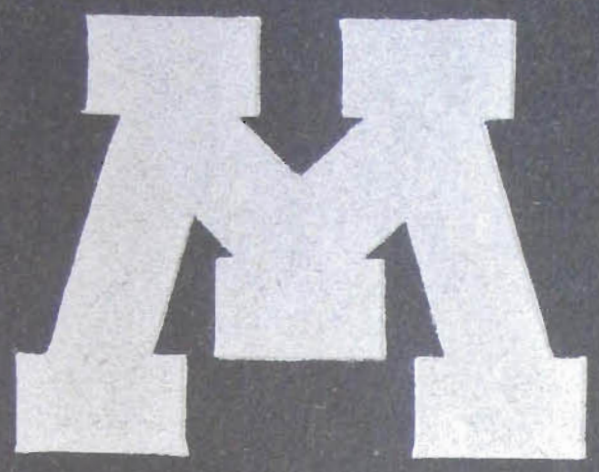

Jaundice

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I. ABSTRACT

JAUNDICE

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Jaundice may be defined as the visible expression of an increased amount of bilirubin in the blood. The foundation of our present knowledge of jaundice was laid by Virchow. Virchow believed that at least some of the bilirubin in the body was formed outside of the liver and offered as evidence of this belief the occurrence of hematoidin, which he believed identical with bilirubin, in old hemorrhages. The concept that bilirubin could be formed outside of the liver was abandoned for many years because of the work of Minkowski and Naunyn. They demonstrated that jaundice did not occur after the liver had been removed from geese in spite of the administration of chemicals which in normal geese readily produced jaundice. It was not until many years later that McNee[1] pointed out that the liver in the goose is almost the sole location of reticulo-endothelial cells which are the cells responsible for the transformation of hemoglobin to bilirubin. McNee was able to show that jaundice readily developed in other animals who had been deprived of their livers. This was particularly true in animals having relatively large spleens, as for instance in the dog. The extrahepatic formation of bilirubin was demonstrated later in a most convincing way by Mann, Sheard and Bollman[2] who employed a new method for keeping animals alive after total hepatectomy. These investigators were able to demonstrate that bilirubin was formed in the bone marrow and in the spleen, as well as in the liver.

Although the chemistry of the transition of hemoglobin to bilirubin is fairly well understood, the mode of this transition in the body has not yet been determined, nor has it been possible to cause this transition to occur in vitro, except with live cultures of cells of mesodermal origin (Rich[3]). It is most probable that the change in the body occurs intracellularly in all instances. For many years, it has been believed that the protein part of the hemoglobin molecule is the first to become split off, and that the substance known as hematin which still contains iron is an intermediate stage in the formation of bilirubin. Recently, however, considerable evidence has been brought forward, particularly by Duesberg[4], indicating that iron is first split out and that the protein, or globin fraction remains even as far as the formation of bilirubin. It is, therefore, possible that the bilirubin as first formed is still in combination with protein, and that this protein is first removed as the bilirubin goes through the liver. Duesberg calls the primary bilirubin, bilrubinoglobin. As will be seen later, this question has considerable importance in regard to the Van den Bergh reaction and also as regards the excretion of bilirubin in the urine. It is now clearly understood that the bilirubin which is formed from hemoglobin in the reticulo-endothelial system passes in the systemic circulation to the liver and thence into the bile. In the intestines, it is reduced to urobilinogen which is an almost colorless substance. Kammerer and Miller[5] have shown that anaerobic or putrefactive bacteria are almost entirely responsible for this reduction. As a corollary of this finding, it may be noted that the amounts of urobilinogen formed are greater in individuals who consume considerable quantities of meat and they are much less in vegetarians and herbivorous animals. Friedrich v. Müller[6] was the first to show that the intestine is the sole site of formation of urobilinogen. His classical experiment which demonstrated this so well consisted of feeding an individual with a complete common duct obstruction due to neoplasm a considerable amount of pig bile. On the third day after this feeding, urobilinogen appeared in the feces and shortly thereafter in the urine. This fundamental experiment was corroborated in many ways by McMaster and Elman[7] who offered further convincing evidence that urobilinogen is solely enterogenous.

Urobilinogen formed in the bowel from bilirubin is in part excreted in the feces and in part is reabsorbed and goes back in the portal circulation to the liver. Recent experiments by the writer indicate that the amount reab-

sorbed probably is considerably more than 50%. Perhaps the best evidence for this is that in instances of extreme grades of liver insufficiency the amount of urobilinogen in the urine, which really represents at least part of the amount reabsorbed from the bowel, is often two to three times that excreted in the feces. Under normal circumstances, urobilinogen which is reabsorbed from the bowel and which goes back to the liver is probably reutilized in the formation of new hemoglobin. Although this has not been proven, it is strongly suggested by the fact that patients with hemolytic jaundice in which the body is given an opportunity to retain the produces of hemoglobin metabolism, are capable of a much more rapid rate of regeneration of hemoglobin than are those individuals who develop anemia because of blood loss. In conditions associated with disturbed liver function due to anoxemia, cloudy swelling, infection in the biliary tract, cirrhosis or other damage of a diffuse type, there is regularly a failure on the part of the liver to take care of the urobilinogen brought back in the portal circulation, and as a result a proportion of this is passed on into the general circulation and excreted in the urine. So far as is known, there is very little, if any, renal threshold for urobilinogen. As a consequence, it promptly appears in the urine if not taken care of by the liver. The amount which appears in the urine is roughly proportional to the degree of disturbance of liver function. These facts have been particularly emphasized by Wilbur and Addis[8], Wallace and Diamond[9], and Watson[10]. Urobilinogen is an almost colorless chromogen and as such is capable of giving an Ehrlich reaction, which is commonly used for determining its presence in urine and feces. Following exposure to light and air, urobilinogen changes, giving rise to two substances which appear to develop in about equal amount. These are: urobilin and mesobiliviolin. Urobilin or stercobilin is a yellow-orange pigment which produces green fluorescence with alcoholic zinc acetate solution. In order to study accurately urobilinogen excretion in feces and urine, it was first necessary to prove that the substance was the same in both excreta, otherwise a common quantitative method could not be employed. This has been accomplished in an indirect way, i.e., by the isolation of crystalling stercobilin from the feces, and crystalline urobilin from urine, and by chemical proof of their identity (Watson[11]).

Many classifications of jaundice have been proposed. Perhaps the most commonly accepted one is that of McNee[1] which divides jaundice into three types: obstructive, toxic or infectious, and hemolytic. Rich[3] has recently proposed a classification which appears to be quite useful. In this, there are only two types of jaundice, i.e. retention and regurgitation jaundice. As a means of separating cases of jaundice into one or another of these two groups, Rich has used chiefly the characteristics of the bilirubin in the plasma in any given instance. These characteristics are: (1) the type of Van den Bergh reaction, and (2) the presence or absence of bilirubin in the urine. Retention jaundice includes all instances of jaundice associated with an increased formation of bilirubin, and instances in which Rich believes there is a failure on the part of the liver to accept bilirubin from the blood. Rich concludes that the Van den Bergh reaction is indirect in this group and that bilirubin is not found in the urine. In regurgitation jaundice, Rich believed the bilirubin occurring in the blood had already passed through the liver cells but had gone back into the blood because of biliary obstruction. In this group, the Van den Bergh reaction is direct, and bilirubin is present in the urine. The difference in these phenomena in the two groups, i.e., the differing Van den Bergh reaction and the absence or presence of bilirubin in the urine is probably to be explained by a physical or chemical difference in the bilirubin in the two groups. One theory holds that the bile acids which are also accumulated in "regurgitation" jaundice, lower the surface tension of the bilirubin molecule, permitting it to give a direct Van den Bergh reaction, and to be excreted by the kidney. Another theory is that the bilirubin in "retention" jaundice is in combination of some sort with protein which retards the Van den Bergh reaction, and prevents passage through

the glomerulus. The latter theory could be correlated very well with the previously mentioned conception of Duesberg, i.e., that bilirubin as first formed is still in combination with the "globin" of hemoglobin. It is hoped that further investigation will answer these questions. Unfortunately, the Van den Bergh reaction does not aid in the separation of the various types of jaundice. The only exception to this statement is for hemolytic jaundice which very characteristically is accompanied by an indirect or purely delayed reaction and in which bilirubin is not found in the urine. However, hemolytic jaundice is usually readily recognized by other means and it is particularly in the group of jaundice due to liver disease and to obstruction to the outflow of bile by the presence of stone or neoplasm that more help in differentiation is needed. Several years ago, the writer[10] presented preliminary evidence which indicated that determination of the excretion of urobilinogen in urine and feces gave great aid in separating these forms of jaundice. Recently approximately 150 cases have been studied with reference to the amount of urobilinogen excreted in each 24 hours. Of these cases, about 100 presented with jaundice or evidence of liver disease. This study has made apparent a number of essential differences in the various forms of jaundice. Based on the excretion or urobilinogen, jaundice may be classified in the following way:

The Characteristic Ranges of Urobilinogen Excretion in the Common Forms of Jaundice

	Urobilinogen in mgs. per day	
	Urine	Feces
I. Jaundice due to obstruction in biliary tract.		
A. Stone, without complications	0 - 6	10 - 250
B. Stone, with complications such as cholangitis, biliary cirrhosis, anemia.	4 - 50	10 - 250
C. Neoplasm.	0 - 0.3	0 - 5
II. Jaundice due to diffuse liver disease.		
A. Cirrhosis.	8 - 100	8 - 200
B. Cirrhosis or liver disease with increased blood destruction.	20 - 200	300 - 1200
C. Acute catarrhal jaundice	8 - 200	10 - 300
III. Hemolytic jaundice.		
A. Uncomplicated	1 - 10	300 - 1800
B. Complicated by infectious disease, severe anemia, infarction, anesthesia.	10 - 300	300 - 1800
Normal or control cases.	0 - 2	40 - 280

From the above, it is seen that jaundice due to neoplasm is rather sharply separated from other forms of jaundice by virtue of the fact that there is regularly complete or almost complete obstruction to the outflow of bile as measured by urobilinogen estimation. Of 34 consecutive cases of jaundice due to stones and 27 cases of jaundice due to diffuse liver disease, such as accompanies cirrhosis of the liver and in acute catarrhal jaundice, the per diem amount of urobilinogen in the feces was in no instance less than 10 mg. and was usually considerably more than this. Of 14 instances of jaundice due to neoplasm, only one exhibited more than 5 mg. of urobilinogen in the feces per day. In this one exception, there were very unusual polypoid metastases in the common duct which had obviously permitted small amounts of bile to pass. It is stated that neoplastic obstruction to the outflow of bile may at times let up, resulting in a diminished jaundice. No such instance has been observed in the present study. Nevertheless, instances are included in which the patient observed that jaundice had definitely decreased. The following is illustrative:

CASE I.

Jaundice of 5 months duration. Extreme weight loss. Patient stated the jaundice had markedly decreased during the month prior to admission to the hospital, and in support of this statement his icterus index was only 67, indicating that the degree of jaundice was much less than is commonly seen with neoplastic obstruction. However, only a trace of urobilinogen was found in the stool and the urine contained none. At operation, carcinoma of the head of the pancreas was found. Because of the history of diminished jaundice and the relatively low icterus index, it might well have been thought that there had been a partial relief of obstruction in this instance. The urobilinogen estimation indicated definitely that this was not the case. Marked variations in the degree of jaundice with persistent complete biliary obstruction are much more readily explained on the basis of variations in the rate of blood destruction. This has been clearly shown to be the case by Rous and Drury[12] who found that the degree of jaundice in dogs whose common duct had been severed between ligatures was entirely dependent upon the rate of blood destruction. With induced blood loss, the degree of jaundice rapidly diminished because of compensatory decrease in the rate of blood destruction. With increased blood destruction produced by hemolytic agents, the jaundice rapidly increased. A very important factor, of course, is the rate of excretion of bilirubin in the urine, and the presence of renal insufficiency will naturally tend to increase the degree of jaundice by renal retention of bilirubin. The following case demonstrates rather clearly the effect of secondary anemia on the degree of jaundice in a patient having complete biliary obstruction.

CASE II.

Male, 59 years of age. Constant dull distress in the epigastrium for three months, increased by eating. Jaundice of only two weeks duration. Markedly enlarged, hard and nodular liver. Tarry stools. X-ray evidence of a large carcinoma of the stomach. Hemoglobin 40%. Icterus index 61. Urobilinogen in feces 4.8 mgs. per day; in urine, 0.3 mg. per day. The rather low degree of jaundice in this instance is almost certainly due to a compensatory decrease in the rate of blood destruction because of blood loss in the feces; the obstruction to the outflow of bile was complete.

The value of urobilinogen estimation in deciding as to whether obstructive jaundice is due to neoplasm or not is further illustrated in the following instances:

CASE III. Minneapolis General Hospital.

Female, 58 years of age. Patient gave a history of repeated previous right upper quadrant colic during past several years. Her present illness, however, was characterized by painless jaundice of 3 weeks duration.

Because of the previous history of what was believed gallstone colic, it was thought that the patient was suffering from a silent common duct stone. The hemoglobin was 82%. Icterus index, 156. Urobilinogen in the feces, 5 mg. per day; in the urine, 0. Because of this evidence of complete biliary obstruction, diagnosis of carcinomatous obstruction was made. At operation, the common duct and hepatic duct were found to be full of a meaty substance, a biopsy of which revealed adenocarcinoma. The gallbladder contained numerous stones.

CASE IV.

Female, 64 years of age. Her present illness was characterized by a totally painless jaundice of 6 months duration with marked pruritus. During this period, a 40-pound weight loss had occurred. The patient stated that she had had a few attacks of colicky pain in the right upper quadrant thirty years before, none during the present illness. The liver was found to be markedly enlarged and its surface felt finely nodular. The spleen was not palpable. The icterus index was 65. Stools were clay colored but were found to contain 10 mgs. of urobilinogen per day. The urine contained, in addition to a large amount of bilirubin, 26.2 mgs. of urobilinogen per day. (Note inverted stool urine ratio.) Because of this definite evidence of incomplete obstruction after a long period of jaundice, a diagnosis of common duct stone with biliary cirrhosis was made. At operation, a very large stone composed almost entirely of cholesterin was removed from the common duct. Six months later, the patient was in good condition. There was no jaundice and the liver was no longer palpable.

In evaluating urobilinogen excretion in the urine and feces, the stool-urine ratio must be clearly appreciated. This fact has been particularly emphasized by Adler and Bressel[13]. The following case is illustrative:

CASE V.

Female, 44 years of age. Jaundice of two years duration following cholecystectomy. Markedly enlarged liver; no ascites. Spleen palpable. Hemoglobin 88%, leucocytes 8,950, neutrophils 84%. Icterus index 85. Urine contained bilirubin and 3.9 mgs. of urobilinogen per day. The feces were clay colored and contained 6.7 mgs. of urobilinogen per day. It is to be noted that the amount in the urine, although actually exceeding the normal only slightly, is relatively greatly increased when one considers the very low value in the feces. The biliary obstruction in this instance was due to common duct stricture and a biliary cirrhosis was present at autopsy.

The striking difference between obstructive jaundice due to stone and that due to neoplasm often cannot be determined with qualitative tests, since it is obvious that they are not capable of demonstrating whether only 2 or 3 mgs. of urobilinogen are present in the feces per day, as is the case with a neoplasm, or whether 10 or more mgs. are represented as is the case with jaundice due to stone.

Graham's conception that diffuse liver injury of temporary nature occurs with cholecystitis is substantiated by urobilinogen estimation in these cases. The following are illustrative:

CASE VI.

Female, 25 years of age. Previous repeated attacks or right upper quadrant colic with occasional jaundice during the past 2 years. Present attack accompanied by marked pain in the right upper quadrant, extreme tenderness with spasm of the right rectus muscle, and fever. Leucocytes 16,700 with 94% neutrophils. No jaundice apparent. During the acute attack, urine urobilinogen was 20.8 mgs. per day. Several days later, the acute symptoms had entirely subsided, the temperature was normal and the leucocytes were 10,500. At this time, the urine urobilinogen was found to be 0.2 mgs. per day.

The following instance illustrates

the effect of cholangitis on urobilinogen excretion and also indicates extremely well the sequence of events with what is known as a ball-valve stone in the common duct.

CASE VII.

Female, 37 years of age. Eleven years ago, the patient had a severe colic in the right upper abdomen accompanied by jaundice. This occurred not long after an appendectomy. There was no recurrence until March 1935 when an attack of right upper quadrant colic without jaundice occurred which was of short duration but recurred on April 17th with fever, chills and jaundice. On admission to the hospital, the patient was acutely ill and markedly jaundiced (icterus index being 92). There was considerable tenderness in the right upper quadrant of the abdomen and muscle spasm. No masses were palpable. The leucocytes were 11,600 with 87% neutrophils. During the first two days in the hospital, there were rather frequent chills and the temperature often rose to 105°. During this period, the urobilinogen in the feces was 12 mgs. per day and in the urine 4.2 mgs. per day. (Note low stool-urine ratio.) Two days after admission, there was sudden improvement with disappearance of chills and fever and marked diminution of jaundice. The icterus index dropped to 38 and was 29 on the next day. At this time, the urobilinogen in the feces was found to be 612 mgs. per day and in the urine 47.5 mgs. per day. During the next four days, the icterus index decreased to 19. There was no recurrence of pain, tenderness or fever. The patient felt immeasurably improved and the urine urobilinogen decreased to 2 mgs. per day. At the same time, there was a marked decrease in the amount in the feces, the value being 120 mgs. At operation, a rather large stone was found in the common duct which was markedly dilated and there were also stones in the gallbladder and cystic duct. The findings in this instance amply illustrate the damming back of bile behind a stone in the common duct with the release of obstruction which presumably occurs when the stone shifts in position in the dilated duct. The temporary very high value in the urine points to liver damage due to infection in the biliary tract concomitant with biliary stasis.

Ever since the clinical studies of Friedrich v. Müller, it has been recognized that urobilinuria is an important sign of liver damage. Later investigators, particularly Eppinger[14], Wilbur and Addis[8], Wallace and Diamond[9] have emphasized this fact. The usefulness of the test, however, has been largely impaired because qualitative tests failed to give differential information. This is largely due to the fact that the urobilinogen excretion is not constant throughout the day, varying considerably, and further that the dilution of urine is subject to marked variations so that if one uses a 24-hour urine for the test, the results may be strong or weak depending upon the amount of urine passed in 24 hours. For this reason, it is essential to know the per diem excretion. This knowledge is of great aid in determining the nature and degree of liver disease. Of 28 cases of what may be spoken of as primary liver disease in the present series, only one failed to show a considerable increase of urobilinogen in the urine. This instance follows:

CASE VIII.

Female, 13 years of age. The patient had had attacks of jaundice, usually associated with fever since infancy. In the last illness, jaundice was of 8 months duration. Urobilinogen studies were not carried out until the last few days of life. At this time, the patient was suffering from a terminal septicemia with positive blood culture. The liver was considerably enlarged with rounded edge and there was no ascites. The icterus index was 56, hemoglobin 59%, erythrocytes 2,730,000, leucocytes 10,800 with 86% neutrophils. Her temperature ranged from 101 to 105°. Urobilinogen in the feces was found to be 14.1 mgs. (feces were acholic). Only a trace of urobilinogen was demonstrable in the urine. From a clinical standpoint, this case corresponds well to the descriptions of Hanot. Necropsy revealed a very advanced

cirrhosis of the liver of Laennec's type with extensive formation of adenomata. It is believed that the lack of urobilinogen in the urine in this one instance was due to the patient's terminal state, which perhaps interfered with the reabsorption of urobilinogen. There was, of course, only a small amount present in the feces, pointing to a fairly high grade obstructive jaundice. All of the other instances of liver disease were accompanied by actual or relative increases of urobilinogen in the urine of considerable degree.

A number of cases of diffuse liver disease show definite evidence of an accompanying hemolytic anemia. These cases closely resemble the effect produced experimentally by toluylenediamine which both damages the liver and increases the rate of blood destruction. The following case is illustrative:

CASE IX.

Female, 31 years of age, admitted to the hospital on 10-17-34, complaining of painless jaundice which had been present since 8-11-34. There was considerable pruritus. The onset of the jaundice had been characterized by anorexia and weakness. The essential findings were considerable enlargement of the liver and of the spleen but no ascites. At the time of admission, the hemoglobin was found to be 89%, two days later 85%. Leucocytes were 4,650 with 40% lymphocytes. The icterus index was 179 and Van den Bergh was of the direct type. On 10-24-34, the urobilinogen in the feces was found to be 803 mgs. per day and in the urine, 66 mgs. per day. Four days later, the amount in the feces had increased to 1257 mgs. and in the urine to 224 mgs. Under observation, the patient now developed a macrocytic anemia with marked regeneration (reticulocytes 15%). The hemoglobin fell to 65%, erythrocytes to 2,680,000. The greatly increased excretion of urobilinogen in both feces and urine continued for 2 weeks, then decreased markedly with coincident subjective improvement and gradual disappearance of jaundice. The hemoglobin rose to 80%. The patient was recently examined again: The liver and spleen are still palpable, but smaller than before. The urine urobilinogen is now 0.2 mgs.; that in the feces, 186 mgs. per day.

Hemolytic jaundice is regularly characterized by a very marked increase in the amount of urobilinogen in the feces. This was first clearly demonstrated by Eppinger[14]. In the familial or constitutional variety, where fragile microcytes are the essential feature of the disease, most of the blood destruction appears to be consummated in the spleen. An extreme decrease in the amount of urobilinogen in the feces may occur shortly after splenectomy. The following case is illustrative:

CASE X.

Female, 8 years of age. Splenomegaly, slight chronic icterus, microcytes, increased fragility, reticulocytes 18%. Several other members of family have disease of same type.

	Urobilinogen in Mgs. per day, in feces.
Prior to splenectomy	1001.0
10 days after splenectomy	15.0
7 months after splenectomy	130.0

It has often been stated that marked increases in urine urobilinogen in hemolytic jaundice are due to increased blood destruction. However, this does not appear to be the important factor as is shown by the following comparisons of urobilinogen in urine and feces in cases of hemolytic jaundice:

Urine	Feces
2.1	794
0.24	428
1.0	1,140
2.3	570
8.3	910
1.4	707.1
9.8	1,103

That large amounts may at times appear in the urine is illustrated by the following cases, but it is seen that these increases were only temporary and

occurred at a time when factors which may well have caused a disturbance of liver function, were also present.

CASE XI.

Female, 18 years of age. Hodgkin's disease. Progressive hemolytic anemia. Reticulocytes 38%. Acute splenic infarction at time of admission to hospital.

	Urobilinogen in Mgs. per day. Urine	Feces
At height of symptoms referable to splenic infarction.	155 33	507
Several days later, above symptoms have subsided.	trace 1.4 1.1	104 707.1 304.7

CASE XII.

Female, 18 years of age. Idiopathic macrocytic hemolytic jaundice, possibly initiated by continuous resorption of hematin from hemorrhagic fluid in a large ovarian cyst. Marked regenerative anemia.

	Urobilinogen in Mgs. per day. Urine	Feces
At time of admission	9.8 2.5	1,106 986
After laparotomy, removal of ovarian cyst.	380.8 34.5 6.2	 1,831.2 1,180.8
After splenectomy	138.0 22.3 35.2 .87	 1,548.0 536.2 406.7
Marked improvement	2.3	429.0

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II. MOVIES

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