DIFFERENTIAL DIAGNOSIS OF JAUNDICE

CHARLES L. HARTSOCK, M.D.

The yellow or greenish yellow staining of the blood plasma and body tissues, to which the clinical term jaundice has been applied, is due to an excessive amount of one of the normal constituents of the blood, viz., bilirubin.

To differentiate accurately the various causes of jaundice, one must understand something about the source, properties, and excretion of bilirubin.

Bilirubin is a product of the normal daily destruction of red blood cells which occurs at a surprisingly rapid rate, the estimated life of a red blood cell being from 4 to 30 days. As formed in the blood stream, bilirubin is strongly combined or attached to the blood proteins. To break up this combination with protein, the action of the liver cells or the presence of bile salts is required. When combined with protein, bilirubin cannot be excreted by the kidneys so that the liver normally acts as the only excretory organ of bilirubin to form the bile pigment of bile.

The liberation of the bilirubin from the protein is not completely understood but liberated bilirubin does not occur in the blood serum except in the presence of disease of the liver or bile ducts. The ease with which these two types of bilirubin can be distinguished by the so-called direct and indirect action of the qualitative van den Bergh reaction serves the very important purpose of immediately separating jaundice into two types:

(1) Hyperbilirubinemia due to increased production.

(2) Hyperbilirubinemia due to decreased excretion.

The first type must be due to some disease that increases the destruction of red blood cells. The second type must be due to some disease that affects the liver or bile ducts, thus interfering with the excretion of the normal production of bilirubin.

Jaundice or hyperbilirubinemia can be predicated in three ways. First is the actual measurement of the serum bilirubin. This is the most accurate but unfortunately not a simple laboratory test. The icterus index, a colorimetric method of studying the yellow pigment in the blood, is a much simpler and usually reliable method of quantitatively studying the amount of bilirubin in the blood serum. The only confusion arising from this test is the presence of extraneous pigments in the serum, such as carotene. The icterus index normally varies from 4 to 6 units. When examined in the best light and under the most favorable locations, the

eye, the third indicator of the presence of jaundice, picks up the yellow tinge when the icterus index reaches 12 to 15 units. Naturally, it is only when the mildest degrees of pigmentation are present that the more accurate method of determination of the serum bilirubin is necessary to differentiate the presence or absence of hyperbilirubinemia as the cause of the pigmentation.

The presence of jaundice determined, and the quantitative amount of the pigment estimated, the next procedure is to determine the cause. As mentioned previously, the simple van den Bergh qualitative test will easily differentiate between a jaundice of overproduction and jaundice of undersecretion. Only in the mild degrees of jaundice is this necessary as the severe degrees of icterus always are caused by disorder of the biliary tract.

If the jaundice is mild and the van den Bergh reaction is indirect, the jaundice must be due to increased destruction of the red blood cells. In such cases, the urine is acholic because combined bilirubin is not excreted by the kidneys. The urobilin content of the urine is usually increased because increased amounts of bile are reaching the intestine.

The problem becomes one of finding the cause of the increased hemolysis. The hemolytic blood dyscrasias, such as hemolytic jaundice, pernicious anemia, sickle cell anemia, paroxysmal hemoglobinuria, etc., must be differentiated. The hemolytic fevers, malaria, hemolytic septicemia, drugs such as phenylhydrazine, and transfusion reactions with hemolysis may cause mild degrees of jaundice. This type of jaundice is called hematogenous jaundice, is easily recognized as such, and the exact cause can usually be determined by appropriate studies.

The real problem in the differential diagnosis of jaundice is presented in those cases in which the hyperbilirubinemia is due to disease of the biliary system. In severe jaundice with icteric index values above 50, hematogenous jaundice need not be considered. The van den Bergh reaction will be direct, the urine will contain bile, and bile in the intestinal tract will be diminished or absent, resulting in low to absent urobilin in the urine. Such observations, however, are of little or no practical diagnostic value.

For practical therapeutic and prognostic purposes, there are three types of disease of the biliary tract that should be differentiated:

1. Cellular damage to the liver—
   Catarrhal jaundice or Weil's disease, acute yellow atrophy, toxic hepatitis due to drugs, etc.
2. Diffuse intrahepatic biliary obstruction.
   The cirrhoses, finely infiltrating malignancies, and other diffuse disease of the liver.

3. Extrahepatic obstruction of the large duct.
   Gall stones, pressure on the duct from tumors and scar tissue, etc.

The therapeutic indications and the prognosis vary so greatly in these three types of biliary jaundice that it is of the utmost practical value to be able to distinguish the type as early as possible.

To the first group in which the obstruction to the excretion of the bile is in the cells and finer biliary passages, the name hepatogenous jaundice is given. To the third group where the obstruction is in the large bile passages, the name obstructive jaundice is given. The second group is a combination of the first and third and might well be called the hepato-obstructive type.

In the hematogenous type, it was seen that laboratory procedure was the *sine qua non* of diagnosis.

In the biliary type, we must rely on much more inexact methods. The history of onset is most helpful. Fairly rapid onset of painless jaundice, preceded by a period of malaise, suggests hepatic damage.

Jaundice which appears rapidly following a painful abdominal episode suggests gall stones. The slow, insidious onset suggests the hepato-obstructive type or obstructive type due to slowly increasing pressure on the ducts.

A history of exposure to chemicals and drugs used as medicines is highly significant. Previous attacks of gall stone colic may be the deciding clue in the diagnosis.

It seems to me that not enough stress has been placed on the presence or absence of pruritis as a diagnostic aid. Acute hepatogenous jaundice in the early stages rarely causes pruritis. An exception to this is the hepatitis of cincophen poisoning where there is frequently an associated urticaria. Early pruritis is in favor of an obstructive jaundice while pruritis preceding the appearance of jaundice practically always means obstruction of the slowly progressive type.

Any marked change in the general health of the individual during the months preceding the onset of jaundice makes one suspicious of some underlying disease, such as cirrhosis or malignancy. If the patient is first seen after the jaundice has been present for some time, the variation in the degree of jaundice may be of some importance. Hepatogenous jaundice will usually be clearing from the second to the sixth week, but jaundice which progresses after the sixth week should be considered of obstructive origin.

It is rare, however, with the exception of the jaundice due to drugs and that following a typical gall stone attack, to learn anything from

the history that is helpful in answering the all-important question in early acute jaundice—to operate or not to operate.

The examination of the patient may furnish some additional information. Evidence of scratching only confirms what the patient was so anxious to tell you about the very annoying pruritis.

Palpation of the region of the liver may reveal changes in the size of the liver, whether smaller or larger than normal, the consistency if palpable, the presence of tumors in or near the liver, the presence of a palpable gallbladder. Ascites, collateral circulation, hemorrhoids, etc., must all be noted and evaluated in conjunction with other findings.

Evidence of malignancy elsewhere in the body, especially the stomach, rectum, and breast must be carefully searched for. The Wassermann reaction may be helpful. If a study of the blood shows macrocytosis, it would suggest that the liver was diffusely damaged.

The longer the duration of the jaundice, the easier it becomes by use of the above methods to make a diagnosis of the type of jaundice present.

Fortunately, in the case of early jaundice, we have a method that is of the utmost practical value in distinguishing between obstructive jaundice in which exploratory operation should be performed and hepatogenous jaundice in which exploration is not indicated. This is the galactose tolerance test. If a patient with jaundice is seen in the first two weeks, this test has a high degree of specificity but its value decreases rapidly if the jaundice has been present for a longer time and may even give just the opposite result from that which it should give. One of the functions of the liver is the storage and conversion of glycogen and glucose. Other carbohydrates, such as galactose, are converted into glucose before they are utilized or stored as glycogen. Galactose in the blood stream has no threshold value in the kidney and is completely eliminated in the urine. If, therefore, the glycogenic function of the liver is impaired to the extent that it will not convert galactose into glucose, there will be an excessive amount passing into the blood and then to the urine when galactose is given by mouth. Jaundice due to cellular damage would most likely interfere with this function, whereas an early jaundice due to obstruction could not damage the liver cells. As time goes on, however, the reverse is true. An increasing obstruction would gradually damage liver cells, whereas the damaged liver cells of an infectious or toxic jaundice would be gradually recovering their properties.

As usually given, this test consists of the administration of 40 grams of galactose by mouth and the quantitative estimation of the amount of reducing substance eliminated over a period of five hours. It is assumed that this reducing substance is galactose. If the quantity of galactose excreted is over 3 gm., it is assumed that the liver was unable to convert

the galactose into glucose and therefore the liver cells are damaged. If the liver cells are functioning properly, it is assumed the jaundice is of the obstructive type.

It can readily be seen how important it is to be able to differentiate between early catarrhal jaundice that should be treated expectantly and the early jaundice of obstruction that becomes an increasingly more dangerous surgical risk the longer the jaundice is present.

Unfortunately, this test is not helpful in distinguishing between the obstruction of the large ducts and the hepato-obstructive group.

I would also like to emphasize again the unreliability of this test after the second or third week of jaundice. Its results are so confusing at this time that it had better be omitted.

Roentgen examination is of little value in jaundice. Its value is limited to searching for malignancy, especially of the gastro-intestinal tract, and looking for the presence of opaque stones on a plain film of the gallbladder. Even their presence may be coincidental and not related to the real etiologic factor.

Other tests of liver function are of little or no value in the differential diagnosis of jaundice.

In the doubtful cases, to differentiate accurately between the obstructive type and the hepato-obstructive type and even at times the unusual hepatogenous type, it is necessary to explore the abdomen. There are many cases in which the exact etiology of the jaundice remains in doubt even after exploratory operation, so it is easy to realize the difficulty of making an exact differential diagnosis clinically.

Everything to gain and nothing to lose should be the idea with which these cases are approached from a surgical standpoint. Operations have repeatedly shown the fallacy of the clinical diagnosis of jaundice. The supposed carcinoma of the pancreas may be a chronic pancreatitis. The supposed cirrhosis may prove to be only an easily removed stone in the common duct with long-continued partial obstruction producing a secondary fibrosis of the liver. Other unsuspected but curable conditions may be found at exploration. I want to emphasize, however, that other methods of examination should be used to determine the diagnosis before surgery is attempted.

Summary

Hematogenous jaundice is easy to recognize and appropriate studies will, in most cases, reveal the underlying disease entities.

In the biliary group, a galactose tolerance test done early in the course

of jaundice should separate off the group due to damaged liver cells in which it is so important that no operation be performed.

Much better diagnostic methods are to be desired to distinguish between the pure, obstructive type that is so frequently amenable to surgery and the hepato-obstructive type in which surgery only shortens the patients' lives. At present, however, exploration must be utilized until better methods are discovered.