known causes of renal failure are absent (Papper 1983).

This is normally thought of as a problem only in severe and rapidly advancing liver disease. However, phenazone and aminophenazone (aminopyrine) clearance, used to indicate the severity of liver disease, has been shown to correlate with measures of both proximal and distal tubular Na^+ handling in patients with chronic stable cirrhosis (Wood et al. 1988) and cirrotic rats (Wensing et al. 1990b). While these changes may reflect an alteration in the handling mechanisms peculiar to Na^+ balance, there remains a possibility of generalised change in tubular function. If this were so, xenobiotic clearance by the kidney which is dependent on tubular mechanisms could be altered in patients with even moderate degrees of liver impairment.

4. Methods and Observations with Drugs and Markers of Drug Disposition

The majority of published clinical pharmacokinetic studies in liver disease have used a relatively simple mechanistic framework to interpret their experimental findings. Thus, changes in the systemic clearance or systemic availability of orally administered drugs have been ascribed to a reduction in hepatic intrinsic clearance and/or effective hepatic blood flow. This approach was the basis for the intact hepatocyte and sick cell hypotheses (Branch 1982; Branch & Shand 1976). With our increasing understanding of the pathological changes and of the mechanisms by which these changes may alter drug disposition in liver disease, it is now possible to interpret experimental findings using a broader mechanistic framework. This section examines the results of some selected studies of drugs and other markers of drug disposition in terms of the mechanisms of altered drug disposition described in section 3. Blaschke (1977) classified the hepatic elimination of drugs according to whether hepatic blood flow, intrinsic clearance or unbound fraction was rate limiting; the same classification is used here, and the review concentrates on more recently published studies.

4.1 Capacity-Limited Binding-Insensitive Hepatic Elimination

Drugs in this category have a low hepatic intrinsic clearance relative to hepatic blood flow and are less than 30% bound to plasma proteins (Blaschke 1977). The hepatic clearance of such drugs is low and will be unaffected by changes in plasma protein binding or hepatic blood flow. Therefore, the interpretation of findings from studies of the disposition of these drugs in liver disease should be more straightforward than that for drugs with flow- or protein binding-limited hepatic clearance. The hepatic clearance of drugs with capacity-limited binding-insensitive hepatic elimination may still be affected in liver disease by loss of cell mass, reduction in enzyme mass per cell, alteration in the intrahepatic distribution of enzymes or sinusoidal capillarisation. Findings with typical drugs in this category are discussed below.

4.1.1 Phenazone

Phenazone is one of the standard model compounds for studying hepatic oxidative drug metabolism (Vesell 1979; Vesell & Page 1968) and has found widespread use in the study of the effect of liver disease on hepatic drug disposition. The clearance of phenazone following oral administration (and assuming complete bioavailability) has been measured in patients with a wide variety of hepatic disorders, but a reduction in clearance is usually observed only in severe disease. For example, there is little impairment in chronic persistent hepatitis, chronic active hepatitis, mild cirrhosis or hepatosplenic schistosomiasis (Daneshmend et al. 1982; Horvath et al. 1986; Villeneuve et al. 1987). However, phenazone clearance is reduced by 50 to 70% in advanced or decompensated cirrhosis (Daneshmend et al. 1982; Kawasaki et al. 1988; Kirch et al. 1989; McQuinn et al. 1988; Mehta et al. 1986; Pentikainen et al. 1986, 1989; Villeneuve et al. 1987) and in certain other severe disorders such as acute episodes of hereditary hepatic porphyria (Birnie et al. 1987).

In many of the studies cited above, phenazone was administered concurrently with another drug

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