Some years ago (Abshagen, 1973) we showed that the pharmacokinetics of β-methyl-digoxin in female SD rats were markedly influenced by a 3-day pre-treatment with 100 mg spironolactone/kg b.i.d. After i.d. administration of 3H-β-methyl-digoxin, the half-life of 3H activity in blood dropped down in controls from 9.18 ± 0.6 h to 3.19 ± 0.08 h in spironolactone-pretreated animals (Fig. 33.1). Since for i.v. administration in man the dethioacetylated spironolactone metabolite with an opened γ-lactone ring, the fairly water-soluble canrenoate-potassium, is widely used, we also tested the effect of pretreatment with isomolar amounts of this drug. Thereby, an enhanced elimination of 3H activity could also be observed but the effect (t½: 4.33 ± 0.55 h) was not as pronounced as after pretreatment with spironolactone. Corresponding to the elimination from blood, the biliary excretion (Fig. 33.2) of 3H activity was almost quadrupled in spironolactone-pretreated rats, whereas a somewhat smaller increase could be observed after pretreatment with canrenoate-K. TLC analysis of the biliary excreted 3H activity (Fig. 33.3) revealed that the 0-demethylation of β-methyl-digoxin — as evidenced by the 12.5 times increase of digoxin — as well as the splitting of glycosidic bonds — as evidenced by the 9.3 times increase of bisglycoside — were enhanced by pretreatment with spironolactone. At the same time, the conjugation reactions leading to polar metabolites were augmented — as can be seen from the low amounts of the monoglycoside which serves as predominant conjugation partner (Abshagen and Rietbrock, 1973) and the concomitant higher amounts of the resulting polar conjugates. The fact, however, that the unchanged mother compound β-methyl-digoxin was also excreted to a higher degree after pretreatment with spironolactone pointed to an additional mechanism besides induction of glycoside degredation. In this respect, an higher uptake of the glycoside into the liver could be demonstrated as a result of spironolactone pretreatment which was evidenced both by experiments with liver slices (Abshagen, 1973) and in vivo (Castle and Lage, 1972).

Alteration of distribution, enhanced metabolism, and increased biliary and fecal elimination with consequently lower blood levels resulting from pretreatment with spironolactone could also be demonstrated in experimental animals for other glycosides, especially for digitoxin, by several authors during the last 4 years (Castle and Lage, 1972, 1973 a, b; Vöhringer and Rietbrock, 1974; Wirth et al., 1974). These phenomena were regarded as the underlying mechanism for
Fig. 33.1. Kinetics of $^3$H activity in blood of biliary fistula rats after intraduodenal administration of 80 $\mu$Ci $^3$H-$\beta$-methyl-digoxin without $\bullet$ and with pretreatment with 100 mg spironolactone $\circ$ or 95 mg canrenoate-K $\Delta$ per kg body weight twice daily for 3 days. ($\bar{x} \pm s \frac{\bar{x}}{x}$; $n = 8$)

the reduction of digitalis toxicity first reported in rats by Selye et al., (1969). In clinical experiments in man, however, spironolactone failed to reduce digitalis toxicity (Krämer et al., 1973 a, b). Therefore, it seemed a priori improbable that such profound alterations of digitalis metabolism as seen in rats and mice could also occur in man. Since both drugs, however, often are combined in clinical practice, this assumption had to be proved in man.

In an intrapatient trial (methodical details, see Abshagen et al., 1976 a), pharmacokinetics of $\beta$-methyl-digoxin were first studied in three persons after oral (2) and after i.v. (1) administration. The persons were treated 8 weeks later with 7 mg spironolactone/kg daily for 7 days and received a second single dose of $^3$H-$\beta$-methyl-digoxin in the morning of the 8th day. Just before administration of the second dose of digitalis, the concentrations of the main metabolites of spironolactone in blood — canrenone and canrenoate-K — were determined in order to assure that the experimental conditions were comparable to our studies in rats (Table 33.1). In man, the concentrations of these metabolites were even distinctly higher than in rats in spite of the by far lower doses of spironolactone/kg. This occurs as a consequence of the more than ten times longer half-lives of these substances with subsequent cumulation during the longer pretreatment period in man (Sadée, et al., 1974; Abshagen et al., 1976 b).