STUDIES ON THE TOTAL BILE.

III. ON THE BILE CHANGES CAUSED BY A PRESSURE OBSTACLE TO SECRETION; AND ON HYDROHEPATOSIS.

BY PHILIP D. McMASTER, M.D., G. O. BROUN, M.D., AND PEYTON ROUS, M.D.

(From the Laboratories of The Rockefeller Institute for Medical Research.)

(Received for publication, December 13, 1922.)

In previous papers the differing influences upon the bile of the gall bladder and ducts have been described,1 and the fact has been emphasized that, in the absence of infection, these influences are responsible for the varied character of stasis bile. The present communication has to do with the changes occurring in the bile when obstruction hinders but does not prevent its flow through the ducts. During the course of observations upon the theme we have been impressed with what is more than an analogy, with an enlightening similarity, between the events following biliary and urinary obstruction respectively; and while reporting upon the effects of a pressure obstacle upon bile secretion we shall take occasion to discuss the larger theme.

A first instance of the bile changes came to us during work for another purpose which need not here be entered into. A balloon of thin rubber, joined to the common duct by a rubber tube and glass cannula, had been placed within the peritoneal cavity of a dog, and the laparotomy wound closed. Once in every 24 hours thereafter the bile that had accumulated in the balloon was drawn off through an outlet tube passing through the abdominal wall. The fact was recognized that adhesions, contracting down about the artificial reservoir for the bile, would eventually put an end to its usefulness. But this took place slowly; and during the days when the pressure of the adhesions gradually interfered with the filling of the balloon, gradual

1 Rous, P., and McMaster, P. D., J. Exp. Med., 1921, xxxiv, 47, 75.
but marked changes were noted in the character of the biliary secretion. A synopsis of the protocol follows.

**Experiment 1. Dog 14.**—A female hound of 12½ kilos was operated upon and the bile-collecting apparatus introduced. Ether was the anesthetic. To rule out gall bladder influences, the organ was tied off at the neck with a series of stout ligatures after it had been emptied by aspiration. The tube from the common duct to the collecting bag—a toy balloon holding 150 cc. without stretching of the walls,—was about 10 cm. long and led, not to the end of the bag near the liver, but to the further one with which it was connected by a curved glass tube. The object of the arrangement was to lessen the danger that infection traveling along the foreign surface would reach the duct; and none did. From the other end of the bag a short piece of rubber tubing led to the body surface through a small stab wound in the abdominal wall. It was kept closed with a clamp, save when bile was to be drawn off, and its tip was stoppered with cotton soaked in 5 per cent phenol, and further swathèd in phenolated gauze. The laparotomy wound was closed in three layers. It healed promptly and perfectly. Throughout the period of the observations the condition of the dog was excellent, and the bile remained sterile.

Once in every 24 hours the outlet tube was opened. The intraabdominal pressure caused the bile to gush forth rapidly, and emptied the thin walled balloon completely, as proven both by the failure to obtain more bile by aspiration, and by washing the balloon out with sterile salt solution. The bilirubin yield was quantitatively by Hooper and Whipple's method, as in our previous work.

For 10 days after operation a bile of ordinary character, yellow-brown and somewhat syrupy, came from the balloon, but on the 11th day, while the amount of fluid was not greatly lessened (58.2 cc. as compared with 86 cc. for the preceding 24 hours) it was far lighter, a pale greenish brown. At this time the body weight was 11½ kilos. Next day, with still less secretion, there was also less pigment (Table I). The fluid was now thin and greenish yellow, as was that of the 13th and 14th days. The urine became icteric; and on the 14th day, when the dog was killed, a slight jaundice of the tissues could be perceived. Prior to evacuation of the bag on this day the pressure within it was measured with the aid of a glass tube of narrow bore, filled with a 5 per cent watery solution of phenol and connected with the outlet tube. The pressure equalled 370 mm., or in other words was at the upper limit of that developing in dogs with total biliary obstruction.² The bag was now emptied, the outlet closed, the animal fed as usual, and after the lapse of 5½ hours, a second manometer determination was made. The pressure was now 300 mm. The bag was forthwith emptied again, 5 per cent phenol solution was run slowly into it, and the pressure changes were

followed. None of the fluid entered until a pressure of 130 mm. had been reached, and after 14 cc. had slowly passed in, the pressure had risen to 160 mm. It should be mentioned that some slight pressure is normally maintained within the duct system by the sphincter of Oddi, though how much is not exactly known.

The outlet tube was now clamped, and the animal chloroformed and immediately autopsied. Except for the minor alterations incident to a moderate general icterus of brief duration, no pathological changes were evident anywhere save in the biliary tract. The ligated gall bladder contained merely a little bile-stained mucus; and, as the original connection between ducts and intestine had not been reestablished, the only path of escape for the bile had led into the bag. The lymphatics from the liver, coursing beside the ducts, were filled with a bright yellow fluid. All the large bile channels were greatly distended with a watery content. The common duct measured more than 1 cm. across near the cannula. The collecting tube and balloon were found swathed in dense adhesions, and the latter was bound thereby to the parietal peritoneum. When the adhesions were cut into there was a gush of serous fluid which had been pocketed about the bag, and this was disclosed empty. But practically at once the contents of the ducts above passed into it, and they themselves collapsed. The fluid transferred so abruptly proved to be the phenol solution previously introduced, now stained a pale yellow with bilirubin. Between bag and ducts no obstruction existed.

Sections of the liver showed a beginning biliary cirrhosis such as is consequent on obstruction.

Here was an animal that during 9 days elaborated a rather syrupy, dark bile. Then the secretion began to diminish in quantity, and became thin and greatly less pigmented (Table I). Some lessening in the concentration of cholates was indicated by Hay's test carried out in graded dilution. Manometer measurements indicated the presence of a pressure obstacle to secretion, which was least immediately after the emptying of the bag, but increased to the degree associated with total obstruction as bile accumulated in the apparatus. The large amount of the secretion obtained from the balloon 51/2 hours after the first emptying on the 14th day is not without significance in connection with the pressure variations. More than 31 cc. had collected within this short time, as compared with 38.5, 58.6, and 47.7 cc. for each of the three preceding periods of 24 hours; but already, at the end of the 51/2 hours, the pressure within the collecting system approached that of total obstruction. One is justified in the belief that there would have been little further

### TABLE I.

**Experiment I. Dog 14. Weight 11½ Kilos.**

<table>
<thead>
<tr>
<th>24 hr. period No.</th>
<th>Bile amount</th>
<th>Bile character</th>
<th>Bilirubin</th>
<th>Bile salts, Hof's test positive in a dilution of</th>
<th>Bilirubin in urine in 24 hrs.</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>cc.</td>
<td>cc.</td>
<td>Per cc.</td>
<td>Per hr.</td>
<td>mg.</td>
<td>mg.</td>
</tr>
<tr>
<td>9</td>
<td>79.4</td>
<td>3.3</td>
<td>0.49</td>
<td>1.62</td>
<td>1 in 20</td>
<td>None</td>
</tr>
<tr>
<td>10</td>
<td>86.0</td>
<td>3.6</td>
<td>0.46</td>
<td>1.64</td>
<td>1 “ 15</td>
<td>1.5</td>
</tr>
<tr>
<td>11</td>
<td>58.2</td>
<td>2.4</td>
<td>0.33</td>
<td>0.79</td>
<td>1 “ 15</td>
<td>4.5</td>
</tr>
<tr>
<td>12</td>
<td>38.5</td>
<td>1.7</td>
<td>0.2</td>
<td>0.31</td>
<td>1 “ 10</td>
<td>5.0</td>
</tr>
<tr>
<td>13</td>
<td>58.6</td>
<td>2.4</td>
<td>0.16</td>
<td>0.38</td>
<td>1 “ 10</td>
<td>6.1</td>
</tr>
<tr>
<td>14</td>
<td>47.7</td>
<td>1.9</td>
<td>0.22</td>
<td>0.42</td>
<td>1 “ 10</td>
<td>8.5</td>
</tr>
<tr>
<td>5½ hrs.</td>
<td>31.2</td>
<td>5.7</td>
<td>0.13</td>
<td>0.74</td>
<td>1 “ 10</td>
<td></td>
</tr>
</tbody>
</table>
secretion into the bag had emptying of it been deferred until the next day. At autopsy the distention of the ducts was found to be as great as after total obstruction of some days duration, while the presence of tissue icterus attested to a prolonged retention of bile constituents. For some time, probably, bile secretion into the ducts had taken place only during the first part of each 24 hour period.

Another similar instance was observed in which adhesions progressively limited the expansion of an intraperitoneal collecting balloon. Bile changes occurred that were identical with those just described. Experiments of the sort were then discontinued. But in the course of collections over long periods of time into a balloon outside of the body we have repeatedly had occasion to note biliary changes, whenever a collecting cannula was gradually obstructed by a calculus, or, — following escape of the cannula from the duct, — when a fistulous channel was obliterated by scar tissue.

**Methods.**

The bile specimens from all our animals were stored in the cold, where they remained without much change for many days, as is usual if the secretion contains little mucus. Whenever alterations in the 24 hour yield pointed to a developing obstruction, all the specimens for some time previous were subjected to quantitative cholesterol determinations by the Autenrieth-Funk method, as were those obtained before total obstruction supervened. Similar determinations were also carried out on successive specimens from animals without any obstruction; but beyond serving as controls these yielded no data of importance in the present connection. The bilirubin output was determined each day by Hooper and Whipple's method, according to a technique already described. No exact quantitation of the bile salts was attempted, but Hay's test was employed in graded dilution to learn of their presence and something of their concentration. It was recognized that the amount, of cholates certainly, and perhaps of cholesterol, can be greatly modified by diet changes. Nevertheless, cholesterol determinations seemed warranted in view of the relation of the substance to human gall stones, and the bearing of partial biliary obstruction on the genesis and development of these latter. The results obtained were clear-cut, and can only be attributed to the progressive obstruction.

---

It will be recalled that dog bile is poor in cholesterol. The stones which were a frequent cause for obstruction in our animals consisted for the most part of carbonates, with never a trace of the substance.

Typical Instances of Progressive Obstruction.

Some specimen protocols will be given.

Experiment 2. Dog 25. Obstruction by Scar Tissue (Text-Fig. 1).—After 37 days of bile collection from a male terrier of 15½ kilos, the output of the secretion, and its pigment content as well, were noted to be growing less, although the animal appeared in good health and spirits. The lessening in pigment continued, despite an intercurrent cholorrhea consequent on feeding sheep bile, and by the 45th day the bilirubin yield had fallen to one-half of the previous "normal."

Text-Fig. 1. Changes in the bile during progressive obstruction by scar tissue.

---

and on the day following to one-quarter the amount. The fluid was now light green. On the 47th day only a few cubic centimeters of secretion, watery and pale green, was obtained in 25 hours of collection. It held mere traces of pigment and cholesterol (Liebermann-Burchard test), and gave a negative response to Hay's test for cholates. 3 hours later the animal was killed. No further secretion into the collecting bag had taken place. There had been bilirubinuria for 2 days and on the final one a well marked bilirubinemia and a dubious tissue icterus.

Autopsy disclosed the fact that cannula and duct had parted company some time previously. It was recalled in this connection that on the 21st day the dog had pulled upon and opened the outlet tube, thus infecting the bile, though fortunately with a saprophyte harmless to the bile pigment, as incubation tests showed. Probably the cannula was pulled out of the duct at this time. Between the ends of the two there was now a small, gristy lump of scar tissue containing a completely occluded fistulous channel; and the duct system above was distended to the extent usual when obstruction is total. No connection was found with gall bladder or intestine. The distended ducts held a colorless, watery fluid, containing a few glairy, discrete strands, like white of egg. The fluid failed to give Hay's reaction and contained only the faintest trace of cholesterol. The liver lymph was bright yellow with bilirubin. Although infection of the collecting bag had lasted for more than 3 weeks, the hepatic tissue and the fluid in the ducts proved sterile on culture. The organs were normal, except for the changes incident to icterus, and for a slight cirrhosis of the liver of the sort that follows biliary obstruction.

Experiment 3. Dog 20. Obstruction by a Stone (Text-Fig. 2).—On the 18th day of bile collection from a male hound of 13½ kilos the pigment yield was noted to be rather low despite a large fluid output (175 cc.). It underwent a temporary increase to the ordinary amount on 1 of the next 3 days, but thereafter, despite a cholorrhea (to 208 cc.) after bile feeding, it fell off rapidly and so too soon did the fluid yield. On the 23rd day of collection, or the 5th from the time when the changes were first noted, only 23.3 cc. of bile was procured, and this appeared pale green, not yellow-brown as before. Marked bilirubinuria had developed. The 11 cc. of the next 24 hours was somewhat more pigmented. The animal was now sacrificed because its behavior suggested that a bile peritonitis was developing. At autopsy the peritoneal cavity was filled with deeply bile-stained fluid; and a rent in the greatly dilated common duct above the cannula disclosed where the bile had escaped. The cannula was still firmly fixed in the duct, but its lumen had been completely occluded with a calculus. The fluid present high up in the ducts was as brown as normal bile, showing that secretion had promptly reasserted itself after rupture of the duct wall. Probably a little of the new, well pigmented output passed into the bag, for the final fluid therefrom contained, as has just been stated, more pigment than that of the preceding day. All the specimens proved sterile on culture.
TEXT-Fig. 2. Changes in the bile during progressive obstruction by a stone.

Experiment 4. Dog 22. Obstruction by Scar Tissue, Relieved and Recurring (Text-Fig. 3).—On the 10th day of bile collection a male bull terrier of 12 kilos yielded somewhat less secretion than usual, with only about half the expected 24 hour yield of bilirubin. On the following day the changes were more outspoken; and on the next, or 12th, a few cubic centimeters only, of very light green, thin fluid, was procured. A marked bilirubinuria was now present. It seemed possible that the trouble might be caused by an abrupt elbow, or kink, in the collecting tube, and with the aim of relieving it, several centimeters of the tube were gently withdrawn from the abdomen. This accomplished the desired effect. During the next few days a dark bile was secreted in relatively enormous amount, and the bilirubinuria disappeared. But soon obstruction developed again, as indicated by the small yield of thin, light-tinted fluid, and it rapidly became total, with result in the development of a marked general icterus during the 3 further days that the animal was preserved, and no bile obtained.

Autopsy disclosed a condition of affairs identical with that of Experiment 2. From first to last the bile was sterile.
Biliary changes like those of the three instances here described (Text-figs. 1 to 3) occurred in all the animals with a progressively increasing obstruction, whatever the cause. The fluid output lessened, and so even more markedly did that of cholesterol and of bilirubin. For not only was the total yield of these substances reduced with the reduction of the fluid output, but the concentration per cubic centimeter as well. The final content of the stopped ducts was a colorless, limpid, "white bile," practically devoid of cholates and cholesterol. At no time as the obstruction developed was there evidence that any of the substances mentioned was secreted in abnormally high concentration; nor was there a thickening of the fluid but always a thinning.

We had planned detailed observations on the character of the bile elaborated against various pressures but were prevented from undertaking them by the difficulty of devising a valve that would precisely

Text-Fig. 3. Changes in the bile during progressive obstruction by scar tissue.
regulate the slight pressure increases compatible with secretion and at the same time control a fluid so variable in consistency as is the bile. Fortunately the progressive obstruction developing in our animals as the result of stones or scarring nearly simulates the clinical occurrence in man.  

DISCUSSION.

The bile changes consequent on a pressure obstacle to secretion are the worst possible ones for the body as so much tissue, since they further a retention of biliary constituents instead of aiding elimination in the face of the difficult conditions. But they could not be better suited to meet the grave problem raised by partial obstruction if they had been planned for the purpose. The fluid elaborated by the liver is of the precise sort required in order to avoid the crisis of total obstruction. In previous papers we have emphasized the activity of the gall bladder to make matters worse during partial obstruction of the common duct by so thickening and concentrating the bile above the obstacle that its escape is hindered and calculus formation promoted. The conditions obtaining in the animals of the present work may be likened with reason to those when there is obstruction of the hepatic duct in human beings, or of the common duct when the activities normal to the gall bladder have been abolished by pathological changes. The fact that gall stones situate in the hepatic duct of man cause relatively little trouble has been the subject of frequent comment in the past. One reason is to be found in the alterations that take place in the bile when obstruction impends. In proportion as the pressure obstacle to secretion develops, the bile becomes poorer in the substances that render it viscous or out of which stones form and enlarge. Furthermore, during the intervals when the bile can escape with ease, the accumulation of its constituents within the body is voided, not in a fluid heavily charged with them, but in one so copious that their concentration is actually less than the normal.

It may be objected that the gall stones which were the agent of obstruction in some of our animals enlarged despite the circumstance that the character of the biliary fluid seemed unfavorable thereto. But there is obviously a limit to what alterations in the fluid may be

\textsuperscript{8} Gorke, H., Deutsch. med. Woch., 1922, xivii, 1166.
expected to accomplish. The stones were situate at and about the constriction in a cannula of not more than 2 mm. greatest diameter, and with rigid walls. It is regrettable that no quantitative observations were made on the carbonates of the bile, of which, as already remarked, the calculi principally consisted.

Comparison of Hepatic and Renal Obstruction.

For any proper comparison of the effects of biliary obstruction with those of obstruction to the ducts of another gland, the complicating activities of the gall bladder must be ruled from account. For the receptaculum bili is much more than its name implies, being an organ of highly specialized functions and quite as unrelated to the secretory system of the liver as the urinary bladder is to that of the kidney. The comparison with the kidney will be extended further, since all the glands with ducts it has been most studied. There are available numerous data upon the effects of a pressure obstacle to secretion by the renal tissue. 8

Both the liver and the kidney go on secreting after the ducts from them have been entirely closed; but as soon as the pressure within the distended ducts has risen to a certain point, the product of their activity is turned back into the organism. The stretching of the tissues incidental to the obstruction is far more marked in the case of the kidney, as would naturally follow from the circumstance that urine does not cease to be secreted into the proper channels until a high pressure has been attained,—50 to 70 mm. of mercury in the case of the dog. 9 There results the hydronephrotic sac. Bile ceases to be secreted when the pressure in the ducts of the dog reaches 350 mm. of the fluid itself, or in other words, when the resistance is only one-third to one-half that required to bring the flow of urine to a standstill. The difference is sufficient to account for the absence of a spectacular bagging-out of the liver, irrespective of any special resistance on the part of the hepatic tissue. In human beings small cystic dilatations on the surface of the liver have occasionally been noted. The urine at first secreted above an obstruction is gradually replaced by a fluid devoid of the typical characters of the secretion.

Kaufmann\textsuperscript{10} has likened it to the fluid of \textit{hydrops vesica fellea}, of a gall bladder pathologically altered. So too the bile at first pent in obstructed ducts is replaced by a non-characteristic "white bile," in the absence of the normal gall bladder activity for concentration. Kauschl\textsuperscript{11} employs the expression hydrops of the biliary system in this connection. When the pressure obstacle to urinary secretion does not wholly prevent it, the output of certain substances is diminished, both as a whole, and per cubic centimeter, just as happens with cholesterol and bilirubin on partial biliary obstruction.\textsuperscript{9} Whether the concentration of certain biliary constituents is increased, as is that of urea,\textsuperscript{9} cannot at this writing be stated.

In any comparison of the renal and hepatic changes after obstruction it is necessary to keep in mind that the kidney tissue is lodged in a pair of organs and the hepatic in but one. Yet the differences thus entailed are not so considerable as one might suppose. The bile radicles draining into one branch of the hepatic duct are so little connected with those to another\textsuperscript{13} that the liver mass may be thought of as consisting of a number of separate biliary units within a single capsule, like separate watershed systems eventually tributary to a single river. Obstruction to the duct from one of these systems may in many respects be likened to obstruction of a single kidney. The ensuing changes are strikingly similar.

The pressure under which the fluid is held on urinary obstruction is such as to bring about a compression of the renal veins with serious circulatory disturbance. Similarly when the bile ducts from a part of the liver are stopped, the portal flow through the region is impeded and diverted.\textsuperscript{13} As a result of the circulatory changes in the kidney\textsuperscript{14} the organ, after passing through a hydronephrotic stage, becomes atrophic and shrunken.\textsuperscript{13} So too a complete parenchymal atrophy,\textsuperscript{16}

\textsuperscript{12} McMaster, P. D., and Rous, P., \textit{J. Exp. Med.}, 1921, xxiii, 731.
\textsuperscript{13} Rous, P., and Larimore, L. D., \textit{J. Exp. Med.}, 1920, xxxii, 249.
\textsuperscript{14} Kornitzer, E., \textit{Z. urol. Chir.}, 1922, ix, 165.
and from a like cause,\textsuperscript{17} follows on local biliary obstruction. A progressive connective tissue overgrowth accompanies the atrophy in both kidney and liver. The causes for it need not be gone into. When hepatic or renal obstruction affects all of the gland, permitting no escape whatever of secretion, death ensues, before the tissue changes just enumerated have progressed far.

Stasis, distention, vascular disturbance, sclerosis, and parenchymal atrophy,—these are common not merely to the liver and kidney but to all glands of which the ducts have been obstructed. It is safe to say that the underlying physiological pathology is much the same for all. And yet the essential identity of the liver changes with those occurring in other glands seems not to have been recognized in the past. A principal reason is to be found in the activities of the gall bladder to cloud the issue in a literal sense by thickening and concentrating the bile retained above an obstruction. As result of this, and of infection, and of differences in the agents determining biliary obstruction, the conditions found at autopsy or operation in human beings have an appearance of great diversity. Of necessity each instance has been considered by itself; and the lack of a comprehensive term to join one with another and to cover the general state of affairs has not been felt. In the present paper and those preceding it the nature and relative simplicity of the physiological factors responsible for the liver findings have been brought out. With this approach to an understanding of the physiology of biliary obstruction there would seem to be some usefulness in a word designating its results. We suggest that \textit{hydrohepatosis} would be no misnomer, and that the term may be helpful as indicating the likeness of the liver changes to gland changes in general after duct obstruction, and to those of the kidney in particular. When, through gall-bladder activity, the duct content above an obstruction is permanently thickened and pigmented, the hydrohepatosis is \textit{concealed}; but in the absence of this disturbing influence, when the duct system is filled with a clear, watery fluid, the condition is a \textit{manifest hydrohepatosis}.

\textsuperscript{17} Rous, P., and Larimore, L. D., \textit{J. Exp. Med.}, 1920, xxxi, 609.
In bile that is secreted against an abnormally high pressure, as during partial obstruction, the pigment, cholate, and cholesterol outputs are all cut down, and so much more than is the fluid bulk that the concentration of the substances per cubic centimeter of bile is notably lessened. The fluid obtained at the greatest pressure compatible with secretion contains traces only of the typical biliary constituents. The bearing of these alterations in the bile on the consequences of partial biliary obstruction is discussed.

An analysis of the liver changes following biliary obstruction brings out their essential likeness to the changes that occur under similar circumstances in glands in general and the kidney in particular. The major physiological factors concerned in the development of hydronephrosis and in the liver changes after biliary obstruction are identical. We would suggest that the term hydrohepatosis as applied to the liver condition would be useful not merely to designate it but to indicate the principles underlying its development. In clinical instances of biliary obstruction, the likeness to hydronephrosis is often hidden because of the activity of the gall bladder to render the stasis bile dark and thick. There is then a concealed hydrohepatosis, differing merely by the character of the duct content, from the manifest hydrohepatosis with “white bile,” that is found when the gall bladder fails to act.