A Patient with Circulatory Complications Following an Exploratory Celiotomy for Unexplained Jaundice

By Joseph E. Flynn, M.D. and Frederick R. Bailey, M.D.

A

n internist is often called as a consultant for certain postoperative complications. One of these is lower nephron nephrosis; another is hemorrhagic pancreatitis. Both are associated with some degree of shock, but in lower nephron nephrosis the shock usually precedes the renal ischemia, whereas in pancreatitis, the shock usually follows the pancreatic involvement.

In the case to be presented, the patient had both a pancreatitis and a lower nephron nephrosis. The appearance of the two lesions following an exploratory celiotomy accounted for a complex clinical picture. In this instance, the autopsy permitted an accurate reconstruction of the sequence of events.

It should also be mentioned that in this presentation, the discussions by the clinician and the pathologist were originally given at a clinicopathologic conference.*

CLINICAL HISTORY

A 34-year-old man was admitted to the hospital April 4, 1953, because of chills, fever and jaundice of three days' duration. His previous health had been excellent. His position as a trade representative necessitated frequent trips to the tropics. On such journeys, episodes of diarrhea were not unusual. These were afebrile and were characterized by the presence of watery stools which did not appear grossly to contain blood or pus. The diarrhea promptly disappeared when he returned to a temperate climate.

Five months before his death, he had been admitted to a hospital for appraisal following an attack of diarrhea. There were no significant abnormalities on physical examination, except for an allergic rhinitis. The urine, blood counts, sedimentation rate, basal metabolic rate, serum nonprotein nitrogen, blood sugar and electrocardiogram were all normal. X-ray films of chest, a barium enema and proctoscopy were negative. Two examinations of the stool for protozoa and ova were negative. Four months prior to his final hospital admission, he went to Trinidad. Again he developed diarrhea. In Trinidad he swam in stream-fed pools, but he did not subsequently develop a rash or itching of the skin. He then went to Rio de Janeiro. His diarrhea disappeared, but while there he had an illness characterized by cough, pain in the chest and a rise of temperature to 104 F. A diagnosis of pneumonia was made. Following treatment with penicillin, he promptly recovered, except for a dry cough which persisted, and a loss of 16 pounds. While still in Rio de Janeiro, three months before his final admission, he received an injection of influenza vaccine. A common syringe and needle were used for the inoculation of several people, but the needle was said to have been blamed between injections. He then went to Argentina where his diarrhea returned. It was characterized by three or four bowel movements a day. Two and one-half months before his last hospitalization he went to Panama. Here he had a sore throat and was given aureomycin. The next six weeks were spent in New York. Self administration of aureomycin was continued. His sense of well being gradually returned; his diarrhea disappeared and he regained all of his lost weight. One month before admission,
he went to Mexico for 10 days. While there his diarrhea recurred and he had night sweats. Following his return to New York he tired easily and continued to have a mild diarrhea. Four days prior to entry he became extremely weak after chopping down some trees. He had a shaking chill and a rise of temperature to 108 F. Following an injection of penicillin, his temperature returned to normal and remained there. However, anorexia, persistence of diarrhea and the appearance of dark urine led to admission to the hospital.

Physical examination on the day of admission revealed a temperature of 100 F., a pulse of 90 beats per minute, and a blood pressure of 130/90 mm. Hg. He did not appear to be acutely ill. There was slight icterus. Examination of the heart and lungs was negative. The liver edge was tender and could be palpated three-finger breadths below the costal margin. One observer believed he could just palpate the tip of the spleen. There were no other abnormal findings.

Laboratory studies were reported as follows: The urine contained bile and a very faint trace of albumin. A complete blood count was normal save for the presence of nine per cent eosinophiles. The erythrocyte sedimentation rate was normal. The stool contained no blood. Seven specimens of stool were examined for ova and protozoa and four specimens were cultured for enteric pathogens with negative results. Three examinations of the sputa were negative for parasitic ova. No bile was obtained on duodenal drainage, and no crystals were found in the material aspirated. The serum bilirubin was 3.6 mg. per 100 cc. (immediate, direct); the alkaline phosphatase was 2.7 Bodansky units; the non-protein nitrogen was 28 mg. per 100 cc.; the serum protein 7.5 Gm. per 100 cc. (albumin 4.7, globulin 2.8); and the serum cholesterol was 181 mg. per 100 cc. The cephalin-flocculation and thymol-turbidity reactions were negative as were the intracutaneous test for schistosomiasis, the heterophile and brucella agglutinations, and the Widal test. The prothrombin time was 16.3 seconds (control 15).

The patient’s course in the hospital was afebrile. Itching of the skin was troublesome, and spider angiomata appeared. The alkaline phosphatase rose to 14 Bodansky units and later fell to 10. The serum bilirubin rose gradually to 16.7 mg. per 100 cc. The serum cholesterol rose to 415 mg. per 100 cc. with 25 per cent esters. There was a 17 per cent decrease in free cholesterol on 24-hour incubation.1 The cephalin-flocculation test became unquestionably positive, and the thymol-turbidity reaction was 3 plus.

One month following entry, an exploratory celiotomy was performed. The liver was found to be of normal size. The biliary passages were slightly smaller than normal. The common bile duct and the gall bladder were collapsed and empty. The ampulla of Vater was normal. Exploration of the common bile duct with a probe was difficult because of its small size. The junction of the hepatic ducts appeared to be about 1.5 cm. within the substance of the liver. A probe could not be passed beyond this point. The surgeon thought the inability to pass the probe was probably related to the presence of a neoplasm. The entire operation lasted four hours. A biopsy of the liver and the ampulla of Vater was obtained. The pathologist’s report was “obstructive condition of the bile duct system and focal necrosis of the liver; normal ampulla of Vater.”

The post-operative course was stormy. There were nausea and vomiting. Oliguria was present for the first three days. The non-protein nitrogen rose to 127 mg. per 100 cc. and continued to rise even after the output of urine had returned to normal. The jaundice increased with the serum bilirubin levels varying from 20 to 30 mg. per 100 cc. He developed an anemia, hypotension, and edema. Death occurred three weeks after the operation.

**DISCUSSION**

**Dr. Bailey:** In attempting to arrive at a diagnosis I shall try to exclude certain conditions. The possibility of extrahepatic obstruction of the biliary tract is eliminated by the findings at operation. There is no evidence to support the diagnosis of schistosomiasis. Amebiasis is unlikely because of the tendency of the diarrhea to subside promptly on each return from the tropics and the reputedly negative stool examinations for amebas. A pure hepatocellular type of hepatitis seems unlikely in view of the chemical studies of liver function.

I shall accept the illness in Rio de Janeiro as being pneumonia and unrelated to the present illness.

The elevation of the serum bilirubin, alkaline phosphatase and total cholesterol levels points to the presence of obstructive jaundice. The moderate rise in globulin, the positive thymol-turbidity reaction and the moderate drop in the percentage of esterified cholesterol are consistent with derangement of cellular function secondary to prolonged obstruction.

The findings at operation clearly place the obstruction as intrahepatic. Therefore, I believe that the differential diagnosis must lie between cholangiolitic hepatitis and a car-
cinoma at the exact point of junction of the hepatic ducts to form the common bile duct.

What did the surgeon’s probe hit? Was it a carcinoma or was it stopped by the small caliber of the biliary ducts?

There is much in the history to suggest that the patient might have had the so-called cholangiolitic type of hepatitis. He had been traveling in the tropics and received an injection with a possibly inadequately sterilized needle. Furthermore, he was an allergic individual (as evidenced by a vasomotor rhinitis) and he had received penicillin on two occasions as well as large amounts of aureomycin. In this connection, Hanger and Gutman2 have called attention to drug sensitization (arsenicals) as a possible factor in the causation of cholangiolitic hepatitis.

I therefore favor the diagnosis of cholangiolitic hepatitis. While it is impossible to rule out the presence of carcinoma at the junction of the hepatic ducts, the rarity of this lesion puts it distinctly in second place.

Why did he have renal “shut-down” and uremia postoperatively? It must be remembered that the operation lasted four hours, that the common duct was opened and probed and that a careful exploration was carried out. Patients with severe disease of the liver are less likely to tolerate prolonged anesthesia and lengthy surgical procedures. Moreover, they are often susceptible to postoperative shock. I suspect therefore that the renal failure was due to acute tubular necrosis (“lower nephron nephropathy”).

My clinical diagnoses are: 1. Cholangiolitic hepatitis. 2. Acute tubular necrosis.

Autopsy

Dr. Flynn: At the time of autopsy, the main anatomic lesions were present in three organs: the liver, the pancreas and the kidneys. The other viscera, including the brain, showed no significant abnormalities.

We shall begin first with the liver. It was grossly normal. There was no intrahepatic biliary obstruction and there was no extrahepatic biliary obstruction. You will recall that the surgeon thought an intrahepatic biliary obstruction might have existed. Actually, the difficulty the surgeon had in probing the duct, was related to the early bifurcation of the somewhat-smaller-than-normal intrahepatic bile ducts. The severe jaundice the patient had was related to a hepatitis; a hepatitis that was obviously present in the original biopsy, but which was not properly diagnosed at that time, because the pathologist was swayed by the belief that the surgeon had found an intrahepatic biliary obstruction.

You will recall that a hepatitis of viral origin is sometimes divided into two types: the hepatocellular, and the cholangitic or cholangiolitic.3 These two types differ clinically as well as anatomically. The hepatocellular type commonly involves the liver cords, usually in the center of the lobule, whereas the cholangitic type involves the portal canals and occasionally, to some extent, the periportal hepatic tissue. Figure 1 shows the microscopic appearance of the biopsy of the liver. Near the center of the photograph is an area of necrosis. These areas were numerous but fairly small and would not in themselves explain the severe clinical findings of liver damage. However, there was also a cholangitic involvement. Figure 2 shows the low-power appearance of the liver biopsy. It is obvious that the portal canal is edematous and heavily infiltrated by inflammatory cells. The cholangitic lesion helps to explain the severe jaundice because of the reduction in the width of the bile ducts. Although it is not well appreciated, a slight reduction in the width of the biliary tree enormously retards the rate of flow of bile. It will be recalled that the expression for the rate of flow of liquid in a capillary is given by the formula

\[ Q = \frac{\pi R^4 P}{8VL} \]

where \( Q \) is the rate of flow, \( R \) is the radius, \( P \) is the pressure, \( V \) is the viscosity and \( L \) is the length. In this formula the fourth power relationship of the radius is very important. For example, if the lumen of a bile duct had a radius of 1.0 mm., then \( R^4 \) is 1.0. If the lumen were reduced in size to a radius of 0.5 mm., then \( R^4 \) will be 0.0625. Obviously, as the numerator of this equation becomes smaller, the rate of flow \( (Q) \) is reduced.
Fig. 1. A section of liver biopsy showing focal necrosis and an inflammatory cell infiltration. These changes are most marked in the center of the field. The space on the right is the lumen of a small hepatic vein.

Fig. 2. This section of the liver biopsy includes the portal canal and adjacent parenchyma. The latter is seen at the upper left, upper right and lower left margins. The arrow points to a small compressed bile duct. The cellularity of the portal canal is increased due to the presence of numerous inflammatory cells.
Fig. 3. This is a section of kidney with severe lower nephron nephrosis. The tubular epithelium is markedly necrotic. In addition there is dissolution of the basement membrane of the necrotic tubules and a peritubular inflammatory cell infiltration.

Fig. 4. Passing obliquely across this section of kidney is a distal convoluted tubule. Its lumen contains amorphous fragmented material.
At the time of autopsy, the hepatitis had largely subsided. The patient, however, as you recall, continued to be jaundiced. This was related to another complication: acute hemorrhagic pancreatitis. The incidence of acute hemorrhagic pancreatitis is approximately 0.01 per cent to 0.1 per cent in exploratory celiotomy. When it occurs, the diagnosis is seldom made before death. The pancreatitis was probably due to a variety of factors including trauma to the pancreas, reflux of bile into the pancreatic duct and, possibly, to the jaundice itself. It is known that jaundice predisposes the pancreas to this change, but why it does is not clear. At the time of autopsy, the pancreas was merely a necrotic bag of blood.

In addition to the pancreatitis, there was a severe lower nephron nephrosis. This explains the very severe oliguria and electrolytic changes in the blood that developed terminally. The lower nephron nephrosis was characterized, as it always is, by patchy tubular necrosis, segmental disruption of the basement membrane, and a peritubular inflammatory reaction. Figure 3 shows the microscopic appearance of the kidney. It is obvious that considerable peritubular inflammation is present. Figure 4 indicates that this inflammation is secondary to tubular necrosis. On one side the tubular epithelium is intact and the basement membrane can be identified. On the opposite side the epithelium is necrotic, the basement membrane is segmentally disrupted and the tubular lumen is exposed to the interstitial connective tissue. Within the tubular lumen are desquamated epithelial cells, bile-stained cellular fragments, leukocytes and precipitated material of undetermined origin. At one time the casts were thought to explain the oliguria on the basis of mechanical obstruction. It is now known, as Oliver and his co-workers have pointed out, that this is probably related to decreased glomerular filtration and reduced tubular flow because of a loss of fluid through the necrotic tubular wall. Also, as Oliver and his co-workers pointed out, a lower nephron nephrosis represents an anatomic syndrome that follows renal ischemia. This explains why the lower nephron nephrosis occurs in such a wide variety of conditions, including the transfusion reaction, shock, crush syndrome, and so on. The amount of renal damage following renal ischemia is related in large part to the degree and duration of the ischemia. Characteristically, the necrosis involves the tubules, not the glomeruli. There are at least two reasons for the predilective tendency to involve the tubular epithelium: (1) what blood does reach the kidney supplies the glomerulus first, before it enters the peritubular network to supply the tubule; (2) the tubular epithelium is far more metabolically active than is the glomerulus and is, thus, more sensitive to a reduction of blood flow with the concomitant decrease in local oxygen supply. At any rate, the oxygen consumption of the tubule is considerably higher. It is known, of course, that the renal ischemia may persist long after the condition which produced it has disappeared. This can be demonstrated by catheterization studies. The question remains as to why the ischemia persists. Is it related to compression of the blood vessels by the peritubular edema and inflammatory reaction or is it a more subtle mechanism depending upon some humoral or reflex process?

In summary then, the most likely sequence of events would seem to be, first of all, a viral hepatitis, characterized by hepatocellular and cholangitic components. To rule out a mechanical obstruction, an exploratory celiotomy was done. This was followed by an acute hemorrhagic pancreatitis and a lower nephron nephrosis.

REFERENCES

A Patient with Circulatory Complications Following an Exploratory Celiotomy for Unexplained Jaundice

JOSEPH E. FLYNN and FREDERICK R. BAILEY

Circulation. 1955;12:921-926
doi: 10.1161/01.CIR.12.5.921

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1955 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/12/5/921.citation