elucidated. For wider background information the reader is referred to reviews by Becker (1973), Hays (1974), Starzl and Terblanche (1979), Karran and Eagles (1979), and Bucher and McGowan (1979). Criteria of liver regeneration involve a wide range of morphological, histological, chemical, and isotopic tracer techniques. Early methods were based on determinations of weight and volume of the organ, coupled with measurements of
protein and DNA content. Mitotic index enjoyed some popularity but was plagued with sampling errors and subjectivity in the counting; these methods have been largely replaced by more accurate isotopic techniques based on the rate of incorporation of $^3$H-thymidine into DNA (Bucher 1963). This point requires emphasis in view of certain conflicting observations to be discussed later.

Liver regeneration is also a matter of clinical relevance, since it is the common mechanism by which a patient will recover from a liver injury, be it infectious, surgical, toxic, or traumatic. In the Western world, alcohol is the most important etiological factor associated with liver disease. In North America, 80% of all liver cirrhosis is thought to be related to abusive alcohol consumption (Garceau 1963). In large urban areas, cirrhosis of the liver is the third major cause of death in patients between 35 and 54 years old (Galambos 1979). Liver injury is explained by a combination of a number of factors deleterious to the liver: intracellular accumulation of acetaldehyde, microsomal activation of hepatotoxins, alterations in the redox state, and enhancement of lymphocyte cytotoxicity (Lieber 1978). Ethanol by itself, however, appears to be a rather benign hepatotoxic: a man of average size who drinks 170 g ethanol a day stands only a 50% chance of developing liver cirrhosis (Pequignot 1963). In the strictly controlled environment of the laboratory, it has been very difficult to induce cirrhosis in rats by alcohol consumption only (Lieber et al. 1963). If ethanol by itself does not constantly produce irreversible liver damage, it appears to increase the vulnerability of liver cells to additional trauma, be it malnutrition (Lieber and Rubin 1969), infection, or chemical toxins (Joly and Hetu 1978; Hetu et al. 1983). These observations have led to speculations that ethanol might interfere with the capacity of the liver to regenerate. The available information on the subject is reviewed.

**Effect of Ethanol on Liver Regeneration**

Studies on the effects of ethanol on liver regeneration in the rat are summarized in Tables 1–3. Protocols differ in the dose of ethanol administered, the time of ethanol administration, and the times at which incorporation of DNA precursors were assessed following partial hepatectomy. Of 13 studies, 11 reported an inhibition of tritiated thymidine incorporation into hepatic DNA, while two found no such inhibition. The measurement of parameters such as liver mass, total liver protein, and DNA content in three studies did not lead to the conclusion that ethanol inhibits liver regeneration following hepatic resection; total liver mass and DNA content were the same as in controls when measured 4–15 days after surgery (Frank et al. 1979; Posó et al. 1980b; Orrego et al. 1981).

The studies reviewed are grouped on the basis of the timing and frequency of ethanol administration in relation to partial hepatectomy. Data on the effect of acute ethanol administration within 24 h of a 67% hepatic resection are summarized in Table 1. In Table 2 are summarized results of studies on the effects of short-term (up to 6 days) ethanol administration following partial hepatectomy. Results of the effect of chronic (10 days to 8 months) ethanol administration prior to partial hepatic resection and summarized in Table 3.