THE SO-CALLED HEPATO-RENAL SYNDROME

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SINCE 1924, when Heyd[24, 25] called attention to the unusual postoperative course pursued by some patients after gallbladder surgery, there have appeared many articles on this subject, a careful analysis of which indicates that a few important points have been presented by three or four contributors and that most of the remaining articles contain confirmatory experiences by their authors.

It will be remembered that Heyd in his original and subsequent papers[24 to 29] described a series of postoperative complications other than those which may reasonably be expected, as, for instance, hemorrhage, shock, gastric dilatation and embolism in the first 24 hours, and infection resulting in peritonitis or abscess formation in the succeeding 48 to 72 hours. He divided these unusual cases into three clinical groups:

Group I.—After a simple cholecystectomy in a patient in good general condition and whose preoperative studies have indicated competent renal, cardiac and respiratory function, recovery from the anesthetic is unduly delayed. The patient remains semicomatose for four to six hours, develops a talking delirium, subsultus tendinum, rapidly passes into coma with high temperature and dies.

Group II.—In this group, the patients have had a rather severe form of biliary infection with a history of jaundice and possibly a previous gallbladder operation. Following a choledochotomy with common duct drainage, the postoperative progress seems satisfactory for 36 to 48 hours. The patient then becomes irritable and nervous and passes into a pronounced vasomotor collapse with cold clammy extremities, and death finally supervenes. This clinical course was noted by Heyd in spite of a definitely diminishing jaundice and ample renal function. He considered these cases to be due to the liberation of some pancreatic toxins with inadequate liver protection. These patients did not exhibit alkalosis as did some in Group I.

Group III.—In a series of patients admitted with a clinical picture of calculus cholangeitis, pancreatitis or, rarely, carcinoma of the head of the pancreas, operation was undertaken for the relief of these conditions and included, often, the institution of biliary drainage, either externally, or internally by cholecystogastrostomy. The immediate postoperative course seemed satisfactory. Icterus diminished appreciably and dehydration was overcome. If external biliary drainage was utilized, the patient was refed his own bile. After five or six days, in the presence of a constantly diminishing jaundice,

Submitted for publication March 23, 1937.

these patients became somnolent, and soon passed into a state of coma which ended in death.

Heyd excluded infection as the cause of the syndrome presented in Group III, although his articles contain little mention of autopsy findings. He presented the theory that an increased burden was thrown on an already compromised liver of detoxifying a further increment of poisonous products and that the liver was unable to perform this function, resulting in a progressive exhaustion of liver capacity. In support of this view, he quoted Graham's[15] work which stressed the frequent association of disease of the gallbladder and definite evidence of hepatitis. May we, at this time, call attention to the paper of Colp, Doubilet and Gerber[10] whose findings are at some variance with those of Graham. They performed liver biopsies in 49 cases of acute and chronic cholecystitis with and without jaundice. Studies with finer histologic technic revealed no changes in the liver cells in biliary tract disease without jaundice. Focal liver cell degeneration seen in cases with jaundice represented, in their opinion, a reaction to bile stasis and was in no way related to the primary disease of the gallbladder. They believe that the periportal infiltrations observed in biliary tract disease are not specific of the disease but represent a reaction of the liver to extrahepatic infection. They conclude that hepatitis is not an accompaniment of cholecystitis as evidenced by the absence of inflammatory and parenchymal changes in the liver.

Heyd's observations aroused considerable discussion and there soon appeared a series of communications which more or less corroborated his clinical findings. Boyce and McFetridge[3 to 7] feel that the so-called "liver deaths" after biliary surgery fall into two distinct groups:

Group I.—Death occurs shortly after operation with hyperpyrexia as the outstanding symptom and degenerative changes in the liver the only positive finding at autopsy.

Group II.—Death is deferred for 10 to 14 days when uremic symptoms predominate and postmortem examination reveals the degenerative liver damage plus similar degenerative changes in the convoluted tubules of the kidneys.

They attempted to reproduce these clinical syndromes experimentally, but were successful with Group II only. Using dogs, they ligated the common duct and maintained the obstruction for 18 days. Following release of the obstruction, the clinical picture presented by the cases in Group II was reproduced. Uranalysis and blood chemistry revealed the changes characteristic of an acute renal insufficiency. All the animals died in uremic coma and autopsy revealed the degenerative changes in the liver and kidneys seen in humans.

These authors contend that the release of the biliary obstruction rather than the obstruction itself is responsible for the fatal outcome in some cases of biliary surgery. The hepatic changes present in biliary disease are aggravated in some cases by the surgery instituted to relieve it, which imposes upon an already damaged liver an intolerable burden. This includes anesthesia, surgical trauma, a drop in intra-abdominal temperature and changes in intra-

hepatic and biliary pressure. They state that, as a result of the degenerative hepatic changes, seen also in cases of liver injury, hyperthyroidism, intestinal obstruction and burns, there is released into the circulation a toxic substance which is presumed to be a water-soluble foreign protein. When, after liver function fails, the kidneys take up the function of detoxification, there is resulting damage to their convoluted tubules, through which foreign proteins are excreted. These authors conclude that the hepato-renal syndrome is a single pathologic process of which the kidney disturbance represents the second stage. In view of the fact that most of these cases must, by inference, have a considerable degree of impairment of hepatic function, these authors suggest preoperative renal function tests as an indication of liver function, with the hope that these tests may actually reflect the efficiency of the liver. The same suggestion was made by Wilensky and Colp,[41] in 1927.

On the other hand, the observations of Helwig and Schutz[19] are worthy of note. In those cases coming to autopsy, they were struck with the fact that most of the definite pathologic findings were confined to the liver and kidneys. The liver usually appeared enlarged, presented fatty degeneration, cloudy swelling and polymorphonuclear leukocytic infiltrations with focal hemorrhages and parenchymatous cell necrosis. The kidneys were usually enlarged. Histologically, there was evident necrosis of the tubular epithelium. On the basis of the clinical course of a patient who received a laceration of the liver in an automobile accident and who developed symptoms identical with those under discussion and, also, because of the report of a similar instance of liver trauma by Furtwaengler, Helwig and Schutz conducted a series of experiments on dogs which consisted essentially of pulpification of most of the liver. Those animals that died within 12 hours from hemorrhage and shock were found to have albumin, casts and red blood cells in the urine. Those that survived the operation showed a rise in blood nitrogen, albumin, casts and red blood cells in the urine and progressive oliguria. In the first group, autopsy disclosed degeneration of the kidney epithelium and hemorrhagic necrosis of the liver. In another series of experiments, the same results were obtained by ligation of the hepatic artery which caused primarily a liver necrosis.

The clinical behavior in these traumatic cases and their similarity, both clinically and at necropsy, to those described by Heyd and others, have led these authors to assume that liver damage, whether traumatic or infectious in origin, produces a selective toxin which may severely damage the kidneys. In view of the fact that this syndrome has always followed damage to the liver and has occurred in individuals with previously normal kidneys (determined by kidney function tests), they believe that the pathologic changes in the kidney are secondary to the liver changes and are dependent upon a specific toxin elaborated in the course of liver cell destruction.

Our interest in this mysterious syndrome was recently intensified by the clinical course and subsequent pathologic studies of a patient who was operated upon for calculus gallbladder and bile duct disease. We believe that this case is of considerable importance: First, because of the careful studies conducted

both before and after operation; and second, because the autopsy findings are at such variance with those reported in the literature on the subject.

Case Report.—Hosp. No. 375648: R. B., white, female, married, age 54, was admitted to the Mt. Sinai Hospital January 14, 1935. Her personal, family, and past histories were irrelevant. Her present illness began two years before admission, with pain in the right upper quadrant which radiated around to the back. The pain was always related to the ingestion of fatty foods. These symptoms occurred only rarely after a self-imposed fat restricted diet. During the period of her present illness she had lost 30 pounds in weight. She also suffered from generalized pruritis and was told she was a diabetic. During the year prior to admission, and especially in the latter half, she experienced frequent attacks of abdominal pain associated with jaundice, fever, and occasional chills. The last episode of jaundice occurred one week before admission to the hospital. At no time was the jaundice pronounced. With the subsidence of the pain the jaundice rapidly disappeared.

Physical Examination disclosed a moderately obese woman whose skin presented a yellowish color. The conjunctivae and sclerae, however, were not icteric. There was a herpes simplex on the upper lip. Her heart and lungs were negative. The abdomen was soft not distended. There was tenderness in the right upper quadrant and epigastrium, and a mass which was thought to be gallbladder was palpable as far as the umbilical line. There was no evidence of ascites. Oral cholecystography failed to visualize the gallbladder. No evidences of gallstones were seen. The clinical diagnosis on admission was chronic cholecystitis and cholelithiasis with hydrops of the gallbladder.

Laboratory Data: Hemoglobin 90 per cent; white blood cells 9,000, of which 68 per cent were polymorphonuclear neutrophiles, 26 per cent lymphocytes, 4 per cent monocytes, and 2 per cent eosinophiles. The blood smear appeared normal. The stools were colored and contained bile and urobilin. Guaiac test for occult blood was faintly positive. The urine was always negative for sugar, acetone, and diacetic acid. The specific gravity varied from 1016 to 1020: albumin negative. Microscopic examination negative. On three occasions before operation, bile in the urine was reported 1 plus. Urobilin on four occasions was present 1:20. The Janney test for glucose tolerance evoked a normal response. The blood Wassermann was negative. Blood chemistry studies revealed the following:

Urea nitrogen:	9 mg. per 100 cc.
Sugar:	110 mg. per 100 cc.
Cholesterol:	275 mg. per 100 cc.
Cholesterol ester:	145 mg. per 100 cc.
Icteric index:	15
van den Bergh:	direct—faint delayed positive, indirect—1:250,000, Mg. 0.4

The electrocardiogram showed no definite abnormality. Blood pressure 100/64.

Operation: January 22, 1935, eight days after admission (J. H. G.). Spinal anesthesia was employed, using 120 mg. of neocaine. An upper right rectus incision was made. Some difficulty was encountered in entering the peritoneal cavity because of rather extensive adhesions. The great omentum was adherent to the parietal peritoneum. The liver edge was obliterated by adhesions which anchored it to the costal margin. After combined blunt and sharp dissection, the stomach, duodenum, and colon were finally separated from the under surface of the liver. The latter structure was freed from the costal margin. The liver was slightly enlarged, normal in appearance, with a slightly rounded anterior edge. The gallbladder was small and shrunken and contained a few stones. Further exploration showed an unusual condition of the common and hepatic ducts. The duct system, which was easily brought to view through its entire extent, was found to be enormously dilated. The common duct was fully two inches in diameter. Each hepatic duct measured about one inch in diameter. The entire common duct down to the ampulla of Vater and both hepatic ducts as far as their tertiary divisions were

filled with biliary calculi. A vertical incision was made in the common duct about two inches above the duodenum and through which 48 calculi of various sizes and shapes were removed. The duct system was irrigated. A free flow of yellow bile followed the removal of the calculi. A subserous cholecystectomy was performed. The liver bed was sewn over. A No. 22 French catheter was placed in the common duct and the remainder of the incision in the duct sutured snugly around the tube. Two cigarette drains were placed down to Morrison's pouch and the wound closed in layers. Time of operation: One hour and five minutes.

Postoperative Course: There was no variation in the blood pressure postoperatively.

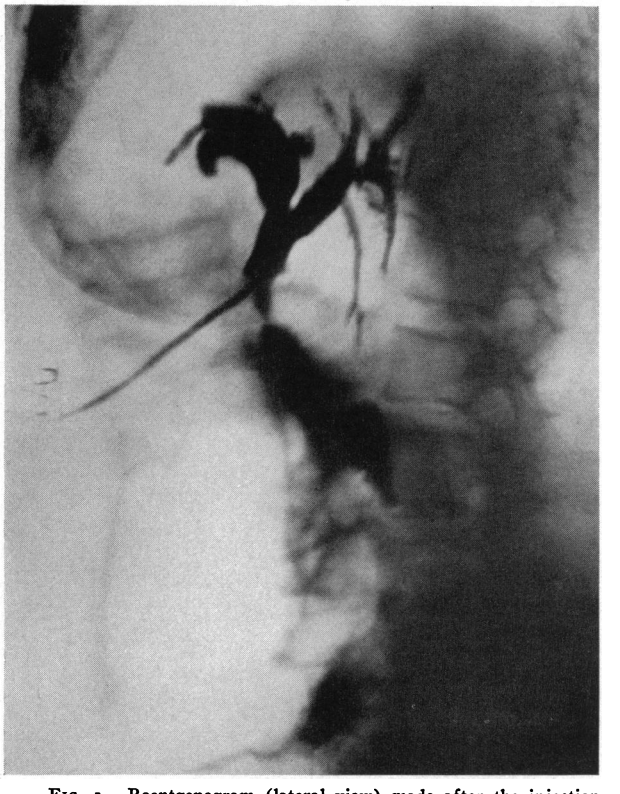

FIG. 1.—Roentgenogram (lateral view) made after the injection of lipiodol through the choledochostomy showing the enormous dilatation of the bile ducts.

First Postoperative Day: Hemoglobin, 93 per cent. Temperature, 101.2° F. Patient comfortable. No distention. Profuse drainage of bile through common duct tube.

Second Postoperative Day: Urine negative for bile and urobilin. Icteric index, 20. van den Bergh: direct—prompt positive. Indirect—1:100,000 Mg. 1.0.

Third Postoperative Day: Urine negative for bile. Urobilin 1:10. Roentgenologic examination was made after injection of lipiodol into the common duct drainage tube. This showed the biliary radicals to be irregularly outlined. There was marked dilatation of the hepatic and common ducts (Fig. 1). No evidence of obstruction and nothing to suggest the presence of stones. Temperature 101.8° F. Wound clean. No cough or chest pain. Abdomen soft. Condition excellent.

Fourth Postoperative Day: Roentgenologic examination 24 hours after the lipiodol injection showed a small amount of opaque material still present in the biliary system. The common duct was completely empty.

Fifth Postoperative Day: It was noted that the patient presented marked asthenia. Had drained about 15 ounces of bile daily since operation. The asthenia was thought to be due to long standing chronic prancreatic and intermittent biliary obstruction plus the recent loss of bile and pancreatic ferments through the common duct tube. For this reason the refeeding of the drained bile was instituted. This was continued until two days before death. The wound appeared clean. Blood count: white blood cells, 14,650; polymorphonuclear leukocytes, 72 per cent; lymphocytes, 10 per cent; monocytes, 16 per cent; eosinophiles, 1 per cent; basophiles, 1 per cent.

Sixth Postoperative Day: Temperature, 100.4° F. Wound edges reddened and puffed. The skin sutures were removed and about one ounce of thick sanguinopurulent material was evacuated from the upper and lower angles. A smear of this material showed a moderate amount of pus cells and debris, but no organisms. The culture, however, revealed *B. coli*, enterococcus and *Staphylococcus albus*. The chest was clear; the abdomen was soft and not distended. Marked asthenia persisted. Bile was being refed by mouth. Hemoglobin, 75 per cent; blood pressure, 100/72. Patient was given a transfusion of 500 cc. by the citrate method.

Seventh Postoperative Day: Hemoglobin, 90 per cent; white blood cells, 15,900; 90 per cent polymorphonuclear leukocytes; lymphocytes, 4 per cent; monocytes, 6 per cent. Urine, bile negative; urobilin 1:5.

Eighth Postoperative Day: Patient appeared profoundly asthenic. Eyes sunken, conjunctivae injected, voice subdued and monotonous, and reaction to stimuli sluggish; beginning to ooze blood from the wound. There was no icterus. The clinical condition was ascribed to either hepatic or pancreatic insufficiency. However, because of apparent tenderness on pressure over the right lower chest near the axillary region, the possibility of a subphrenic infection or an abscess of the liver was considered. Consequently, aspiration was performed. Liver blood was obtained, which was negative upon culture. Because of the oozing of blood from the wound, the packing was removed to facilitate investigation. The wound surfaces were found separated down to the peritoneum with hemorrhage coming from several small vessels and oozing from the entire wound surface. The vessels were ligated and the wound was packed. Urine was negative for sugar, acetone and bile. Blood calcium 9.7 mg. per 100 cc. Hemoglobin 72 per cent. Patient given 500 cc. of blood by the citrate method. Blood urea nitrogen 69 mg. per 100 cc.

Ninth Postoperative Day: Blood urea nitrogen rose to 105 mg. per 100 cc. Urine, cloudy, acid, sp. gr., 1018, albumin 2 plus, sugar and bile negative, urobilin present in 1:5 dilution. Hemoglobin 88 per cent, white blood cells 28,000; 88 per cent polymorphonuclear neutrophiles, and 8 per cent lymphocytes. General condition seemed slightly improved.

Tenth Postoperative Day: Urine, cloudy, acid, sp. gr., 1010; albumin 1 plus. Microscopic examination showed a few white blood cells, very few red blood cells, and epithelial cells. Culture of urine revealed *B.* coli and the enterococcus. The biliary drainage which was still profuse, was slightly positive for diastase and trypsin. Blood chemistry determinations were as follows:

Cholesterol:	200 mg. per 100 cc.
Cholesterol ester:	105 mg. per 100 cc.
Total protein:	6.4%
Albumin:	3.9%
Globulin:	2.5%
Carbon dioxide:	44 volumes per cent
Urea nitrogen:	76 mg. per 100 cc.
Sugar:	195 mg. per 100 cc.
Chlorides:	535 mg. per 100 cc.
Uric acid:	4.0 mg. per 100 cc.
Creatinine:	3.5 mg. per 100 cc.
Icteric index:	17

Eleventh Postoperative Day: Patient's condition became grave. Seemed stuporous and could be aroused only with great difficulty. Pulse weak and rapid. Blood pressure 90/60. The course was progressively down hill. Several foci of local infection were now present: (1) The wound; (2) a gangrenous patch on the anterior wall of the vagina; (3) a right parotitis. Blood culture, negative. Hemoglobin, 88 per cent; red blood cells, 4,810,000, platelets 240,000; white blood cells, 38,700; polymorphonuclear neutrophiles, 85 per cent, of which there were 15 per cent with segmented nuclei and 70 per cent non-segmented; lymphocytes, 6 per cent; monocytes, 9 per cent; reticulocytes, 0.5 per cent. Blood volume studies:

Relative cell volume:	38%
Serum volume:	3,500 cc.
Cell volume:	2,140 cc.
Total blood volume:	5,640 cc.
Blood volume per kilo:	85 cc.

She had been receiving liver extract intramuscularly, two cubic centimeters twice daily.

Twelfth Postoperative Day: Urine, sp. gr., 1012, albumin 2 plus, bile negative, urobilin 1:20, occasional erythrocytes and clumps of leukocytes seen microscopically. Blood urea 90 mg. per 100 cc., cholesterol 180 mg., serum calcium 9.6 mg., chlorides 510 mg. Stool examination, tan color, urobilin present. Guaiac test positive for occult blood. Icteric index 30. A note by the medical consultant read: "From the history and the operative findings, there is every reason to believe that this patient had a very badly damaged liver parenchyma before operation. I believe that the postoperative asthenia is probably due largely to liver insufficiency, perhaps combined with pancreatic insufficiency, and that the nitrogen retention is the result of the prolonged low blood pressure. The blood pressure at the time of examination was 74/46, just barely sufficient to maintain a minimal amount of kidney function."

Thirteenth Postoperative Day: Blood chemistry:

Urea nitrogen:	114 mg. per 100 cc.
Creatinine:	3 mg. per 100 cc.
Cholesterol:	160 mg. per 100 cc.
Calcium:	8.7 mg. per 100 cc.
Phosphorus:	3.9 mg. per 100 cc.
Chlorides:	575 mg. per 100 cc.
Carbon dioxide:	34.5 volumes per cent
Total protein:	5.6%
Albumin:	3.4%
Globulin:	2.2%
Icteric index:	30
van den Bergh:	direct—Prompt positive, indirect—1:60,000, mg. 1.5

Oozing from the wound continued from the eighth postoperative day. Tonight patient had a profuse epistaxis. Pulse gradually became weaker and the patient died with a terminal temperature of 107.4° F. (Table I.)

Postmortem Examination: The body was that of a pale, well-developed, well-nourished female of 54. The skin was light yellow, but the sclerae were not icteric. An incision into the subcutaneous tissues in the left upper margin of the wound disclosed white turbid fluid exuding from the fat. The peritoneum was everywhere smooth and glistening. There was no free fluid in the abdominal cavity. Several small areas of bronchopneumonia were present in the left lower lobe. There was a small blackish-red ulcer on the anterior vaginal wall just inside the labia minora. The stomach was dilated and filled with a large amount of bloody fluid. The gastric mucosa was pink and congested. On the anterior

TABLE I

SUMMARY OF THE POSTOPERATIVE TEMPERATURE, PULSE, BILIARY DRAINAGE, FLUID INTAKE AND URINARY OUTPUT

Date	Pulse	Temperature	Urinary Output	Biliary Drainage	Fluid Intake By Mouth	Fluid Intake Intravenous
Jan. 22 (oper.)	88	100° F.		12 ounces	54 ounces	
Jan. 23 (1st p.o. day)	100	102° F.	33 ounces	10 "	65 "	
Jan. 24	110	101° F.	57 "	10 "	72 "	
Jan. 25	100	101.6° F.	65 "	10 "	58 "	
Jan. 26	100	101° F.	38 "	7 "	80 "	
Jan. 27	100	100.8° F.	48 "	10 "	74 "	
Jan. 28	112	100.4° F.	30 "	5 "	42 "	
Jan. 29	104	100.2° F.	22 "	4 "	40 "	
Jan. 30	122	102.8° F.	Incontinent	3 "	Nothing p.o.	10 ounces
Jan. 31	130	Chill 106.8° F.	"	10 ounces	38 "	25 "
Feb. 1	126	101.2° to 104.2° F.	"	Profuse	40 "	96 "
Feb. 2	120	104° F.	14 ounces	?	4 "	71.5 "
Feb. 3	120	104° F.	18 "	?		58.3 "
Feb. 4	120–160	Died 107.4° F.		?		

wall near the lesser curvature was a small superficial erosion 0.5 cm. long. There were also many tiny homogeneous red areas. The duodenum, small intestine, colon and rectum were congested and filled with bloody contents. The pancreas was moderately fatty. The pancreatic duct was slightly dilated and opened into the common duct 1 Mm. above the papilla of Vater.

The liver weighed 2,165 Gm. The anterior and superior surfaces were adherent to the diaphragm. The capsule was covered by fibrous adhesions. The organ was firm and its inferior edge was sharp. On section, the surface was pale and grayish-green. The lobular structure could be identified. The bile ducts in the larger portal fields were thickened and contained turbid yellow-brown bile. On the anterior surface of the liver in the region of the gallbladder fossa there was a white cylindrical prominence, which, on section, was found to be a thick-walled channel filled with turbid milky fluid. This channel was found to communicate with the bile ducts. The gallbladder fossa was clean. In the floor of the walled-off drainage tract a longitudinal opening into the common duct was present. The common bile duct was distended to 2 cm. in diameter and contained a small amount of bloody mucus. The mucosa was thickened and red. The duct opened into the duodenum by a patent orifice. The common bile duct, traced upward, was distended throughout and became continuous with the two distended, thickened, congested hepatic ducts. The intrahepatic bile ducts were dilated throughout. There were no stones in any of the biliary ducts.

The kidneys weighed 360 Gm. together. They were of equal size and flabby. The capsules stripped with ease, leaving a smooth grayish-yellow surface. The cut surface presented a somewhat widened cortex which was jaundiced. The markings within it were fairly well delineated. The corticomedullary demarcation was sharp. The pelves were congested. The ureters were narrow and pale. The renal arteries and veins were smooth and clear.

Microscopic Examination.—Kidneys: The capsule was thin. The general architecture of the kidney appeared unchanged. The convoluted tubules of the cortex were, in general,

of normal size and width. In some areas, they were closely approximated; in other places, however, they appeared separated by a widening of the intertubular stroma which was spongy and frequently infiltrated with lymphocytes, occasional polymorphonuclear leukocytes and rare plasma cells. The intertubular capillaries, for the most part, contained few red blood cells; in places, however, they were congested. The walls of the interlobular arteries were normal. The afferent arterioles occasionally showed slight hyalinization. The lumen of the convoluted tubules frequently contained granular masses, occasionally desquamated epithelial cells. The epithelial lining of the convoluted tubules did not show striking changes. However, on close examination, one quite frequently found the epithelial cells vacuolated, with occasional loss of nuclei. Some of them contained yellowish-brown material, which was apparently bile pigment. Some of the tubules presented a flattened epithelium, and such tubules contained a few polymorphonuclear leukocytes. Only rarely were tubules found where the epithelium showed more severe degenerative changes, such as hyaline droplet degeneration.

The majority of the glomeruli were well preserved; only a very few were fibrotic.

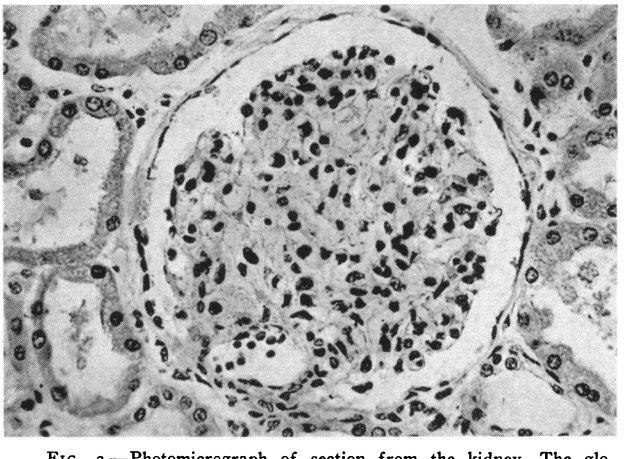

FIG. 2.—Photomicrograph of section from the kidney. The glomerulus is enlarged, and the intercapillary stroma is prominent and spongy as if distended with fluid.

In the vicinity of such fibrotic glomeruli the tubules were atrophic, the stroma increased and infiltrated with lymphocytes. Most of the glomeruli were strikingly large. Their capsules were not thickened; the parietal epithelial cells were flattened; in general, Bowman's space was empty. In spite of the striking size of the malpighian corpuscles, there was no increase in their cellularity. The covering epithelial cells of the tufts were not enlarged, neither were the endothelial cells unduly prominent. The capillaries contained a normal amount of red blood cells and only occasional leukocytes. The intercapillary connective tissue framework (Zimmermann[42]) was prominent and it appeared spongy, as if distended by fluid (Fig. 2).

The medulla of the kidney showed frequent nests of lymphocytes, plasma cells and infrequent polymorphonuclear leukocytes within the stroma. The Henle's loops contained inspissated homogeneous material and occasional leukocytes. Bile stained casts were seen and occasional granular and hyaline cylinders. Very infrequently, round calcified masses were noted enclosed within the lumen. In one area where the medulla bordered on the peripelvic connective tissue and fat tissue there was a hemorrhage, and some of the adjacent tubules contained blood. One section showed a large hemorrhage beneath the pelvic epithelium extending into the peripelvic fat tissue. Around this hemorrhage there was considerable infiltration with polymorphonuclear leukocytes.

Liver: The capsule was thin. The lobular structure was distinct and intact. The

periportal connective tissue seemed markedly increased. The central veins contained but little blood. The liver cells about the central veins appeared somewhat shrunken and contained some yellowish-brown granular pigment. The sinus walls and Kupffer cells were separated from the liver cords, forming appreciable Disse spaces. The latter contained much granular débris, rarely a red blood cell. In places, large amounts of bile pigment were contained within vacuolated, swollen, or shrunken liver cells, surrounded or compressed by fibrous tissue from the portal fields. The latter were much enlarged by fibrous tissue and infiltration with inflammatory cells consisting mainly of lymphocytes, some plasma cells and polymorphonuclear leukocytes (Fig. 3). The bile ducts within the portal fields were increased in number. In some of the bile ducts there were polymorphonuclear leukocytes between the epithelial cells. The portal veins and hepatic artery presented no changes. A section of a large bile duct slightly removed from the region of the hilus showed an edematous wall and infiltration by numerous polymorphonuclear leukocytes, eosinophiles, active phagocytes, and fibroblasts. There was hemorrhage into some of the

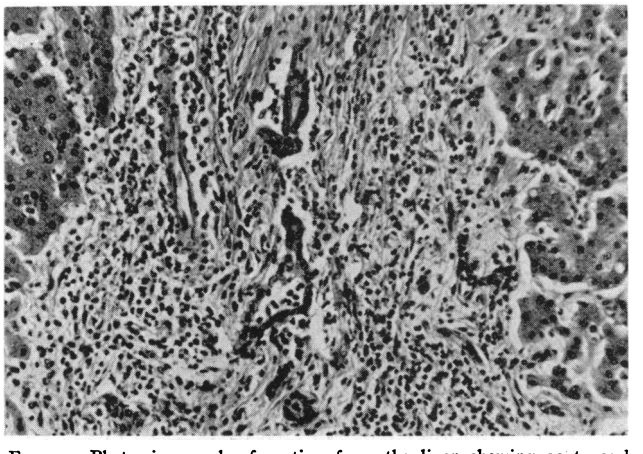

FIG. 3.—Photomicrograph of section from the liver showing acute and chronic cholangeitis.

liver cords abutting upon this duct and some hemorrhage into the wall of the duct. There was much bile pigment in the cells about the portal fields. Throughout the sections, there was no evidence of liver cell necrosis.

SUMMARY: The liver showed the pathologic picture of an acute and chronic cholangeitis and cholangeiolitis with icterus. There was no evidence of severe parenchymal damage.

The kidneys showed focal interstitial inflammation and edema. There was, however, no evidence of severe degenerative change in the tubular epithelium, but there was a striking glomerular lesion.

Anatomic Diagnosis: Acute and chronic cholangeitis. Acute intercapillary glomerulonephritis (MacCallum[32]). Jaundice (slight). Gastric erosions. Vaginal ulcer. Bronchopneumonia, left lower lobe. Pulmonary edema and congestion. Mild parenchymatous degeneration of the liver, heart and kidneys. Acute congestion of the spleen. Fibrous pleural adhesions.

Discussion: Concerning the cases in Group I of Heyd's classification, namely, those characterized by hyperpyrexia and death within 48 hours of operation, considerable disagreement and controversy already exist. Thus,

Touroff,[38] in a recent communication, is rightfully cautious against entertaining a diagnosis of "liver shock," unless there has been a corroborative complete postmortem examination. He reviewed a series of cases from the Mt. Sinai Hospital that were subjected to simple cholecystectomy with drainage. The patients were neither jaundiced nor acutely ill at the time of the operation and had not been subjected to any previous operative procedure on the biliary tract. Without apparent cause, they developed the classic picture of rapidly rising temperature, shock and early death. In a number of instances, the clinical diagnosis of "liver shock" was entertained, yet careful postmortem examination revealed a previously unrecognized intra-abdominal or pulmonary infection to explain the whole picture.

On the other hand, the experiences of the senior author (J. H. G.) 12 or 13 years ago at the old New York Hospital came to mind and those records were recently reviewed in order to corroborate the impression gained at that time. On the Second Surgical Division, in those days, many cases of acute cholecystitis were treated as emergencies, as is being advocated by a number of surgeons at the present time. A group of the patients so treated developed the typical picture under discussion and died within 48 hours with hyperpyrexia as the outstanding symptom. Yet, careful postmortem examination, in two instances, failed to reveal the cause of death. There was not the slightest evidence of infection and the liver sections showed only occasional periportal accumulations of polymorphonuclear leukocytes. These cases were disconcertingly puzzling at the time and the thought was entertained that a profound physiologic or chemical change had taken place which could not be determined by any known clinical or laboratory methods. Since then, as far as we know, nothing of any importance has developed to throw light on this obscure picture.

The various clinical and pathologic aspects of the so-called "hepato-renal" syndrome, as reported in the literature, deserve careful consideration, in the light of the case reported herewith. Many of the reported instances of "hepato-renal" syndrome are based on clinical grounds only and lack corroborative autopsy findings. Those reports that include postmortem examinations present a curious lack of uniformity of the pathologic picture. Certainly, the degree and extent of the degenerative changes encountered in the liver and kidneys vary considerably. Why should one patient present minimal postmortem findings while another, with the identical clinical picture, exhibits extensive degenerative changes? This considerable variation in the degree and extent of the pathologic findings suggests to us a possible explanation. It seems possible that many of these patients have some degree of kidney damage before the surgical attack on the biliary system and that their margin of safety from the standpoint of kidney reserve is indeed small. This impairment may not be apparent before operation or may not be demonstrable by any known laboratory methods. Following the procedure on the diseased biliary tract, with its associated surgical trauma and the greatly altered physiology that must necessarily follow, the already impaired kidneys are unable to cope with the

additional load thrown upon them and soon break down completely. Certainly, the clinical picture with the relatively free interval of five to ten days after operation is suggestive confirmation of this thought. It must not be forgotten, too, that the same syndrome has been known to follow operations upon the gastro-intestinal tract and also, after extensive cutaneous burns, conditions known to be closely linked with disturbances of protein metabolism.

There is another group of patients who develop the typical so-called "hepato-renal" syndrome and, yet, the findings at autopsy are minimal and offer no anatomic explanation of the cause of death. Doctor Klemperer, pathologist at Mt. Sinai Hospital, has given the case herewith reported considerable study and thought, and he feels very definitely that the slight parenchymatous degeneration of the liver and kidneys found at necropsy is insufficient to explain the cause of death. Certainly, the liver sections aside from the cholangeitis show nothing of great moment, and the reason for the hemorrhages from the mucous membrane surfaces cannot be demonstrated. In reviewing the sections of the kidneys, however, one is impressed by the peculiar appearance of the glomeruli. Most of them are strikingly large without any cellular increase. The intercapillary connective tissue framework (Zimmermann) is prominent and appears spongy, as if distended by fluid (Fig. 2). The term "serous glomerulitis" is suggested to describe this feature. A similar finding has been described by W. G. MacCallum.[32] In reviewing the kidney sections of hundreds of cases showing glomerular changes in a series of about 5,000 autopsies, he noted a peculiar exudation into the glomeruli of patients dying of an acute illness, which resulted in toxic injury to the kidneys. The most striking feature was the distension of the lobules of the glomeruli into a club shape by an exudate which separated the capillaries from one another and from the overlying basement membrane. The latter structure was stretched and smooth and widely separated from the underlying capillaries. His illustration of this condition strongly resembles that presented by the kidneys in our case. In other cases, where the illness was of longer duration, the lobules were adherent and covered over by a smooth basement membrane, while the capillaries were separated by definitely stainable connective tissue. He concluded that the first picture might very well be interpreted as the initial stage of glomerular injury which goes on, with continuation of the disease process, to the chronic form known to clinicians as glomerulonephritis.

After a critical review of the literature and a careful study of the case reported herewith, we have formed the opinion that no logical or satisfactory explanation of the syndromes originally described by Heyd has as yet been offered. Although thought by many authors to follow surgery of the biliary tract only, these clinical pictures have appeared also in cases of intestinal obstruction, cutaneous burns, *etc.* The lack of uniformity of anatomic changes to explain the cause of death is noteworthy, as is also the variation in the extent of the degenerative changes. We believe that the syndromes under discussion are dependent upon profound chemical changes which we are

unable to definitely determine by the clinical and laboratory methods available at the persent time.

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