SIMULTANEOUS RENAL AND HEPATIC EXCRETION OF WATER, CYANOL, AND AZOFUCHSIN I IN RABBITS*

By WILLIAM E. EHRICH, M.D.

(From the Department of Pathology, The School of Medicine, University of Pennsylvania, Philadelphia)

(Received for publication, June 11, 1942)

In a previous study of the renal excretion of water, cyanol, and azofuchsin I in rabbits (1), about 90 per cent of the injected amount of azofuchsin I appeared in the urine within 2 hours after injection, while only about 30 per cent of the cyanol was recovered during this time. On the other hand, considerable quantities of cyanol were found in the contents of the intestine, while azofuchsin I was not observed in this location.

Since little is known about the relationship between renal and hepatic excretion of dyes and other substances, and this relationship appears to be important to the student of both renal and hepatic excretion, a study was undertaken of the behavior of the two types of dyes when given simultaneously; and cyanol and azofuchsin I were selected to be studied first because their renal excretion had been investigated previously (1).

**Methods**

All experiments were performed in male Chinchilla rabbits weighing about 2000 gm. In a first series of experiments the animals received 100 cc. of tap water by stomach tube, and a catheter was placed in the urinary bladder. About 1 hour later when diuresis was in progress the rabbits were anesthetized with ether, and a cannula inserted into the common bile duct. Again, about 1 hour later when the rabbits had recovered somewhat from the anesthesia, 2 cc. of a 0.1 per cent solution of either cyanol or azofuchsin I was injected intravenously; and urine and bile were collected 30, 60, and 90 minutes after the injection of the dye. The concentration of cyanol and azofuchsin I in urine and bile was tested as in our previous experiments by using a comparator (1).

In addition to these simple bile drainage experiments, others were performed in which either the renal or the hepatic excretion was changed by various experimental procedures. Thus in a second series of experiments, in order to stimulate diuresis 2 gm. of urea were given intravenously shortly after the injection of the dye. In a third series of experiments the renal arteries and veins were ligated so that renal excretion was stopped completely; while in a fourth series the bile was not drained, but the common bile duct ligated. In a last small group of animals the common bile duct was ligated and portions of the liver excluded from the circulation by throwing a ligature around the base of one or several lobes of this organ.

* Aided by a grant from the Pennsylvania Chapter of the Society of Sigma Xi.
RESULTS

Text-fig. 1 presents the behavior of the rates of the urine and bile flow during the three periods of our experiments, namely: (a) before operation; (b) between operation and dye injection; and (c) after injection. The white circles refer to animals which received 100 cc. of tap water by stomach tube the day before the experiment as well as 1 hour before the operation ("wet" animals), while the black circles represent results obtained in animals which had water only before the operation ("dry" animals). Both groups of animals had access to drinking water throughout the preoperative period.

Urine Rates.—In simple bile drainage experiments (Text-fig. 1, A), the average urine rates, instead of rising as in untreated animals, remained low or dropped slightly during the 2nd hour after the introduction of water (between operation and dye injection), to drop even further during the 3rd hour (after dye injection). In the group which received urea after injection of the dye

1 Both "wet" and "dry" animals were used because in previous experiments wet animals were found to develop a much better water diuresis than dry animals (1).
(B, c) the urine rates rose to more than twice the amount observed in simple bile drainage experiments. If, finally, the common bile duct was ligated (C), the rates closely resembled those in simple bile drainage experiments except in two animals which reacted with a marked increase in urine production (+).

**Bile Rates.**—In simple bile drainage experiments (Text-fig. 1, D) and in urea experiments (E) the average bile rates dropped from about 0.2 cc. per minute before dye injection to 0.14 cc. per minute after dye injection. In animals in which the renal arteries and veins were ligated (F) the bile rates were markedly depressed. It is noteworthy that the bile rates in our simple bile drainage experiments (D) were about 3 to 4 times the urine rates (A); while after introduction of urea the two were about the same (E, c and B, c).

**Excretion of Cyanol and Azofuchsin I.**—If we turn now to the excretion of the dyes and first consider their renal excretion (Text-fig. 2), we find that practically all our results are well within ±20 per cent of the normal excretion.
curves. This is true for both the dyes, whether in simple bile drainage experiments (©), urea experiments (©), or those in which the common bile duct was ligated (●). However, if in addition to the ligation of the common bile duct, parts of the liver were excluded from the circulation, the renal excretion of cyanol (the only dye tested in such experiments) was definitely increased (Table I).

As to the hepatic excretion of the two dyes (Text-fig. 3), it appears that the results are not numerous enough to permit a conclusion as to whether they conform to definite curves. However, it can be seen that in a large majority of the experiments the results in the urea experiments (©) tend to be lower than those of the simple bile drainage experiments at comparable bile rates (©), and especially those in which the renal arteries and veins were ligated (●). The greatest amount of cyanol excreted in the bile within 90 minutes after injection of the dye (C) was about 1 mg., approximately twice the amount observed in the urine during this period; while the greatest amount of azofuchsin I excreted in the bile within 30 minutes (D) did not exceed 0.08 mg., or about 1/15th of the largest amount which, during this period, was observed in the urine.

It can then be said that after ether anesthesia and drainage of the common bile duct a water diuresis failed to develop; and that ether anesthesia and ligation of the common bile duct in most cases had a similar effect; while 2 gm. of urea intravenously definitely stimulated diuresis. The excretion of bile, on the other hand, was the same in both simple bile drainage experiments and in those in which urea was given; while in animals in which the renal arteries and veins were ligated the bile flow appeared to be depressed.

The normal excretion curves have been drawn from a large number of data obtained in normal Chinchilla rabbits weighing about 2000 gm. About half of these data have been presented in a previous publication (1).

After the first 30 minute period the concentration of azofuchsin I in the bile became so low that in many instances it could no longer be determined. It is for this reason that the data of the first 30 minutes only are given.

<table>
<thead>
<tr>
<th>Rabbit No.</th>
<th>Weight</th>
<th>Urine rate</th>
<th>Cyanol excretion (per cent of normal)</th>
<th>Portion of liver ligated</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>gm.</td>
<td>cc./min.</td>
<td>cc./min.</td>
<td>30 min.</td>
</tr>
<tr>
<td>B 12</td>
<td>1800</td>
<td>0.09</td>
<td>0.03</td>
<td>0.08</td>
</tr>
<tr>
<td>B 13</td>
<td>1980</td>
<td>0.02</td>
<td>0.01</td>
<td>0.10</td>
</tr>
<tr>
<td>B 11</td>
<td>2040</td>
<td>0.17</td>
<td>0.01</td>
<td>0.05</td>
</tr>
</tbody>
</table>
It can be stated further that in simple bile drainage experiments, urea experiments, and those in which the common bile duct was ligated, the usual amounts of cyanol and azofuchsin I were excreted through the kidneys. It is true that the absolute quantities of dye that were recovered from the urine within 30, 60, and 90 minutes after their injection were smaller than those which were found in similar experiments in intact animals (1); however, all the results were well within ± 20 per cent of the normal excretion curves. In other words, there was no true reduction in dye excretion; only the diuresis was depressed. However, if parts of the liver were excluded from the circulation, the renal excretion of cyanol was augmented.

On the other hand, the hepatic excretion of the dyes appeared to be not only a function of the bile volume, but also of their renal excretion, because with the same bile volume the hepatic excretion tended to be slightly greater in animals with a low diuresis than in animals with a better diuresis; and it was greatest in experiments in which the renal arteries and veins were ligated.

It thus appears that under the conditions of our experiments the renal excretion of water was independent of its hepatic excretion, and vice versa; while the renal and hepatic excretion of our dyes were interrelated.

**DISCUSSION**

Though comparable observations are scanty, the few data which have been published are in good accord with our results. For instance, in rabbits weighing 2000 to 3000 gm. Halpert (2) observed an average bile rate of 0.15 to 0.19 cc. per minute during the 1st hour after insertion of a cannula into the common bile
duct, and a rate of 0.12 to 0.17 cc. per minute during the 2nd hour; while in our simple bile drainage experiments and those in which urea was given the average bile rate amounted to 0.19 to 0.23 cc. per minute during the 1st hour, and 0.13 to 0.155 cc. during the following 1½ hours. In obstructive jaundice in man no change was observed in the renal excretion of phenolsulfonephthalein (3, 4). After ligation of the common bile duct in dogs, a slightly elevated output was found by some (5) workers, but a normal or depressed output by others (4), while in our rabbits after ligation of the common bile duct no change in dye excretion was observed. The latter observation may be explained by the assumption that in these cases the liver continued to function, that is to say, it continued to take up dye so that the amount of dye offered to the kidneys was not materially altered. This is in accord with the fact that after destruction of parts of the liver by chloroform an increase in the renal output of phenolsulfonephthalein was observed (Hanner and Whipple (5)); and a similar increase in the renal excretion of cyanol was noted in our experiments in which, in addition to ligation of the common bile duct, parts of the liver were excluded from the circulation by throwing a ligature around the base of one or several lobes of this organ.

It can be said then that in normal kidneys the renal excretion of a given dye is chiefly a function of the urine volume except in cases of severe destruction of the liver, for then the renal excretion may be augmented. The hepatic excretion of our dyes was found to depend on the urine volume, i.e., the renal excretion of the dyes, as well as on the bile volume; and this was observed even if the

**Text-Fig. 4.** Relationship between urine-bile ratio and that of hepatic and renal excretion of cyanol within (A) 30, (B) 60, and (C) 90 minutes, and (D) that of azofuchs in I within 30 minutes after their injection. The ratios have been calculated as per cent of the total amount excreted. O, simple bile drainage experiments; O, urea experiments.
kidneys were normal. This difference can be explained by the fact that diuresis fluctuates a great deal, while the bile rate tends to be more steady. It is obvious that a greater fluctuation in diuresis, and consequently in renal dye excretion, should result in a greater variation in the amount of dye still in circulation, which in turn should bear on the hepatic excretion of the dye. In the kidney, on the other hand, on account of the greater steadiness of the bile rate, this effect would not manifest itself.

In view of these observations it seemed clear that a mathematical relationship between the renal and hepatic excretion of the two dyes could not be found by simply comparing the quantities of dye that were excreted through kidneys and liver. However, when the ratio between the amount of dye excreted through the liver and that excreted through the kidneys was plotted against the ratio between urine rate and bile rate (Text-fig. 4), hyperbolas resulted showing that a logarithmic relationship exists between the renal and hepatic excretion of cyanol and azofuchsin I.

Considering finally the practical question whether or not the hepatic excretion of dyes introduces a noteworthy error into their use as a measure of renal function, we can safely conclude from our experiments that this is not the case except in those instances in which the liver is severely damaged. This conclusion is in accord with the experience of those who use phenolsulfonphthalein for testing the kidney function.

SUMMARY

1. The renal and hepatic excretion of water, cyanol, and azofuchsin I was studied in rabbits under various conditions. It was observed that under the conditions of our experiments the urine rate was independent of the bile rate, and vice versa. The renal excretion of these dyes also was independent of their hepatic excretion except in cases in which the liver was severely damaged. On the other hand, the hepatic excretion of these dyes depended also on their renal elimination.

2. The relationship between the renal and hepatic excretion of cyanol and azofuchsin I could be expressed in the form of hyperbolas.

3. In the use of dyes as a measure of renal function, no noteworthy error is introduced by their hepatic excretion except in cases in which the liver is severely damaged.

BIBLIOGRAPHY