SUPPRESSION OF BILE AS A RESULT OF IMPAIRMENT OF LIVER FUNCTION.

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To all practical purposes a suppression of bile has taken place whenever the secretion fails to reach the intestine. But it would be best, in the interests of clearness, to apply the term only to instances in which no evidence of mechanical obstruction to outflow can be found. Whether such obstruction exists is another matter. A large body of workers believe that it always does whenever bile flow stops, whereas a second group of equal influence hold that a genuine cessation of liver activity as concerns the secretion of bile not infrequently occurs. In the present paper we shall report and examine an example of biliary suppression for what it may be worth in connection with this conflict of opinion, but more especially for its importance in the interpretation of clinical experience. The suppression referred to is consequent on the liver damage caused by chloroform.

Bile Suppression after Chloroform Anesthesia.

When prolonged chloroform anesthesia has been induced in dogs intubated for the collection of the total bile under sterile conditions, there ordinarily follows a noteworthy change in the character of the secretion. Four typical instances are recorded in Table I (Chart 1). The methods for determination of the data have been described in other papers. The bile of the first 24 hours after the anesthesia is usually somewhat though not greatly less in amount than before; and the amounts of pigment and cholesterol are also lessened.


The cholesterol estimations were kindly carried out for us by Dr. P. D. McMaster.
### TABLE I.

The Bile Changes after Chloroform Anesthesia (See Chart 1).

<table>
<thead>
<tr>
<th>Day</th>
<th>No. 6. Male, 10 1/2 kg</th>
<th>No. 16. Male, 15 kg</th>
<th>No. 18. Female, 18 kg</th>
<th>No. 28. Male, 12 kg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Amount</td>
<td>Color</td>
<td></td>
</tr>
<tr>
<td>3 preliminary days</td>
<td>400</td>
<td>63</td>
<td>Brown-black, watery</td>
<td>1,100</td>
</tr>
<tr>
<td></td>
<td>700</td>
<td>51</td>
<td>Brown-black, watery</td>
<td>750</td>
</tr>
<tr>
<td></td>
<td>1,000</td>
<td>65</td>
<td>Dark olive, watery</td>
<td>1,450</td>
</tr>
</tbody>
</table>

CHCl₃ given during................. 60 min. | 90 min. | 85 min. | 90 min. |
| 1 | 350 | 31 | Dark olive, watery | 700 | 99 | Medium brown, watery | 140 | 140 | Light brown, watery |
| 2 | 350 | 24 | Medium olive, watery | 0 | 8.2 | Light yellow, watery | 650 | 41 | Pale yellow-green, slightly syrupy |
| 3 | 400 | 34 | Pale yellow, slightly syrupy | † | | Characteristic necrosis of more than 2/3 of each lobule. | 650 | 91 | Greenish yellow, watery |
| 4 | 200 | 51 | Medium olive, watery | † | | Characteristic necrosis of nearly 2/3 of each lobule. | 1,050 | 158 | Light brown, watery |
| 5 | 400 | 52 | Dark olive, watery | † | | Characteristic necrosis of nearly 2/3 of each lobule. | 1,500 | 165 | Medium brown, watery |
Chart 1. Changes in the bile on chloroform poisoning.
tion during the next 24 hours is greatly diminished, and so too with the concentrations of bilirubin and cholesterol, whence it follows that the total output of these materials frequently becomes negligible. If the injury has been lethal, the animal usually dies on the 2nd or 3rd day. The fluid secreted during the period when it is moribund has usually none of the characters of bile, being colorless, cholesterol-free, and free from cholates on Hay's test. When recovery is to follow there takes place, during the third 24 hours, an abrupt return toward the previous average in the amounts of bile, bilirubin, and cholesterol; and within 2 or 3 days thereafter secretion has assumed the general characters of that observed before the chloroform was given. When but little of the anesthetic has been administered, and the animal in consequence does not appear ill but is lively and with a good appetite, striking alterations in the bile may yet occur of the sort described. Should hemorrhages into the tissues take place, as not infrequently happens, blood cells may appear in it.

For 40 years the fact has been recognized that agents damaging the liver or the blood act more or less incidentally to diminish the bile and alter its character. In the classic instances of phosphorus and toluylene diamine injury there is often to be noted a period in which the ducts are choked with a glairy, more or less opaque, material wherein the formed débris of liver and duct inflammation may be recognized. In the jaundice consequent on frank hemolysis a natural injection of the smaller ducts with a heavily pigmented, tenacious secretion is encountered. Were the findings after chloroform either of these, they would merit passing mention only. But they are not. The abnormal fluid secreted by the liver is watery in type instances, or no more syrupy than are many specimens of ordinary duct bile when the bulk of the secretion is diminished through physiological causes; and careful examination of fresh and stained sections fails to disclose any material making for obstruction of the ducts. Bile thrombi are notably rare in scrapings from the hepatic parenchyma; and only exceptionally is any cellular débris to be recovered from the secretion. Occasional desquamated cells from the ducts, red cells, and even parenchymal elements may then

be found; but usually no leucocytes or bacteria. To all immediate intents and purposes the phenomenon is one of acute bile suppression.

**Factors Concerned in the Suppression.**

Injury from chloroform is often attended by jaundice, but in the absence of complication this is notably mild in character. Our animals never showed a general tissue icterus. Indeed the observations suggested the possibility that such cells as are responsible *ab initio* for the production of bile pigment might have been functionally damaged so that it was not formed. To determine the matter, total biliary obstruction was produced in five etherized dogs by cutting the common and cystic ducts between ligatures, and at various periods thereafter they were anesthetized with chloroform. A sixth animal was not chloroformed. At the time when the experiments were carried out we had not recognized the fact, brought out in an accompanying paper, that jaundice is a condition so largely confined to the blood pool that intercurrent variations in the amount of bile pigment formed within the body find an immediate expression in terms of bilirubinemia, even during a prolonged jaundice. It seemed likely to us that any alteration in the rate of formation of bilirubin, induced by chloroform in animals already jaundiced, would be masked, so far as bilirubinemia was concerned, by an immediate redistribution of the pigment already present in the bile-suffused organism. For this reason the majority of the dogs were given chloroform soon after obstruction had been produced, on the assumption that if it acted to inhibit bile pigment formation there would be a delay in the development of the bilirubinemia inevitable to the retention. The findings are given in Charts 2 and 3. The blood bilirubin was followed by both the Meulengracht and the indirect van den Bergh methods, the discrepancy in the results with the two being due to the amount of pigment lost in the sediment by the van den Bergh technique. It will be seen that, far from acting to diminish bilirubinemia, the chloroform brought about a notable temporary increase in it. This was true even in cases in which tissue icterus had become well established (vide Chart 3). The increase in bilirubinemia was most

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CHART 2. The effect of chloroform anesthesia on a developing bilirubinemia. The further course of the curves has no interest for the present work. In the case of two of the animals it is depicted in another paper.8
CHART 3. The effect of chloroform anesthesia on bilirubinemia. The enduring increase in the circulating bile pigment that followed is highly unusual.
pronounced within 24 hours in the three instances in which judgment upon the point is possible (Chart 2, Dogs 8 and 17; Chart 3), that is to say before any marked changes would have been evident in the bile itself had there been no obstruction. The increase in the renal output of bilirubin concurrent with the increase in the amount of the pigment in the blood sufficiently proves that the latter cannot have been due to accumulation as result of a lessened elimination through the kidneys. In view of the known relationship of bilirubin formed to hemoglobin destroyed, and the direct effect on the intensity of jaundice of day-to-day alterations in corpuscle wastage, one may suppose chloroform anesthesia to be responsible for a practically immediate blood destruction. The occasional finding in intubated dogs, that, against the rule, the bile elaborated soon after chloroform is for a brief period more pigmented than before may be laid to this cause.

If chloroform does not act to diminish the activity of the cells fundamentally concerned in the production of bilirubin, how then does it act to bring about jaundice? Does it affect the ability of the liver to secrete bile? Assuredly it does in the case of much of the parenchymal tissue for it kills this outright. Chloroform produces characteristically a central necrosis of the liver cells, which may affect three-fourths or more of the entire lobule. In our animals which succumbed there was always an extensive liver necrosis. It is with the remaining parenchyma, a considerable amount in surviving animals, that our problem lies. For this remainder, were it even approximately normal, should be more than sufficient for bile excretion, a process that can be effectually accomplished by less than one-quarter of the liver. The hepatic changes induced by chloroform have long been familiar to pathologists. At the height of them one finds, in animals destined to survive, a zone of fatty degeneration about the central necrosis, and beyond this again a border of cells approximating the normal in appearance. May one assume that these cells are incapable of secretion, or, instead, that secretion occurs but that the way out for it is mechanically blocked? The problem as posed is the long debated one of functional versus mechanical suppression.

The gross appearance of the liver, which in some of our cases was only faintly icteric, the scarcity of bile thrombi in scrapings from it, the appearance of the cells, and the general character of the organ in fresh and stained sections, all, like the watery character of the secretion, may be taken to favor the view that the bile suppression is due to a functional inability. Eppinger's method for the demonstration of dilated and ruptured bile capillaries does not, unfortunately, yield results with canine tissues. But presumably one can determine whether there exists an obstruction above which secretion takes place as ordinarily, by giving substances which are excreted into the bile, and are recognizable thereafter within the canaliculi—for that bile secretion by the liver cells into the canaliculi still goes on, obstruction or no obstruction, is an assumption essential to the view that all suppression is due to such a cause. In order to test whether it goes on during the suppression after chloroform anesthesia we decided to use sodium indigotate.

The Suppression of Indigotate Secretion.

When a solution containing indigotate is given into the blood stream, there follows an injection of all of the bile capillaries with the dye. It is easy to show, as we have done in the course of our experiments, that the injection of the capillaries results from a falling out of solution of the indigotate. One need only make scrapings from the parenchyma of the deeply blue liver into a specimen of bladder bile from the same animal, which has previously been saturated in vitro with indigotate. Amid the resulting cell suspension there will be found, floating free, innumerable attenuated, dark blue, sharp-ended, twig-like forms, sometimes branching—little casts of the bile radicles that is to say. When placed in salt solution these rapidly dissolve and one can perceive for an instant afterward colorless shadows of them, being the mucoid material carried out of solution with the indigotate. When the dye is slowly injected into an etherized animal and pieces of the liver removed at short intervals, sectioned while frozen, and examined in acetone, one can follow step

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by step the blocking of the radicles with indigotate throughout the liver lobule. When such a blocking is brought about in intubated animals the small amount of "bile" voided during its continuance may have but a negligible content of bilirubin and cholates.

These preliminary findings appeared to justify the expectation that with indigotate direct tests of the mechanistic explanation of bile suppression could be carried out. But that has not turned out to be the case. For the liver cells in animals with simple biliary obstruction produced by tying the common duct proved unable, not alone to secrete indigotate into the bile capillaries but to take it out of circulation. In normal dogs receiving for each kilo 20 cc. of a solution that contains 0.4 per cent of indigotate and 0.6 per cent of sodium chloride the liver and kidneys are regularly the most deeply colored organs in the body, the hepatic tissue containing great quantities of the dye. But when the common duct has been previously tied, even for so short a time as 24 hours, the liver contains no indigotate whatever either as such or as the leucobody (peroxide reaction), except of course that incidental to the blood content of the organ. Instead of being a darker blue than the rest of the dark blue body, the liver now stands out in buff, or in the yellow of icterus, from amidst its indigo-colored surroundings. In such instances there can be no question but that the biliary obstruction has resulted in a derangement of secretory function. This being so, tests with indigotate of the condition of affairs produced by chloroform could have no value.

DISCUSSION.

The fluid elaborated by the liver injured with chloroform is a typical "white bile," but one that differs significantly in association and import from other material of like character that is formed under conditions of obstruction. There is a kind of white bile which accumulates above an obstruction in any duct deprived of connection with the gall bladder or connecting with one so altered pathologically as to have lost the ability to concentrate stasis bile. In such cases the colorless fluid which gradually replaces this last is derived

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from the duct system itself which elaborates a similar fluid under normal circumstances. White bile is also formed whenever the liver secretes against a pressure obstacle. Whether under the latter circumstances the fluid comes in part from the parenchyma or wholly from the duct walls cannot be said as yet. None of these white biles is significant of a functional derangement of the liver other than the one inevitable to the condition of obstruction; and that the derangement when it occurs is usually not serious follows from the resumption of true bile secretion when the obstacle to it is removed. Such instances, as encountered in dogs, have a close resemblance to not a few which the surgeon may meet in human beings, instances which in the absence of complication should have a happy outcome.

But there is yet another type of white bile, the occasional occurrence of which renders the finding of any material of the sort a matter of grave concern to surgeons. This is the white bile indicative of a fundamental liver injury. One encounters it in dogs to which chloroform has been administered. The derivation of the thin, clear fluid then elaborated remains to be determined, as for that matter do the relative shares of the parenchymal cells and the duct tree in furnishing the menstruum of normal bile.

During an acute illness in which the liver is not primarily concerned the quantity of bile secreted may yet be so far cut down as to be almost negligible. We have observed the 24 hour secretion of an intubated dog to diminish from 160 cc. to less than 1.0 cc. during the course of a severe coryza. But in such instances there is far from being any suppression; the fluid vehicle for the essential bile constituents is merely lessened in amount. Under circumstances of injury to the liver parenchyma as after chloroform anesthesia in dogs, and in clinical instances of liver disease such as Walters and Parham have reported, an essentially different state of affairs prevails.

There has been much debate on how chloroform injury to the liver comes about, and why it should be histologically visible only after a lapse of time. According to one view, the eventual evidence

12 McMaster, Broun, and Rous, p. 395.
of damage is merely an expression of secondary changes taking place in elements which were killed, or severely injured, at one stroke so to speak. The present findings are against this interpretation of the facts. The progressive diminution in the secretion of bile and the occurrence of suppression at the period when the histological changes are most marked both point to a cumulative derangement.

Our demonstration that even when one is supposedly dealing only with mechanical obstruction there may be a superimposed functional biliary disturbance—a point attested by the failure of the liver parenchyma to take sodium indigotrate out of the blood—constitutes additional evidence to that already given for the truth of the view that functional impairment is a potent cause of bile suppression.

SUMMARY.

Prolonged chloroform anesthesia causes an acute suppression of bile, as evidenced by the secretion of a thin “white bile” from which bilirubin, cholesterol, and bile salts are absent. The failure of the liver to secrete bilirubin under such circumstances is not due to failure of the pigment to be formed within the body. Indeed an unusual amount is elaborated after chloroform anesthesia because of a blood destruction. The evidence all goes to show that the bile suppression is consequent upon a functional disturbance of the liver, not upon obstruction to outflow. Even uncomplicated biliary obstruction, as when the common duct is tied in animals otherwise normal, results in a disturbance of the liver cells such that their secretory function is impaired, as shown by the inability to take up and secrete sodium indigotrate.

The various circumstances under which white bile may be formed are considered and the clinical implications of the phenomenon are discussed.