quivalents of NaCl per liter), these concentrative properties are shown to provide unique pharmacologic parameters of renal function such as the relative salinity or ionic fraction of the total solute concentration. In conjunction with specific electrolyte analyses, *e.g.*, Na, K, and Cl, expressed in similar equipollent units (mEq/l), other singular relationships in urinary function are demonstrable.

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Passing of Insulin from Plasma into the Bile.* (32245)

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Previous studies have shown that insulin is present in the bile of different species and that the concentration of insulin in the bile flow increases after stimulation of endogenous insulin production(1,2). These findings suggest the possibility that the bile is an avenue for the loss of insulin from the circulation. This possibility is confirmed in the present paper as insulin injected in circulating blood was recovered in the bile.

Material and methods. Insulin in the bile was determined according to method C of Hales and Randle(3). The bovine insulin used for standards in the immunological test was obtained from Eli Lilly Co. Iodinated insulin-I-125 was supplied by the Radiochemical Centre, Amersham, Buckinghamshire, England. Insulin binding serum was obtained from Wellcome Laboratories. Insulin concentrations are expressed as bovine equivalent, since bovine insulin was used as a standard.

Rabbits (1.5 to 2.0 kg) were deprived of food for 18 hours. To obtain the bile the animals were anesthetized with ether and then a catheter was placed in the choledochus through a medial abdominal incision. The cystic duct was ligated and the gall bladder removed, the catheter was guided to the exterior, where the bile could easily be collected in a test tube. Insulin was injected rapidly into the abdominal vena cava and samples of bile were taken at different time intervals. The hepatic bile flow, up to 7 hours following cannulation of the choledochus, was 7-9 ml per hour. Blood glucose(4) and plasma insulin were determined at the end of each experiment.

Results. The results obtained by analysing the presence of insulin in the bile flow after i.v. administration of 2 mg (50 IU) of bovine insulin in normal rabbits are summarized in Fig. 1. Large concentrations of insulin appeared immediately in the biliary flux; highly significant concentrations of insulin were still found in bile even 3½ hours after injection of the hormone. It is very possible that the significance of these experiments lies in the shape of the recovery curve, the first part of which lasts approximately one hour. This may be related to the affinity of insulin for the liver.

In the experiments described above, blood glucose was very low from the beginning (25 ± 4 mg/100 ml) and the insulin concentration in plasma was very high, even at the end of the experiment (>500 μU/ml). These are abnormal conditions. It was there-

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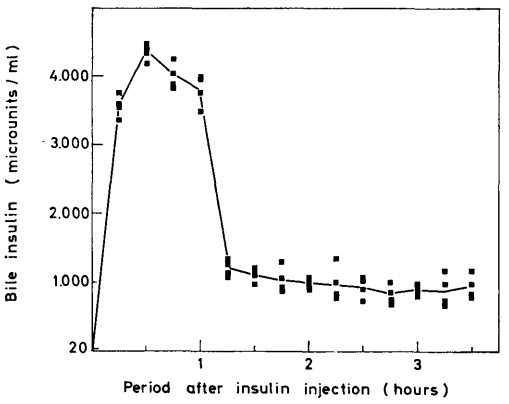

FIG. 1. Recovery of insulin in the bile at different times after administration of 2 mg (50 IU) of bovine insulin in rabbits. Insulin was injected rapidly into the "abdominal vena cava" after choledochus cannulation. The figures shown are mean values obtained in 4 different animals. Insulin concentration expressed as bovine equivalents (potency 25 international units/mg).

fore necessary to repeat the experiments using doses of insulin which would not decrease blood glucose and increase plasma insulin above physiologic limits.

The results obtained after i.v. injections of bovine insulin in low concentrations are shown in Fig. 2. The two smallest concentrations (1.4 and 2.8 μg) did not modify the blood glucose and the higher one (5.6 μg) affected it only slightly (78 $\pm$ 7 mg/100 ml). It is interesting to observe the parallelism in the recovery curves and the similarity of the time required for the insulin to reach maximum values in the bile.

The results obtained by this method are also in good agreement with those of our studies using insulin-I^{131}, indicating that even when as little as 0.04 μg of labeled insulin were injected, significant amounts of immu-

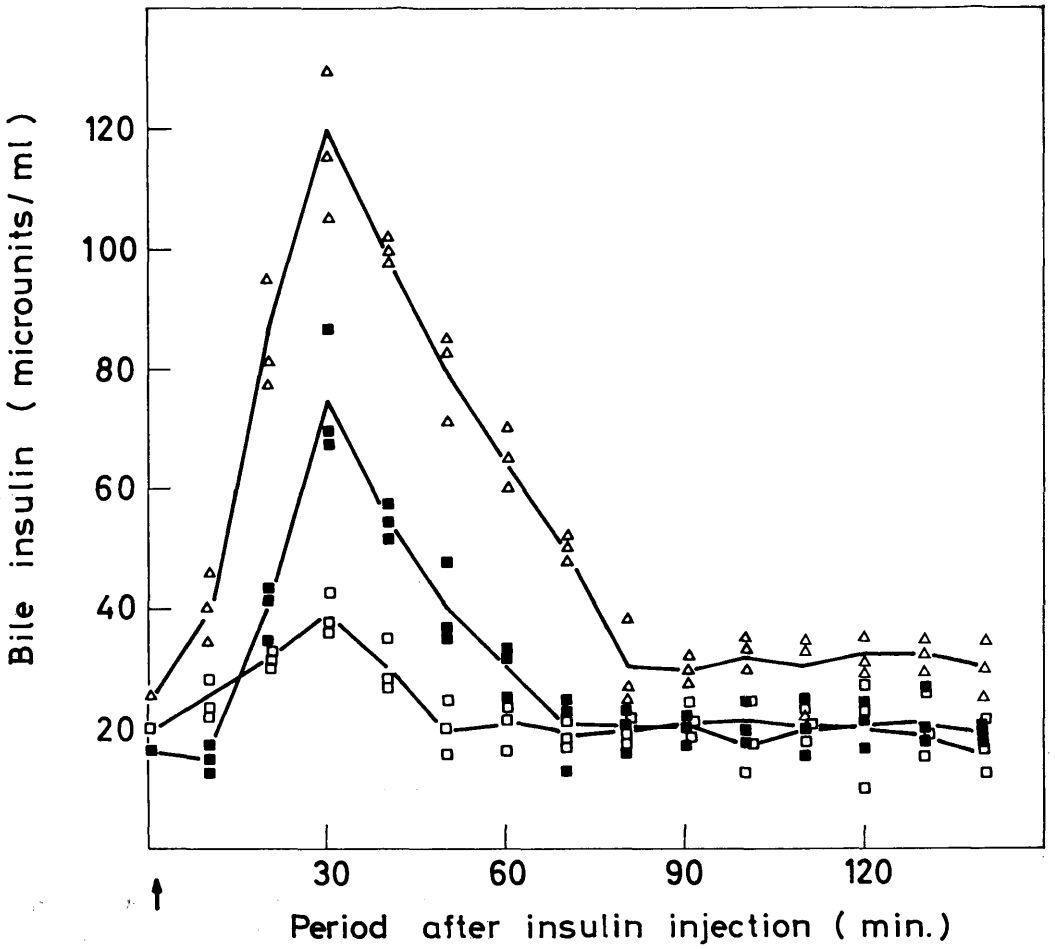

FIG. 2. Recovery of insulin in the bile at different times after injection of different amounts of bovine insulin. Insulin was injected rapidly into the "abdominal vena cava" at time indicated by arrow. Each curve shows mean values for 3 different animals after insulin injection of 5.6 μg (0.14 IU) △———△; 2.8 μg (0.07 IU) ■———■; and 1.4 μg (0.035 IU) □———□. Insulin concentration expressed as bovine equivalents (potency 25 international units/mg).

nologically active insulin were recovered in the bile of rabbits. Detailed results of these studies will be published elsewhere.

Discussion. The results presented above show that heterologous insulin flows from plasma into the bile even at physiological concentration. In the first 30 minutes after i.v. injection of insulin a rapid increase in the concentration of hormone occurred in the bile and insulin continued to be eliminated through the bile in smaller amounts for several hours. The increased concentration of insulin in the bile coincides in time with the disappearance of plasmatic insulin according to Croughs(5) and also with an increase of the radioactivity when insulin-I^{131} is injected, which may be noted with surface detectors in the hepatic area(6).

These findings are in accordance with the hypothesis that labeled and unlabeled insulin can enter into the liver cell(7).

Summary. Large amounts of insulin appear in the bile of rabbits after i.v. administration of 2 mg (50 IU) of bovine insulin. Insulin was recovered from the bile also after the administration of heterologous insulin in low concentrations. The hormone concentration in the bile reached a peak in the first 30 minutes after i.v. injection of insulin, showing that the bile is avenue for the loss of insulin from the circulation.

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Effect of pH and of Urea on Nitrofurantoin Activity. (32246)

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The clinical effectiveness of nitrofurantoin (Furadantin; 1-[(5-nitro-furfurylidene) amino] hydantoin) in the treatment of various urinary tract infections has been reviewed (1,2). This chemotherapeutic agent has been found useful in the control of both Gram-positive and Gram-negative organisms, including some cases of *Proteus vulgaris* infections. In general, the results of treatment of Pseudomonas infections have not been encouraging(3) although occasional cases(4,5) have responded. It was called to our attention some time ago in a personal communication from Dr. Charles Norfleet that the effectiveness of nitrofurantoin was improved in Pseudomonas infections when an acidifying agent was administered concurrently. Richards *et al*(6) found that the activity of nitrofurantoin *in vitro* against *Escherichia coli* was greatest at pH 5.4 and considerably decreased at pH 8.1. Mou(7), reviewing the effect of urine pH on the antibacterial activity

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