amyloidosis, and intravenous injection of different enzymes (papain, elastase, hyaluronidase, trypsin, chymotrypsin); controls received intravenous ovalbumin and saline. Significant increase of serum haptoglobin was found in acute scurvy (average 8 times normal), carrageenan granuloma (4 times normal) or both combined (5 times normal), and after intravenous injection of papain, elastase and of hyaluronidase (average of 2 to 2.5 times normal). Particularly striking results were obtained with papain and elastase which in some cases produced an increase in haptoglobin up to 7 times the starting value. These methods may be used to obtain reproducible experimental hyperhaptoglobinemia.

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Received February 3, 1961. P.S.E.B.M., 1961, v107.

Interrupted Enterohepatic Circulation of Bile and Its Effect on Urinary and Biliary Excretion of I^{131}.* (26668)

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Any alteration of hepatic physiology markedly affects iodine metabolism. Carbon tetrachloride-induced liver injury results in both increased hepatic retention and decreased thyroid uptake of subcutaneously administered I^{131}(1). Shunting portal circulation by an Eck fistula leads to a decreased thyroid uptake of I^{131} following its intragastric administration(2). Absence of bile in the intestinal tract impairs the absorption of orally administered I^{131}(3). It is not known, however, whether bile loss will modify the metabolism of I^{131} intravenously administered.

The purpose of these experiments was to study the effect of interrupted and uninterrupted enterohepatic circulation on the biliary and urinary excretion of iodide administered intravenously. Also, efforts were made to ascertain the conditions necessary to maintain normal urinary iodide excretion after surgery upon the biliary tract and alteration of normal pathways of bile flow.

Materials and methods. Nine groups (Table I) of male Holtzman rats weighing approximately 150 g were used. Surgery was performed under Nembutal anesthesia.

*This investigation was supported by the Research and Development Division, Office of the Surgeon General, Dept. of the Army.

TABLE I. Effect of Total Biliary Diversion on Urinary and Biliary Excretion of I^{131}.

Group	Operation; additional experimental conditions	Urine (excretion/24 hr)				Bile (excretion/24 hr)	
		No. of rats	% of injected I^{131}*	Vol (ml)*	Sodium (meq)*β	% of injected I^{131}*	Vol (ml)*
I	Control, no choledochostomy	14	78.3 ± 3.7	16.7 ± 2.1	1.86 ± .26 (8)		
II	Bile fistula	6	4.9 ± 1.3†	21.2 ± 4.4	0.29 ± .10 (8)†	9.5 ± .49	11.4 ± .5
III	" " , I^{131} inj. 2 hr post-op.	6	18.5 ± 7.8†	26.5 ± 2.4†	.24 ± .10 (8)†	9.5 ± 1.02	15.1 ± .7‡
IV	Sham choledochostomy; reanastomosed bile duct patent	7	78.3 ± 4.8‡	18.7 ± 3.2			
V	" " " " obstructed	4	63.1 ± 8.9‡	12.7 ± 2.3			
VI	Control; fasted during recovery and collection period, no choledochostomy	16	52.6 ± 8.9†‡	15.0 ± 1.4	.42 ± .14 (7)†		
VII	Bile fistula; donor bile introduodenally infused instead of tap water	7	36.2 ±11.4†‡	22.5 ± 6.6		9.5 ± 2.05	15.7 ± .7‡
VIII	Bile fistula; offered I-drinking water instead of tap water	8	48.2 ± 6.2†‡	30.9 ± 9.1		9.0 ± 1.06	11.8 ± .8
IX	Bile fistula; donor bile intraduodenally infused, offered I-drinking water	8	75.5 ± 5.3‡	40.0 ± 8.1		3.9 ± .53‡	16.6 ±1.5‡

* Mean ± S.E. † Significance <5% when compared to Group 1, control. ‡ Significance <5% when compared to Group II, bile fistula.
β Na excretion determined from similarly treated, but different, samples of rats (figure in parentheses denotes No. of rats used for each group).

The femoral vein was cannulated in all groups including the controls. At the end of the designated recovery period 1 μc of NaI^{131},† carrier free and diluted with 5% glucose, was injected into the femoral cannula. All rats were permitted to recover 18 hours before injection of radioactive iodide except those in Group III, which were injected 2 hours after surgery.

In sham choledochostomy, anastomosis of the severed bile duct (choledochocholedocostomy) was established by means of a polyethylene tube. The anastomosis was judged patent (Group IV) if bile did not appear in quantity in the urine during the experiment and if, at the end of the experiment, bile dripped from the end of the proximal portion of the bile duct after severance of the polyethylene tube. Otherwise, the anastomosis was judged obstructed (Group V).

Another control consisted of rats fasted during the 18 hour recovery period and the 24 hour collection period, but not subjected to choledochostomy (Group VI).

The basic experimental preparation was an externally draining bile fistula, and an intraduodenal infusion of tap water (Group II). The common bile duct was divided and polyethylene tubes (Pe-10, Pharmaseal) were inserted into the cut ends of both proximal and distal portions to permit both measurement of total bile output and infusion of tap water into the duodenum. Variations in this basic experimental preparation are described below and indicated in Table I.

In 2 experiments (Group VII and IX) bile was substituted for tap water in intraduodenal infusions. The bile had been previously collected at room temperature from donor rats. Donor bile or tap water was infused by means of a constant infusion pump at a rate similar to that at which bile drained from the fistula (1 cc/hr). In 2 experiments (Groups VIII and IX) iodinated drinking water (Lugol's solution diluted to 24 mg % iodide) was offered 48 hours prior to choledochostomy and throughout recovery and collection periods instead of tap water. Tap water was continuously available to all other

† Abbott Laboratories, Chicago, Ill.

groups; all except the fasted group (VI) were fed Purina Laboratory Chow *ad lib.*

For 24 hours following injection of I^{131}, urine from all groups and bile from those with a bile fistula were collected in 250 ml small mouth bottles to which was added 1 ml of Na OH-Na I solution to prevent loss of I^{131}. The volume of each sample was recorded and then diluted to the volume of the radiation standard. Measurement of radioactivity was conducted with a scintillation well counter united to a Nuclear-Chicago Radiation Analyzer-Scaler combination. Iodide-131 excretion was calculated as percent of the injected dose appearing in urine or bile/24 hours. Bile and urine sodium were determined with a Baird flame photometer.

Results. Table I demonstrates the effect of interrupted enterohepatic circulation of bile on urinary excretion of sodium and intravenously administered I^{131}. Rats normally excrete about 78.3% of injected I^{131} in 24 hours (Group 1, Control). Rats with a bile fistula (Group II) that had drained 18 hours prior to injection of I^{131}, however, excreted only 4.9% of the I^{131} in the same period. Also less sodium was excreted by bile fistula animals than by controls. Sodium and I^{131} excretion were also depressed in bile fistula rats that had been injected with I^{131} only 2 hours postoperatively (Group III).

The possibility that the decrease in urinary excretion of I^{131} was due to operative trauma was tested with Group IV. These rats, with reanastomosed bile ducts, excreted I^{131} at the same rate as the controls. Similarly, rats with partial obstruction of the reanastomosed bile ducts (Group V) showed no significant reduction in excretion of I^{131}.

Some diminution of urinary excretion of I^{131} occurred in rats fasted throughout the 18 hour recovery period and the 24 hour collection period (Group VI). However, I^{131} excretion in these fasted controls was significantly greater ($p<.05$) than that of the bile fistula rats (Groups II and III). Sodium excreted by fasted controls was not significantly greater than that excreted by bile fistula rats.

Bile fistula rats in which the collected bile was replaced with rat donor bile (Group VII) or which were supplied with iodinated drinking water (Group VIII) or subjected to a combination of both treatments (Group IX) showed a significant increase in the 24 hour urinary excretion of I^{131} as compared to non-treated bile fistula rats (Group II).

An average of 9.5% of injected I^{131} (Table 1) was excreted in bile from bile fistula rats (Group II). Essentially the same activity appeared in bile of rats with a bile fistula injected with I^{131} within 2 hours after choledochostomy (Group III), rats infused with bile (Group VII) or offered iodinated drinking water (Group VIII). Rats with a bile fistula but treated with a combination of bile and iodinated drinking water excreted significantly less ($P<.05$) I^{131} in the bile than did untreated bile fistula rats.

Discussion. Several methods of investigation have shown that the liver plays an important role in iodide metabolism. Alterations in hepatic function lead to changes in PBI levels(4) and affect the thyroid uptake of I^{131}(5). Bile has been implicated in the metabolism of I^{131} by Friedman and Kowalewski(3) who reported that the absence of bile in the intestinal tract markedly suppressed absorption of orally administered I^{131}. They were unable to explain this lack of absorption.

The present report demonstrates the influence of total biliary diversion on metabolism of I^{131} administered parenterally. Rats with an externally draining biliary fistula excreted significantly less I^{131} in urine than controls. In view of the findings by Friedman and Kowalewski(3) it was necessary to determine if this reduced I^{131} excretion was related to an absence of iodide absorption through the intestinal wall. This was accomplished by the fasting controls. Although the excretion rate of I^{131} in fasting controls was less ($P<.05$) than non-fasted controls, it was still significantly greater than that of bile fistula rats and comparable to bile fistula rats treated with either bile or iodinated drinking water. It is possible that diminished iodide absorption plays a minor role in the studied effect.

Fasting and trauma suppress sodium excretion to a much greater extent than they

suppress iodide excretion. Sodium excretion is reduced through emotional stress(6) and surgical trauma(7). Trauma was dismissed as a factor in urinary excretion of I^{131} by Van Middlesworth and Berry(8) who reported that intestinal injury, starvation, lack of Vit. A_1, B_2, and B_6, or injections of cortisone had little effect on urinary excretion of I^{131}.

Bile loss appears to affect metabolism of iodide to a much greater degree than the iodo derivatives, thyroxine, and triiodothyronine. The liver is mainly responsible for deiodination of thyroxine and triiodothyronine(9). However, dogs with a biliary fistula given Lugol's iodine solution orally metabolized and deiodinated triiodothyronine as affectively as controls(10).

Total biliary diversion markedly suppressed urinary excretion of sodium. This effect may be related to loss of electrolytes in bile as the concentration of sodium in bile‡ was similar to that of blood. However, urinary excretion of I^{131} did not parallel that of sodium in these studies. The sodium content of urine from bile fistula or fasted control rats was similar, but urinary I^{131} of fasted rats was greater than that of bile fistula rats. Conservation of sodium in the fasted or bile fistula rat was probably influenced by hormones since salt depletion has been shown to result in an increased 17-ketosteroid secretion(11).

Intact adrenals were necessary for normal urinary excretion of I^{131}(12), but cortisone treatment fully restored I^{131} excretion in adrenalectomized rats(12) and mice(13). The main site of corticosteroid inactivation is the liver(14), and chronic external diversion of bile produced histological signs of hyperfunction in the adrenals and thyroid(15). The influence of total biliary diversion on the urinary excretion of I^{131} intravenously administered may be mediated through the adrenals.

Summary. Total biliary diversion markedly depressed urinary excretion of I^{131} intravenously administered. The effect was apparent within 2 hr post choledochostomy. Fasting reduced urinary excretion of I^{131} to a minor extent; operative trauma had no effect. Treatment of bile fistula rats with donor bile and/or iodinated drinking water significantly increased I^{131} excretion. I^{131} content of bile was significantly reduced in bile fistula rats only through combined treatment with donor rat bile and iodinated drinking water. I^{131} content in urine paralleled that of sodium under some conditions but not in others.

The author is grateful to Roy Marrero for expert technical assistance in this study.

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‡ 139 ± 3 meq/l, Group II.

Received February 24, 1961. P.S.E.B.M., 1961, v107.