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DISSOCIATED JAUNDICE *

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The subject of dissociated jaundice has been discussed by a number of French physicians during the past five years. There have been in all about thirty articles on the subject published in French medical journals. A fairly complete bibliographic reference will be found in an article by Lemièrre, Brulé and Garban.¹

In all the published articles there are several weak points for criticism. There was not sufficient correlative control of biliary elements in the plasma and urine. The adsorptive property of plasma for bile salts as well as bile pigment was not clearly perceived. As will be seen from our observations, the plasma may under some conditions, not yet clearly understood, retain a large amount of bile pigment and yield none of it to the kidney, although the kidney function may be perfectly normal. This adsorptive property of the plasma may hold bile pigment so firmly in its grasp that no pigment will be yielded to the tissues, so the disparity between icterus of the plasma and icterus of the skin may in some few instances be as striking as the disparity between cholemia and choluria. Adsorption of bile salts is not nearly so marked as adsorption of bile pigment, but in primary anemia, particularly, the presence of bile salts in the plasma without the presence of bile salts in the urine has been abundantly confirmed in our experience.

And, finally, without some improvement over the old method of separating bile salts from the plasma, it is impossible to make any progress in the clinical studies of jaundice. The older methods of separation were too time consuming, too uncertain, and required too much plasma for routine clinical work. The use of the collodion sack as a dialyzer affords a very simple, and we believe the most delicate, method thus far proposed for the purpose.

The term "dissociated jaundice" carries with it the inference that either the pigment or the salts of bile formed within the liver are separately shunted from the biliary path into the lymph or blood ves-

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1. Lemièrre, Brulé and Garban: Les retentions biliaires par lésion de la cellule hépatique, *Semaine méd.*, 1914, xxxiv, 301.

sels of the liver. We have succeeded thus far in showing that bile salts may be shunted in this manner, but we are not yet certain that bile pigment formed in the liver is separately shunted into the blood stream. This is what we should a priori expect when we consider the comparative facility with which the salts will pass through a dialyzing membrane, as shown by the concentrations of bile required to yield pigment and bile salts, respectively, to the dialysate when collodion sacks are employed for dialysis, and also when we consider the fact that the renal filter will yield bile salts to the urine from a lower grade of cholemia than is required for bile pigment to appear in the urine.

There have been several causes which have delayed the analysis of this very common problem in clinical pathology. Medical men generally have been for many years misled by the erroneous interpretations of jaundice made by Stadleman and Naunyn and Minkowski, who arrived at the very definite conclusion that there can be no jaundice without the agency of the liver. According to these observers, all jaundice is hepatogenic, and hematogenic jaundice does not exist. Although many clinicians have been skeptical toward the teaching that all icterus is hepatogenous, the first satisfactory experimental evidence of the truth of hemolytic icterus I have found is that of Lyon-Caen,² 1910, and the final absolute proof of extra hepatic jaundice was given by Whipple in 1916.

Briefly stated, the following problems are to be solved in the clinical study of icterus. If pigmental cholemia is present without bile salts, the pigment may originate from the formation of bilirubin from hemoglobin within the blood vessels, as occurs in hemoglobinemia from any cause; or after complete cholemia of hepatic origin the bile salts have been yielded to the kidney and the adsorbed bilirubin remains fixed to the plasma. The latter instance is not dissociate jaundice of hepatic origin, but is merely separation of the two biliary elements by renal elimination of the bile salts. When bile salts without bile pigment are found in the plasma, we are bound by our present knowledge to assume there exists a genuine dissociate jaundice of hepatic origin. For thus far there are no clinical or experimental evidences to show there can be an extra hepatic origin of bile salts, and in all our experimental and clinical studies we find no evidence that bile pigment can be eliminated through the kidney and bile salts retained in the plasma. If the two biliary elements are separated by renal elimination, it will always be bile pigment which will be retained in the plasma and not bile salts. To avoid confusion in using the term "dissociation icterus" it will be advisable to employ a terminology which will indicate the source of the dissociation of biliary elements in the plasma. "Complete icterus" will mean the presence of bile pigment and bile salts in the

2. Lyon-Caen: *Jour. de physiol. et de pathol. gén.*, 1910, xii, 526, 758.

blood. "Hemolytic icterus" implies the presence of bilirubin in the blood without bile salts, when bilirubin is formed extra hepatically. "Hepatic dissociation icterus" implies the presence of bilirubin or bile salts separately in the plasma, due to one or the other of the bile elements being separately shunted into the blood stream. By "renal dissociation icterus" we mean the presence of bile pigment in the plasma due to separation of the biliary elements through renal filtration of the bile salts.

METHODS OF STUDY

The simplest and best method of detecting bilirubin in blood plasma is Gmelin's test. Between the white coagulum and the underlying nitric acid there is a yellow granular zone. Within the white coagulum there will be seen a line more or less broad, varying with the concentration of bile in the plasma, which has a distinct blue-green color. This blue-green line will appear immediately in high concentrations of bile, but in the very low concentrations of bile in the plasma the blue green line will not appear until after a lapse of half an hour. After the test has stood for a longer time, the white coagulum will ascend in the zone of plasma, but will always preserve the same thickness. The blue-green line holds its relative position in the white coagulum as this ascends, and the lower yellow zone increases in depth as the coagulum ascends.

The best method of detecting bile salts in the plasma we have found in the use of collodion sacks. A mixture of equal parts of alcohol and water is the best medium with which to surround the collodion sack containing the plasma.

In testing for bile salts we use two or three dialyzers, each containing about 5 c.c. of plasma. After the dialyzers have stood for twelve hours, the several dialysates are concentrated, and then the concentrated dialysate is tested with Pettenkofer's method. Simply the color test and spectroscopic absorption band in the purple can not be accepted as proof of the presence of bile salts. If no further criticism is employed, there is great danger of accepting a test as positive which is really spurious. We have adopted the plan of accepting as positive only those tests which give the characteristic color reaction to furfurol and sulphuric acid; then the spectroscopic examination of the reaction will give an absorption band in the purple. After the reaction stands for twelve hours or more a darker purple color supersedes the original pink reaction, and then spectroscopic examination will reveal a disappearance or diminution of the original absorption band in the purple and the appearance of a new, sharply defined band in the orange. The alteration in color on standing and the movement of the absorption band into the orange are essential to prove the correctness of a Pettenkofer test. The dialysate from many serums will give the original pink color

and purple absorption band, but when the reaction is allowed to stand, it will not change to the pink-purple color; neither will the absorption band move over to the orange. This further observation in the Pettenkofer test has saved us from making many errors in detecting bile salts in the plasma. Without this control we would have pronounced many tests as positive which were really spurious.

We find the collodion dialyzer to be a great aid in detecting bile salts. It is a very simple method and is much preferable to the old method of separating the bile salts from the protein by repeated precipitations and filtering and washing, which is practiced in the Hoppe-Seyler method. Much less serum is required for the process, and in the Hoppe-Seyler method the Pettenkofer reaction is the final test, just as we employ it with the dialysate from the plasma. The delayed spectroscopic control is applicable to the Hoppe-Seyler method of separation of the bile salts as well as in our method of separation by means of the collodion dialyzer.

We tried electrolytic dissociation to detect bile salts in plasma, but met with no success. The dialyzer is much simpler and much more delicate. To procure bile salts from a solution by electrolysis requires a much higher concentration of bile salts than we find in the plasma of jaundiced patients.

We have found the collodion dialyzer and the spectroscopic control of the Pettenkofer test equally important. Both these measures have been essential to our clinical analyses of jaundice. Without a satisfactory method of detecting bile salts in plasma no progress can be made toward a study of dissociated icterus.

A review of the literature on dissociated icterus will show how the want of a satisfactory method for isolating bile salts from the plasma has hindered the progress of clinical studies of jaundice.

BILE SALTS AND PIGMENT IN THE URINE

Hammersten's method is the most satisfactory means of detecting bile pigment in the urine. This is the method we always employ when any case is reported as a positive test for bile pigmentation in the urine. Bile salts in the urine have given us more trouble than in the plasma. Pettenkofer's test is not so satisfactory as Hay's sulphur test, which can be inspected most satisfactorily when viewed from underneath the surface of the urine by aid of an electric lamp held between the observer's eye and the specimen which is being examined. The sulphur test is very delicate and simple and gives unequivocal results. We did not go far in studies of cholemia and choluria before we were impressed with the striking inconsistencies between these two conditions. For instance, in primary anemia we have studied fourteen cases and we failed to find bile pigment or bile salts in the urine in a single instance.

although all the patients examined had bile salts or bile pigment or both in the plasma. It is surprising to see how high a concentration of bile pigment will occur in the plasma of primary anemia without choluria.

In hemolytic jaundice with infection and without infection it is also surprising to see how deeply jaundiced the plasma will become without bile pigment appearing in the urine. This is the one point which serves to distinguish obstructive jaundice from other sources of jaundice. In obstructive jaundice the bile pigment appears in the urine much more promptly and with much lower concentrations of bilirubin in the plasma than must occur in hemolytic jaundice before the urine becomes bile stained. We find an unvarying consistency in the behavior of bilirubin toward the collodion dialyzer (with rather thick wall) and toward the renal filter.

If a patient has bilirubin in his blood and none in his urine, the dialysate from his plasma will contain no bilirubin. If bilirubin occurs in both plasma and urine, the dialysate will contain bilirubin. We have had only one experience which was apparently an exception to this rule. The patient had severe hemolytic dissociated icterus caused by streptococcus infection. The plasma was deeply stained with bilirubin, but no bilirubin could be found in the urine. The plasma dialyzed bilirubin in large amounts. The disparity in this instance was traceable to a severe disease of the renal filter, as shown both clinically and at necropsy. During life the alveolar air had a carbon dioxide partial pressure of 26.7 mm. of mercury. The nonprotein nitrogen of the blood was 0.076 gm. per 100 c.c. of blood. The carbonates of the blood by Van Slyke's method were 37.9 c.c. per 100 c.c. of blood. It seems very reasonable in this case to ascribe the apparent exception to the rule to the impermeability of the renal filter.

When bilirubin from the plasma passes neither the renal filter nor the collodion sack, the phenomenon is due to adsorption of pigment by the plasma. We showed in one of our first clinical studies of a case of dissociated hemolytic jaundice due to secondary syphilis that the renal filter was unimpaired; not only was there a want of all evidence of impaired renal function on the part of the urine and blood, but at the same time the plasma was so deeply jaundiced as to give a very strong Gmelin's test and no bilirubin occurred in the urine, while the phenolsulphonephthalein test for renal function was perfectly normal. Unfortunately the phenolsulphonephthalein test was neglected in the streptococcus case, which gave us the single exception to consistency of behavior toward bilirubin on the part of the renal filter and the collodion sack.

The importance of adsorption of bile pigment in blood plasma is very significant in another phase of jaundice. We find the plasma deeply stained with bilirubin in some cases of primary anemia when

there is not only no bilirubin in the urine, but no trace of jaundice to the skin or sclera. This has occurred in several cases of primary anemia with complete cholemia and also in hemolytic dissociated cholemia. In several of these cases the cholemia was of such intensity that a like degree due to obstructive jaundice would invariably cause choluria and jaundice. From the pronounced disparity between cholemia, choluria and jaundice of the skin and the varying disparity in different sources for jaundice, it seems very clear that the degree of fixation of bilirubin to the plasma depends on some chemical alteration in the protein or lipoids of the plasma.

Furthermore, we are impressed with the fact that a large amount of bile pigment and also bile salts may be in the plasma and entirely disappear from the plasma without either salts or pigment making their appearance in the urine. A priori, we should say in view of all these facts that the plasma has the first call on the biliary elements and holds them with considerable tenacity away from the renal filter and in some instances away from the tissues also. This adsorption of bile pigment by the plasma readily accounts for the disparity generally seen between the concentration of bilirubin in the serum of ascitic fluid and pleural fluid and the subarachnoid fluid, on the one hand, and the concentration of bile pigment in the blood plasma in cases of jaundice, and it also accounts for the fact that large amounts of bilirubin may be found in the serum of fluid contained in the pleural cavity in cases of hemothorax without bilirubin appearing in the plasma of the circulatory blood. In other words, whether the bilirubin is adsorbed primarily to plasma within or without the blood vessels the plasma does not yield the bilirubin to the vessel wall any more readily than it is yielded to the renal filter or to the collodion sack. However, if we have a normal plasma and a normal liver the bile pigment and bile salts are readily yielded to the liver, as is clearly shown by animal experiment. The Gmelin test for bilirubin in plasma is not sufficiently delicate to give the blue-green zone in the coagulum when bile is added to the plasma in sufficient amounts to give a visible yellow stain to the plasma. So the best method is to compare the plasma of an animal, before the injection of bile into the blood, with the plasma after the injection into the vein has been made.

The concentration of bile varies greatly. In order to give us some conception of the pigment concentration of a specimen of bile and also to give some comparative idea of the quantitative value of bilirubin concentration in plasma, we record what proportion of bile or cholemic plasma must be added to a column of water 1 cm. deep to give a visible yellow tinge to the water.

When we refer to a specimen of bile as having a concentration of 1 to 100 or 1 to 3,000 and a specimen of cholemic plasma as having a

value of 1 to 20 or 1 to 100, we mean that that proportion of bile or plasma respectively must be added to a 1 cm. column of water to give a visible color.

Experiment 1.—Into the brachial vein of a dog weighing 17,000 gm. 40 c.c. of human liver bile were injected. This bile had a color value of 1 to 1,000. Estimating the circulatory blood in the dog at 1,300 c.c., we get a proportion of 30 to 1,000 of bile to blood. Oxalate plasma, procured by tapping the dog's heart five minutes after the injection of bile, had exactly the same color as the oxalate plasma procured immediately before the injection of bile. The plasma gave a negative reaction to Gmelin's test. Hueppert's test for pigment and the dialysate gave a doubtful reaction to Pettenkofer's test for bile salts. Five minutes after the first injection of bile, 40 c.c. more of bile were injected into the vein, and in another five minutes a third specimen of oxalate plasma was procured by tapping the cava. This plasma had a slightly jaundiced hue and gave a positive reaction for bilirubin to Gmelin's and Hueppert's tests and the dialysate gave a slight reaction for bile salts to Pettenkofer's test. The urine procured from the dog's bladder contained no biliary elements.

From previous experiments we found that after intravenous injections of bile the dogs had diarrhea with intestinal hypercholia. This suggested that the reason why the dog's plasma was not stained with bile was because the liver had the first call on bile pigment from the plasma when the plasma and liver were both normal.

Experiment 2.—Under scopolamin and ether anesthesia the abdomen of a dog weighing 13,000 gm. was opened and the superior mesenteric artery and the trunk of the portal vein were clamped to throw the biliary function of the liver out of commission. When this had been done 20 c.c. of human liver bile with a color value of 1 to 1,000 were injected into the femoral vein immediately after a specimen of oxalate plasma had been taken and found to contain neither bile pigment nor bile salts. Two minutes after the 20 c.c. of bile were injected a second specimen of oxalate plasma was taken. This specimen had a slightly jaundiced color and gave a positive test to Gmelin's reaction. There were neither pigment nor bile salts in the dialysate from the plasma.

Seven minutes after the first injection of bile a second injection of 20 c.c. was made and two minutes thereafter a third specimen of plasma was procured, which showed a distinct increase in the yellow color and a much stronger Gmelin reaction than in the preceding specimen.

When the liver was eliminated from the circulation, the animal's plasma was stained with bile about as one would expect it to be stained were the same concentration of bile in plasma made *in vitro*.

Experiment 3.—We then undertook to eliminate the liver, inject bile into the veins and then release the clamps on the superior mesenteric artery and portal vein to see how promptly the bile would disappear from the blood. From a dog weighing 6,500 gm., under scopolamin and ether anesthesia, specimen 1 of plasma was procured. The abdomen was then opened and the superior mesenteric artery and the portal vein were clamped. Then 30 c.c. of human bile, 1 to 1,000, the same as in Experiments 1 and 2, were injected into the femoral vein. Five minutes after the injection of the bile, Specimen 2 of oxalate plasma was procured, and five minutes thereafter Specimen 3 was taken. Then the clamps on the superior mesenteric artery and portal veins were released and the mesenteric and portal flow of blood were reestablished. During the procedure the pulse volume changed very little, so there could have been little change in the minute volume of blood through the heart and the hepatic artery. Five minutes after Specimen 3 was procured, Specimen 4 was taken. In five minutes more Specimen 5, and in ten minutes Specimen 6, of the plasma was procured.

The results of examination of the plasma gave:

Specimen 1, clear and colorless.

Specimen 2, clear, distinctly yellow; Gmelin's test positive; dialysate with faint color and bile salts positive.

Specimen 3, clear, yellow; Gmelin's test positive; dialysate with faint color; bile salts positive. The clamps on the artery and the vein were released.

Specimen 4, clear, slightly yellow; Gmelin's test negative; dialysate had no color; bile salts positive.

Specimen 5, clear, less yellow than 4. Gmelin's test negative; dialysate had no color; bile salts negative.

Specimen 6, clear, very slight yellow; Gmelin's test negative; dialysate had no color; bile salts (?).

We then proposed to see what results a temporary obstruction of the common bile duct would give in a comparative study of the biliary elements in the plasma and in the urine. In six trials we succeeded in getting one successful experiment, in which the catgut ligature on the common duct was absorbed and the path of the common duct reestablished, as was shown at necropsy on the dog. The common duct of a dog was ligated with catgut and nine specimens of oxalate plasma were procured by heart puncture from ten to 192 hours after the ligation of the duct. Each specimen of plasma was dialyzed. Seven specimens of urine were procured from twenty to 100 hours after the duct was ligated. The concentration value of the bile pigment in the plasma was determined. The Pettenkofer test for bile salts was employed in the dialysate from the plasma. In the urine Hammersten's test was used for bile pigment and Hay's test was used for bile salts.

The results on the plasma and the urine are shown in Tables 1 and 2, respectively.

TABLE 1.—EFFECT ON THE PLASMA OF LIGATION OF COMMON DUCT

| Specimen | Time after Ligation of Common Duct, Hr. | Color | Gmelin Reaction | Concentration of Pigment | Dialysate | |
|----------|---|------------------------|-----------------|--------------------------|-----------|-------|
| | | | | | Pigment | Salts |
| 1 | 10 | None..... | 0 | 0 | 0 | 0 |
| 2 | 28 | Slight..... | + | 1 to 50 | 0 | + |
| 3 | 48 | More yellow..... | + | 1 to 60 | 0 | + |
| 4 | 72 | Increase..... | + | 1 to 60 | 0 | + |
| 5 | 100 | Less..... | ± | 1 to 50 | Lost | Lost |
| 6 | 120 | Less..... | 0 | 0 | 0 | ? |
| 7 | 144 | Very faint..... | 0 | 0 | 0 | ? |
| 8 | 168 | Fainter..... | 0 | 0 | 0 | + |
| 9 | 192 | Still perceptible..... | 0 | 0 | 0 | + |

From these results it is seen that in temporary obstruction of the common duct, although there was a marked cholemia for both pigment and salts, there was no choluria for bile pigment at any time, although bile salts continued in the urine during the entire period of 100 hours after ligation. At the same time there was marked pigment cholemia without pigment choluria. The dialysate from the plasma contained no pigment at any time, but always contained bile salts, as did the urine.

TABLE 2.—EFFECT ON THE URINE OF LIGATION OF COMMON DUCT

| Specimen | Time of Ligation, Hr. | Bile Pigment | Bile Salts |
|----------|-----------------------|--------------|------------|
| 1 | 20 | 0 | 0 |
| 2 | 28 | 0 | 0 |
| 3 | 36 | 0 | + |
| 4 | 48 | 0 | + |
| 5 | 72 | 0 | + |
| 6 | 96 | 0 | + |
| 7 | 100 | 0 | + |

The dog had a slight icteric hue to the conjunctiva, but the icterus was not marked and would have borne a doubtful interpretation in consideration of the fact the urine contained no bile pigment. If only the scleral icterus and urine had been considered, the picture would have been that of a dissociate jaundice in which bile salts were dissociated from bile pigment. The examination of the plasma, however, showed the dissociation was purely a renal dissociation, and not a hepatic dissociation.

Obstructive jaundice in patients may be interpreted as cases of hepatic dissociation jaundice, if the urine and plasma should be examined during a period of remission.

One of our patients had gallstones with jaundice. The plasma showed an abundance of bilirubin, 1 to 100, and a positive Gmelin test. The urine also contained bile pigment, but there were no bile salts demonstrable in the plasma or in the urine. There was no reason for suspecting a hemolytic jaundice and there were no evidences for hepatitis. The urine at the time of the observation contained only 1 per cent. of the total nitrogen in the form of ammonia, and no urobilin.

The plasma and urine were examined after an acute obstruction had subsided, and on this occasion we found only the adsorbed bile pigment, which was only a survival of a complete jaundice from obstruction. Had the findings in the plasma and urine been considered apart from the clinical history and physical findings, we should have interpreted the case as one of hemolytic jaundice, but when the previous removal of gallstone and prompt recovery from jaundice and the want of any signs of hepatitis were considered, it was quite apparent we were dealing with a renal dissociation of bile salts from the bile pigment which survived in the plasma in a state of adsorption.

Another case of gallstone lodged at the junction of the cystic and common ducts gave similar findings at one examination. When first examined the patient was icteric. The urine contained bile pigment

and bile salts. The plasma was icteric, 1 to 100, and gave a positive Gmelin test. The aqueous dialysate contained both pigment and bile salts in abundance. Fifteen days later the urine contained neither bile salts nor bilirubin and the plasma had a concentration of bile pigment of 1 to 50 and gave a positive Gmelin reaction. The water and alcohol dialysate from the plasma contained bilirubin, but gave only a doubtful reaction for bile salts.

The patient made a prompt recovery after the gallstone was removed by operation. In this instance we again have the renal dissociation of salts from bile pigment in the blood. The bile pigment survived in the plasma after obstruction which originally produced complete jaundice. The following case was apparently an obstructive jaundice attending an acute gastroduodenal inflammation:

The patient was a vigorous young man 21 years old, who came under observation on the third day of his illness, which began with nausea, vomiting, anorexia and jaundice, with a normal temperature. On entering the hospital, the liver was not enlarged or tender. There was moderate jaundice and the stools were clay colored. The mercuric chlorid test to the stool gave only a very faint reaction after standing twelve hours. The intestinal hypocholia was very marked. The duodenal tube was passed into the duodenum and gave only very slight evidences of bile in the duodenum. Microscopically the duodenal content revealed many epithelial cells and an abundance of bacteria. The stomach secretion contained no free hydrochloric acid. The urine contained an abundance of bilirubin and bile salts, but no urobilin. The oxalate plasma was jaundiced with a color concentration of 1 to 100, and Gmelin's test was positive. The aqueous dialysate contained much bilirubin and an abundance of bile salts. Eight days later the jaundice was much diminished. The duodenal contents showed a marked increase in the amount of bile. The urine contained no bilirubin and no bile salts or urobilin. The oxalate plasma still showed the same concentration of bilirubin, 1 to 100. Gmelin's test was strongly positive.

On this occasion alcohol and water, equal parts, were used for the dialysate and the dialysate contained both pigment and bile salts. This was an apparent exception to the rule that bilirubin in the plasma behaved toward the collodion sack as toward the kidney. But as we learned later in our experience that comparisons between the permeability of the collodion sack and the renal filter should be made with water as a medium around the sack and not with alcohol and water, this can not be regarded as a fair exception to the rule, namely, that bilirubin in the plasma has the same threshold to renal filter and collodion sack.

Thus far we are justified in saying that in obstructive jaundice there may be cholemia without choluria and also there may be a renal dissociation jaundice of the plasma if the blood should be examined at a suitable time after the retention of bile (from the liver) has ceased.

HEMOLYTIC JAUNDICE

The first patient with a clear hemolytic jaundice whom we studied was a woman who was profoundly anemic from a profuse hematemesis (ulcer). Transfusion was employed to combat the anemia. The husband acted as donor. Severe hemolysis followed the transfusion, as was shown by the chocolate colored urine, due to hemoglobin.

The following morning, twelve hours after the transfusion, the patient was observed to be icteric. The urine contained no bile pigment or bile salts. The oxalate plasma was icteric (1 to 60). The dialysate from the plasma contained no bilirubin or bile salts.

Another patient, a woman, who had always been in good health until an abortion was induced, which caused a streptococcus infection resulting fatally in ten days, entered the hospital with profound jaundice. On the day the plasma was examined the urine contained neither bilirubin or bile salts. The plasma was deeply jaundiced (1 to 275); Gmelin's test was very strongly positive. The aqueous dialysate contained neither bilirubin nor bile salts. The dialysate from alcohol and water contained bilirubin but no bile salts.

A man suffering from syphilitic myocarditis attended with general anasarca developed erysipelas on both thighs, where he violently scratched the skin with his finger nails. Within a few days after the onset of the erysipelas, the patient became icteric. The urine contained an abundance of bilirubin and no bile salts. The plasma was deeply stained (1 to 175). Gmelin's test was positive. The dialysate from the plasma (aqueous) contained bilirubin, but no bile salts.

The following case illustrates the behavior of bilirubinemia when the bilirubin is hemolytic in origin, but develops extravascularly.

A young man in perfect health received a stab wound of the left thorax four days prior to his admission to the medical ward of the hospital. A large amount of blood was found in the left pleural cavity, and 500 c.c. of the unclotted blood were withdrawn by paracentesis. The blood when centrifuged yielded only about 10 per cent. of its bulk in plasma. The blood did not clot on standing or after the addition of calcium. The plasma contained a small amount of oxyhemoglobin and a very large amount of bilirubin, and was not turbid. The bilirubin concentration was 1 to 450. Gmelin's test, also Huppert's and Hammarsten's test for bilirubin were strongly positive. The water dialysate from this plasma contained neither bilirubin, bile salts nor urobilin. The water and alcohol dialysate contained bilirubin, but no bile salts or urobilin. Blood from the patient's veins contained no bile pigment or bile salts and the urine contained no biliary elements.

This is a very striking instance of the adsorption of bile pigment in plasma. The concentration of bilirubin was much higher in the thoracic plasma than we have found in endovascular plasma in jaundice of any kind, and in spite of the very great accumulation of bile pigment in the intrapleural plasma no bilirubin was yielded to the collodion

dialyzer when water surrounded the sack. Some unknown change in the plasma occurs, to heighten its adsorptive power for bile pigment when blood escapes into a serous cavity in a healthy person.

In another patient who acquired a blood-serous exudate in the left pleural cavity on account of carcinoma of the pleura we found the same conditions of jaundice of the intrapleural plasma existed as in the case of traumatic hemothorax.

In none of our cases of obstructive jaundice did we find such a great disparity between pigmental cholemia and pigmental choluria as in our cases of hemolytic jaundice. When we speak of the threshold at which a concentration of bile pigment in the plasma will result in bile pigment appearing in the urine, however, it seems to us an error to regard this threshold as assignable to resistance offered by the renal filter to the passage of pigment. There is a wide variation of this so-called threshold, which can not be accounted for by varying renal function. The source of this threshold lies in varying adsorptive power of the plasma for bilirubin. On this basis we can account for the disparities which exist between the cholemia and choluria, and also for the varying disparities (in some patients) between the concentration of bilirubin in the blood and serous transudates, and the varying disparities between the jaundice of plasma and jaundice of the sub-arachnoid fluid; and finally for the varying threshold concentrations of bilirubin in the plasma toward the collodion dialyzer.

HEPATITIS

Hepatic dissociation jaundice in its relation to hepatitis is not clearly depicted in our experience. What constitutes hepatitis in many cases of acute infectious disease is not clear and should there be only bile pigment in the plasma and urine without bile salts, the question to solve is are we dealing with a dissociated pigmental jaundice of hepatic origin, or are we dealing with a hemolytic jaundice which is the result of the general infection? In other words, we are dealing with evidences of blood or liver deterioration as a result of infection. The question presents itself to us in this form, because thus far we have met with no instance of bile salts dissociation in the plasma of patients suffering from sepsis of any kind, or in patients with subacute or parenchymatous degeneration of the liver.

In two cases of pneumonia with jaundice we found only bile pigment in the plasma and no bile salts in either the plasma or urine. So there seemed very good reason for regarding the jaundice as hematogenous and not hepatogenous.

In two cases of acute infection we found large amounts of urobilin in the plasma along with bilirubin and bile salts. Great parenchymatous degeneration of the liver was proved in one of these cases at

necropsy and the other patient recovered after surgical drainage of a perigastric area of infection, which was due to a perforating ulcer at the pylorus.

In two cases of subacute hepatitis occurring in association with chronic interstitial hepatitis we were able to definitely ascribe the jaundice to a subacute hepatitis, and the plasma and urine both contained bilirubin and bile salts. In one case of chronic interstitial hepatitis, however, in which alcoholism and syphilis shared as etiological factors, the patient had an acute enlargement of the liver associated with jaundice. The patient was in the hospital three weeks. When he entered his plasma was icteric (1 to 100) and yielded bilirubin, but no bile salts, to the dialysate. The urine also contained bilirubin and much urobilin; bile salts were absent, and the stools contained an abundance of stercobilin. After a lapse of three weeks, during which time the jaundice diminished and all the other symptoms improved, the plasma was slightly icteric and gave bilirubin in the dialysate to alcohol and water, but no bile salts. The urine contained no bilirubin, bile salts or urobilin. These findings we must accept as a case of dissociated pigment jaundice of hepatic origin for the following reasons:

There was a moderate jaundice (1 to 100) and pigment was liberated through the renal filter and no salts were present in either the plasma or urine. Had there been complete biliary retention in the blood from a hepatic source, both the urine and the plasma dialysate would have contained bile salts or the urine would have contained bile salts before it would have contained bilirubin. This doubt may, however, be injected into the dissociation idea, namely, that the patient had complete jaundice before entering the hospital and renal dissociation of the bile salts may have been accomplished before he came under observation, as we saw him only during a period in which the pigment was a survival of complete jaundice. That we were not dealing with hemolytic jaundice is supported by the presence of a large amount of urobilin in the urine and the fact that bilirubin was excreted in the urine when there was only moderate icterus of the plasma. That we were not dealing with a residue from obstructive jaundice is attested by the abundance of urobilin in the urine and the abundance of stercobilin in the stools.

With the exception of this last case, we have not yet seen an instance in which we could seriously consider a dissociated pigmental jaundice of hepatic origin as a probability.

DISSOCIATED BILE SALTS JAUNDICE OF HEPATIC ORIGIN

Primary anemia affords some of the most striking characteristics of biliary elements in the blood. Of fourteen cases of primary anemia in which the plasma, urine and stools were examined for bile elements,

all but two showed bilirubin in the plasma and bile salts were present in large amounts in the dialysate from the plasma in both these cases. In none of the fourteen cases were either bilirubin or bile salts found in the urine.

In primary anemia we have seen the highest concentration of bilirubin in the plasma (without perceptible icterus of the skin or sclerae) which have come under our observation. It seems in primary anemia the fixation of bilirubin in the plasma is so firm that pigment is not only never yielded to the renal filter, but in some instances pigment is not yielded to the tissues when the plasma has a concentration of bilirubin as high as 1 to 150.

Of these two cases of bile salts dissociation, one, a man 52 years old, gave a history of having been ill for fourteen months. A few months prior to entering the hospital he had a marked lemon yellow color to his skin. On entrance there was no trace of icterus. Blood examination showed red blood cells, 2,312,000; white blood cells, 7,700; hemoglobin 70 per cent.; color index 1.5. A differential count gave polymorphonuclears, 67 per cent.; small mononuclears, 23 per cent.; large mononuclears, 7 per cent.; and transitionals, 3 per cent. The neurologic signs were very marked. There was a loss of both patellar and ankle reflexes, impairment of the vibratory sense in upper and lower extremities, and acroataxia and proximoataxia in both upper and lower extremities. The plasma was colorless and the plasma dialysate gave a reaction to Pettenkofer's test, which was strongly positive. The dialysate not only changed from cherry red to purple on standing twelve hours, but the spectroscopic examination showed that the movement of the absorption band on standing was from the purple into the orange. This was an instance of primary anemia. The patient formerly had pigment as well as salts in his blood, but during the period he was under our observation his blood contained an abundance of bile salts without pigment.

As to the other case of primary anemia which yielded salts from the plasma without pigment, there may be some doubt about the primary anemia. The diagnosis of primary anemia was made from the history of former anemia and the characteristic neurologic signs associated with degeneration of the posterior and lateral columns of the cord, with a normal cell count and negative Wassermann reaction on the spinal fluid. We regarded this patient as one who had recovered from his anemia with persistence of the neurologic symptoms. However this may be, the point of interest in this patient lay in the fact that bile salts were present in abundance in his plasma, as shown from the Pettenkofer test, with spectroscopic confirmation, and no bile pigment was found in the plasma or in the urine and no bile salts were found in the urine.

Two other cases of bile salts dissociation in the plasma were found in two cases of lead poisoning. Both patients had the characteristic lead line on the gums and both patients were exposed to lead poisoning. One was a house painter and the other worked in a storage battery factory. Neither patient had an anemia below 4,500,000 red cells and there was no icterus of the skin; neither was there any bile pigment or bile salts in the urine. The plasma in both cases was colorless, but the dialysate from the plasma in both cases gave a marked Pettenkofer reaction, which was confirmed by the change from a pink to a purple color, and the spectroscopic absorption band after twelve hours moved from the purple into the orange.

SUMMARY

1. We have found true dissociated jaundice of hepatic origin in two cases of primary anemia and in two cases of lead poisoning. In the four cases bile salts were found in the blood in large amounts, that is, the qualitative test for bile salts in the plasma dialysate was quite as strong as we find it in complete jaundice of pronounced severity.

2. Excepting in jaundice of hemolytic origin and in complete jaundice which has undergone renal dissociation, we have never found bile pigment without bile salts in the plasma.

3. Bilirubin and bile salts may both be present in very marked concentration in the plasma and neither pigment nor salts appear in the urine.

4. Adsorption of bilirubin in the plasma may not only withhold the pigment from the renal filter, but also from the tissues; so there may be pronounced cholemia (pigmental) without choluria (pigmental) and also without icterus of the tissues.

5. When pigmental cholemia is present (in varying degrees) without choluria, the collodion sack will yield no pigment to an aqueous dialysate from the plasma. When choluria attends cholemia (pigmental), the collodion sack will yield bile pigment to an aqueous dialysate from the plasma.

6. Bile salts will dialyze from plasma when no bile salts are demonstrable in the urine.

7. Without an examination of the plasma we are never justified in assuming that biliary elements have not been retained in the blood.