Case Report

Chiari's Syndrome: Hepatic Vein Occlusion

A Case of Multiple Venous Thromboses

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FIFTY years ago Chiari[1] described the symptomatology of hepatic vein occlusion. This consists typically of abdominal pain, enlargement of the liver and ascites. The course is usually rapidly fatal but occasionally long drawn out. In Chiari's three cases the pathologic lesion was an obliteration of the hepatic veins which he interpreted as due to an endophlebitis leading progressively to stenosis and occlusion. Since that time the term Chiari's syndrome has come to be applied to hepatic vein occlusion not only by primary endophlebitis but from obstruction of any cause.

Thompson[2] recently has reviewed the clinical and pathologic findings in over 100 cases in the literature. The clinical findings have been fairly constant but the pathology has been varied. The obstruction may be only in the hepatic veins or may involve the inferior vena cava as well. It may be caused by local disease such as abscess or tumor or it may be a manifestation of a general disease process such as thrombosis in polycythemia vera.[3] In many cases, as in those described by Chiari, the obstruction seems to be due to primary disease of the hepatic veins. Even here it may be a local manifestation of a systemic disease for Coronini and Oberson,[4] from careful histologic examination of eleven such cases, found a primary inflammation of veins and capillaries in other organs in addition to the liver.

In the case to be presented here the primary disease was characterized by multiple recurrent thromboses. The predominant pathologic lesion was an hepatic vein thrombosis with obstruction of the inferior vena cava as well. The clinical picture of hepatic vein occlusion was complicated by concurrent endocarditis. The patient's collateral circulation was sufficient to compensate for these lesions until a secondary portal vein thrombosis developed. Terminally there was thrombosis of the renal veins.

CASE REPORT

The patient, T. C., (Goldwater Memorial Hospital, No. 12928), was a young man of Irish extraction, twenty-six years old at the time of his death. He had been a weekend-spree drinker since the age of sixteen but his diet had in general been adequate. He had never had jaundice or other evidence of liver disease. There was no history suggesting nephritis or rheumatism. There had been no exposure to toxic agents other than alcohol. At the age of sixteen he began to have dyspnea and palpitation on exertion. One year later he complained of attacks of pain in the calves of his legs on exertion and occasional swelling of the ankles. On one occasion minor trauma led to marked pain and swelling of the right leg which lasted for two weeks and required several days' rest in bed. At the age of nineteen leg ulcers developed first on the right but later on both legs. These symptoms of ulceration, pain and swelling of the legs, dyspnea and palpitation continued but he was twenty-one before he sought medical advice. During the next three years he received a variety of local treatments for the ulcers with no lasting improvement.

At the end of July, 1946, when he was twenty-

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four years old, he noted malaise and anorexia and began to have evening fever accompanied by shaking chills. The exertional dyspnea and palpitations increased. On about August 1st he began to have gnawing pain in his stomach and back, sometimes severe enough to double him up. There was no accompanying nausea, vomiting or bowel disturbance. He went to his doctor who found an enlarged liver and referred him to another hospital where he was admitted on August 7, 1946. At that time he appeared chronically ill. His temperature was 103°F. on admission. The heart was enlarged. There was an apical systolic murmur, a questionable apical diastolic murmur and also a basal systolic murmur. The abdomen was distended but there were no signs of ascites. The liver and spleen could not be felt but there was tenderness in the right upper quadrant and in the epigastrium. The superficial abdominal vessels were dilated. There were ulcers and edema of both ankles. The red blood cell count was 2.96 million and the hemoglobin was 7.5 gm. per cent. The white count was 9,500 with 78 per cent polymorphonuclears. The urine was normal except for a few white cells. It was thought the patient had rheumatic heart disease and subacute bacterial endocarditis and possibly cirrhosis.

The patient was treated with penicillin at once. The abdominal pain gradually subsided. A week after admission the basal systolic and apical diastolic murmurs were no longer heard. The abdominal signs were unchanged. After three weeks of penicillin therapy and four blood transfusions the patient's temperature, which had risen to about 103° nightly, fell to the range of 99° to 100°. The leg ulcers healed during this time and the patient felt much better. The red count had risen to 3.8 million with hemoglobin of 10.8 gm. The abdominal distention had subsided. The liver was now palpable four finger-breadths below the costal margin. The spleen was not felt. After a week of relatively normal temperatures without penicillin therapy the patient was allowed out of bed. However, the swelling of the ankles and abdomen recurred and there were now definite signs of ascites. The cephalin flocculation test was negative. A diagnostic paracentesis was done with the removal of 350 cc. of fluid which was not remarkable in any way.

At the end of September the patient's fever recurred and penicillin therapy was resumed. During this course a painful bluish spot appeared in the left thenar area, suggestive of an embolus. One definite petechia was noted on the neck. After two weeks of treatment the temperature again fell to normal but penicillin was maintained for a full month after defervescence. The patient now felt almost well although there was still evidence of ascites. The red count rose further to 4.86 million with 11.3 gm. of hemoglobin. There was no recurrence of fever during two further weeks of observation before discharge at the end of November. Numerous blood cultures were taken during his stay; all were sterile. In an attempt to investigate possible causes for the fever other than subacute bacterial endocarditis the following were done, namely, agglutinations for typhoid, paratyphoid A and B, Brucella abortus and Proteus OX19; all were negative. A red cell sickling test was negative. A muscle biopsy was reported to show chronic myositis and intimal thickening of the walls of the medium-sized arterioles but showed no evidence of periarteritis.

The patient was discharged from the hospital considerably improved on November 26, 1946. The diagnosis was Laennec's cirrhosis. There was thought to be insufficient evidence for the diagnosis of endocarditis. The fever was explained on the basis of thrombophlebitis.

The patient's abdomen became swollen again at home and on December 9, 1946, he entered the Presbyterian Hospital, New York. Physical examination showed a normal-sized heart with apical and basal systolic murmurs, a distended abdomen with signs of fluid, an enlarged liver and marked peripheral edema. There were distended veins along the sides of the abdomen running from the inguinal ligaments to the axillas. The blood flow in these vessels was thought to be upward. The red count was 4.34 million with 10 gm. of hemoglobin. The white count was normal. The cephalin flocculation test was 3+. The BSP test showed 15 per cent retention. The serum albumin was 3.8 and the serum globulin 2.7 gm. per cent. The serum alkaline phosphatase was twelve Bodansky units. The urine showed 1+ albumin but was otherwise normal. The blood urea nitrogen was 10 mg. per cent. A phenolsulfonphthalein test showed 70 per cent excretion in two hours. These values were unchanged on repeated determinations.

The clinical picture was thought to suggest inferior vena caval thrombosis rather than Laennec's cirrhosis. In an attempt to confirm

this simultaneous blood sugars were taken from the arm and from an abdominal collateral vein, half an hour after taking 100 gm. of glucose by mouth. If the collaterals were connected with the portal system, their blood should have a higher sugar level than the blood from the arm.[5] Actually the difference was the reverse of this, abdominal vein 111 mg. per cent and arm vein 125 mg. per cent. Venography was attempted on two occasions. Contrast medium was injected by catheter into the saphenous vein near the groin first on one side and then the other. In each case the catheter could not be introduced beyond the saphenofemoral junction. Dye was not seen by x-ray in the femoral-iliac-caval system but passed readily into the abdominal collaterals. The results were interpreted as showing a block in the femoral veins.

During his stay at the Presbyterian Hospital the patient's course was marked by fairly rapid accumulation of ascites. Four paracenteses were done. The patient was comfortable except when ascites was marked and he had a good appetite. In late December, 1946, and early January, 1947, he had a temperature of 101°F. to 102° for which no cause could be found. This returned to normal on symptomatic treatment. The patient was transferred to Goldwater Memorial Hospital on February 10, 1947, for long term care.

The sudden onset of abdominal swelling with pain and the type of abdominal collateral circulation suggested the diagnosis of inferior vena caval thrombosis. The differential blood sugars and the venograms were thought to support this diagnosis. It was believed that the 3+ cephalin-flocculation test pointed to liver disease over and above that which might be produced by congestion of the liver from inferior vena caval block or even from hepatic vein thrombosis.

On admission to Goldwater Memorial Hospital the patient looked thin and pale but had no complaints. The heart was not enlarged and only an apical systolic murmur could be heard. The abdomen was moderately distended with fluid and presented the previously described dilated veins. The liver was enlarged four finger-breadths below the costal margin and was slightly tender. For the first time the spleen was palpable two fingerbreadths below the rib margin. The legs showed brown pigmentation and brawny edema. The red cell count was 4.4 million with 13 gm. of hemoglobin. The white count showed a mild leucopenia. The urine contained 2+ albumin with occasional white cells and casts. The blood urea nitrogen was 17 mg. per cent. A phenolsulfonphthalein test showed 85 per cent excretion in two hours. The antistreptolysin titer was 250. The serum albumin was 4.4 gm. per cent, serum globulin 2.5 gm. per cent. The total cholesterol was 138 mg. per cent with cholesterol esters of 88 mg. per cent. A BSP test showed 15 per cent retention in thirty minutes. The cephalin-flocculation test was 4+. The prothrombin time was twenty-seven seconds. The bleeding time was four minutes and the clotting time twenty-five minutes. The platelet count was 150,000 per cu. mm. A capillary fragility test was markedly positive.

The diagnosis of thrombosis of the inferior vena cava was accepted. Whether the ascites and changes in the serum indicative of liver damage were due to hepatic vein occlusion or to cirrhosis was not decided. The cause of thrombosis in the face of prolonged prothrombin and clotting times and low platelet count was not clear. The patient was given intramuscular mercurial diuretics with a very good response. Over a period of four and a half months the accumulation of ascitic fluid was completely controlled without paracentesis. At that time peripheral edema had disappeared and accumulation of ascites had stopped. Some abdominal fluid remained but this disappeared in another three months. This improvement took place without significant change in any of the laboratory findings except for a return of the capillary fragility test to normal. By the end of 1947 the patient looked and felt almost well. The enlarged liver and spleen and the abdominal collateral veins persisted. There was no ascites or edema. The albuminuria had disappeared. Disturbing factors were a drop in the red count to 3.3 million with 10.4 gm. of hemoglobin and a fall of the serum albumin to 3.4 gm. per cent.

In January and February, 1948, there was a slow gain in weight as edema and ascites reappeared. At the end of February thrombophlebitis of the left leg suddenly developed in the patient, with pain, redness, swelling and high fever. This was treated with penicillin, sulfadiazine and heparin. It responded only partially to treatment and continued to smolder for the next three months. Several acute flare-ups were treated again with sulfadiazine and heparin without noticeable effect on the basic process. During these attacks the prothrombin time was

prolonged, as before, but the clotting time had returned to normal.

Mercurial diuretics were administered again in March, 1947, and were effective in controlling fluid retention for about six weeks. In May, however, two paracenteses were necessary. The patient appeared to be losing flesh rapidly at this time and after the third paracentesis at the end of June his weight was 25 pounds below that of six months before when no ascites or edema was present. His serum albumin had fallen to 2.5 gm. per cent without any other significant change in the blood. The liver was now a little larger and quite tender.

A fourth tap was done in the middle of July. Mercurial diuretics were discontinued at this time because they were ineffectual. Two days after this tap the patient went into a stupor, with nausea, vomiting and oliguria. The urine showed 2+ albumin with many red cells, white cells and casts. The blood urea nitrogen was 59 mg. per cent. It was thought that this episode probably represented an extension of the caval thrombosis to involve the renal veins but on the possibility that it might be due to mercury poisoning from the diuretic administered a course of BAL was given. The patient was maintained on intravenous fluids and during the next week the stupor lightened partially, vomiting stopped and urine output increased. He complained frequently of pain in the lumbar region. The blood urea nitrogen rose reaching a value of 144 mg. per cent. The patient continued in this state for four weeks more but eventually lapsed into coma, pulmonary edema developed and the patient died on August 27, 1948.

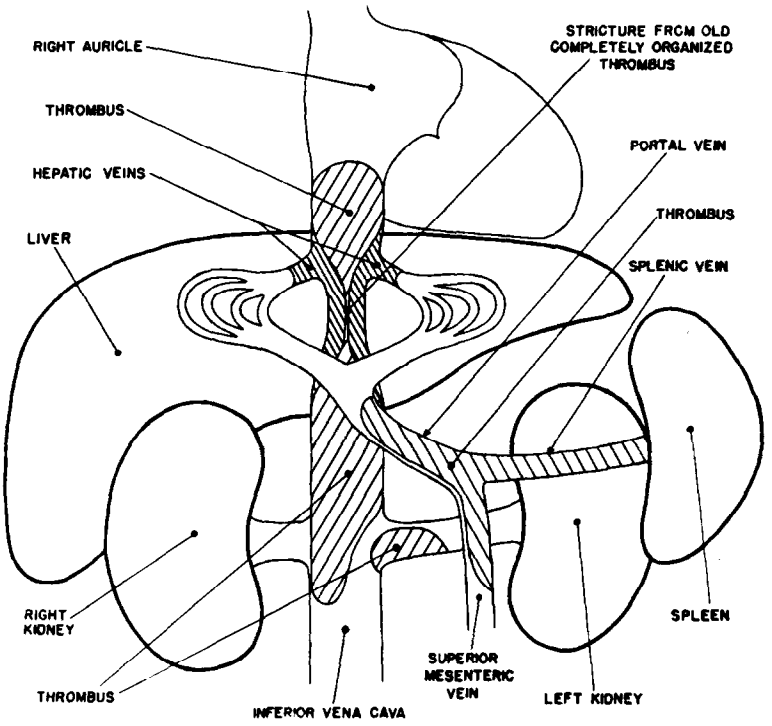

FIG. 1. Diagram of venous thromboses in the abdomen.

The clinical diagnosis was thrombosis of the inferior vena cava, with extension to the renal veins, thrombosis of the hepatic veins, and cirrhosis of the liver.

At autopsy the abdomen was markedly distended, containing about 12 L. of fluid. The inferior vena cava, the iliac, hypogastric and femoral veins were greatly dilated. Permission to explore vessels in the lower extremities was not granted. From about 5 cm. above the confluence a large, well organized thrombus filled the lumen of the cava. (Fig. 1.) This obstructed but did not occlude the renal veins. The thrombus extended upward to a point 3 cm. above the right renal vein. Here the cava was transformed into a small, cord-like structure with a lumen scarcely 3 mm. across. The orifices of the hepatic veins were lost in this scar tissue. The

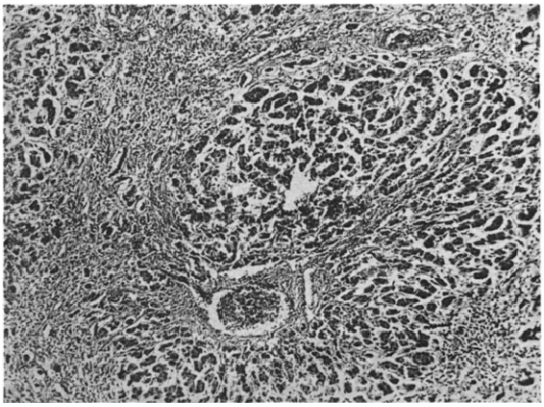

FIG. 2. Liver lobule showing both portal and central cirrhosis. Radially arranged fibrous tissue strands extend from the thick-walled central vein to join the periportal connective tissue bands; hematoxylin and eosin stain, × 153.

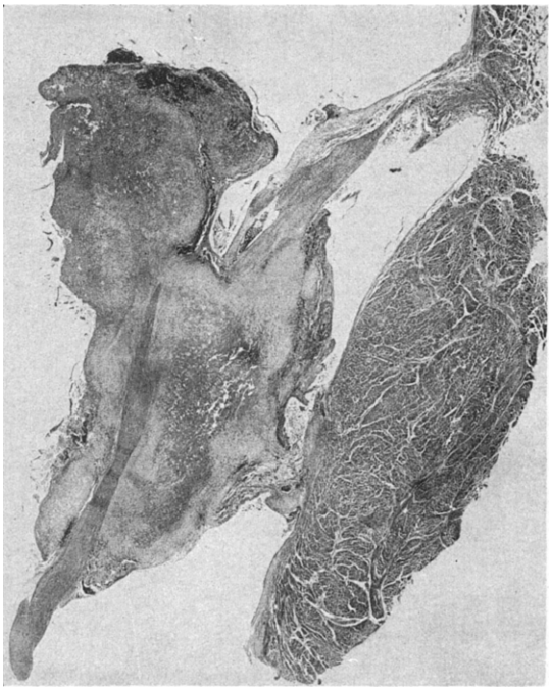

FIG. 3. Mitral valve showing left auricle; deformed valve leaflet with vegetation which is adherent to the endocardium of the left ventricle; hematoxylin and eosin stain, × 7.

cava widened again above the diaphragm but the thoracic portion was also filled with thrombus to the level of the right auricle. The splenic, superior mesenteric and portal veins were dilated and contained thrombi. The liver was enlarged with thickened capsule and rounded edges. The parenchyma was light tan in color and cut with greatly increased resistance. The lobulations were regular. Microscopically, the liver showed both portal and central cirrhosis. (Fig. 2.) Very few central veins remained. Where central veins were patent there were signs of congestion. In other areas in which the veins were obliterated there was extensive collapse fibrosis. Both the central and portal veins were thick-walled and dilated. Except in a few areas the liver cords were not distorted and the hepatic cells were normal. Large engorged venous channels coursed beneath the thickened capsule of the liver. The veins in the round ligament were dilated and many contained thrombi. The umbilical vein was patent. The spleen was greatly enlarged. The parenchyma was dark red and extremely friable. The Malpighian bodies were difficult to distinguish. Microscopically, the spleen showed many epithelioid tubercles with caseating centers. The gastrointestinal tract showed esophageal varices, extensive mucosal erosions of the stomach and hemorrhoids.

In the chest there were old fibrous adhesions covering both lungs. The pleural surfaces were studded with tiny, raised, firm, white tubercles. The lungs were heavy, containing bloody, frothy material but were not consolidated. Microscopically, there were recanalized thrombi in many pulmonary arteries and arterioles. In the heart the mitral and aortic valves were distorted by the presence of large, well organized, white vegetations which extended from the line of closure along the chordae tendineae to the papillary muscles. (Fig. 3.) Microscopically, the vegetations were partially hyalinized but covered by a layer of fresh fibrin. No bacteria could be demonstrated. Throughout the myocardium several coronary veins contained thrombi or had recanalized lumens. There was no evidence of rheumatic carditis.

The kidneys appeared normal grossly. Microscopically, many glomeruli had thickened basement membranes, some severe enough to be classified as wire-loop lesions (Fig. 4.) A few glomeruli were partially hyalinized and some were completely obliterated by hyaline. Many Bowman's capsules were thickened but there were few crescents. The tubular epithelium was swollen and granular. The lumens contained occasional hyaline and granular casts. The venules were dilated. There was generalized enlargement of the thoracic and abdominal lymph nodes. They were congested and on section showed numerous small, caseating tubercles. Microscopically, there were many epitheli-

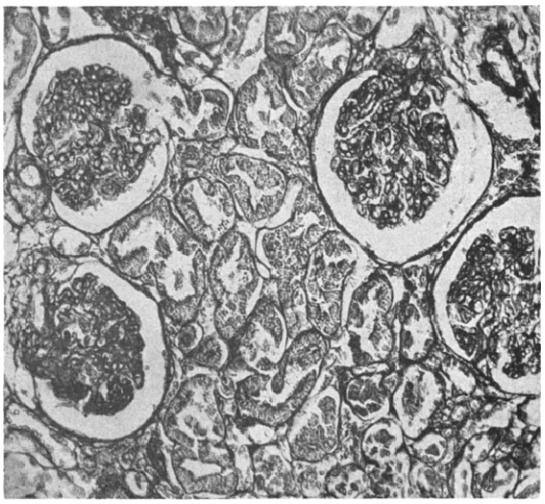

FIG. 4. A group of glomeruli with thickened basement membranes; azan carmine stain, × 220.

oid tubercles with giant cells and caseation. Acid-fast stains showed a few acid-fast bacilli in the abdominal nodes.

The anatomic diagnoses were multiple venous thromboses, atresia of the inferior vena cava due to thrombosis, thrombosis of the hepatic veins, thrombosis of the portal vein, portal and central cirrhosis of the liver, chronic passive congestion of the spleen, esophageal varices, vegetative endocarditis, mitral and aortic valves, chronic intercapillary glomerulonephritis, multiple erosions of the stomach, tuberculous pleurisy, inactive, and tuberculosis of the spleen, thoracic and abdominal lymph nodes.

COMMENT

This patient presented several pathologic processes which may be discussed under the headings of (1) local processes, primarily the result of particular thromboses, and (2) general disease, the cause of the thrombosing tendency. The course and interpretations are summarized in Figure 5.

Chiari's syndrome: In 1946 the patient presented the typical clinical picture of abdominal pain, enlargement of the liver and ascites. Later other manifestations of portal hypertension developed, namely, splenomegaly, esophageal varices and hemorrhoids. The Chiari's syndrome was of the less common, slowly developing type appearing over a period of at least a month. During the latter part of 1947 he lost his ascites and was subjectively well. The collateral circulation had apparently compensated for the hepatic vein block.

Inferior Vena Cava Thrombosis: The clinical evidence for this consisted of the superficial abdominal collateral circulation. Peripheral edema is not seen in inferior caval obstruction unless the leg veins are involved nor is ascites present without concomitant obstruction of the hepatic veins.[6] The collateral circulation beginning in the groin, with blood flowing upward into the axilla,

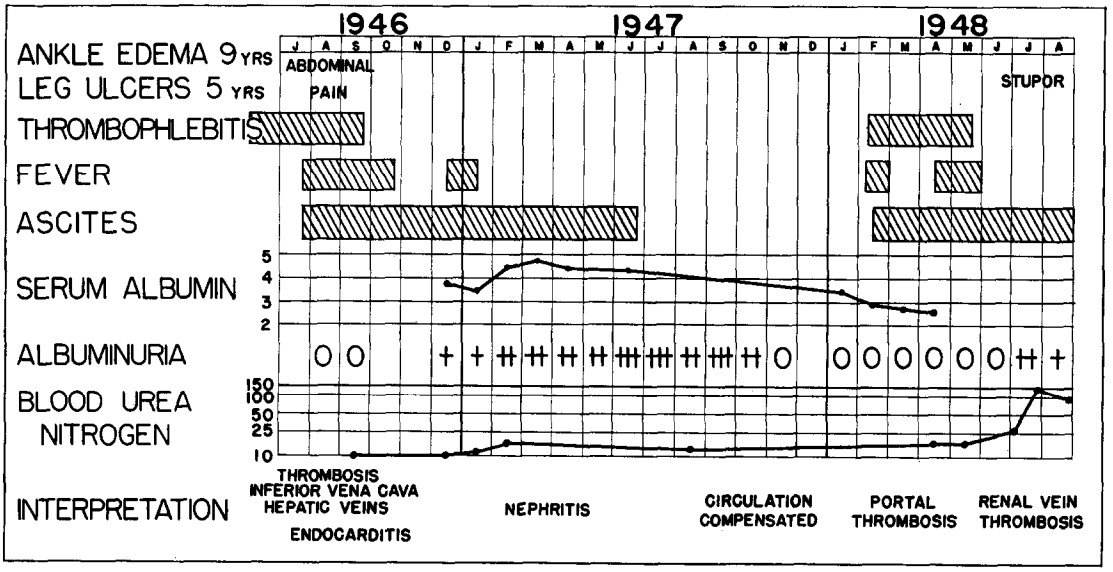

FIG. 5. Graphic summary of the patient's course.

is typical of inferior vena cava block. This patient did not present the typical caput medusa of portal hypertension, with centrifugal blood flow from the umbilical veins, although he did have portal system obstruction. Inferior vena caval obstruction was present in 21 per cent of Thompson's cases of Chiari's syndrome.

Portal Thrombosis: At autopsy thromboses of the portal, splenic and superior mesenteric veins of fairly recent origin were encountered. In Thompson's series this was seen occasionally as a terminal event. In this case the portal vein obstruction probably started six months before death when the ascites recurred.

Renal Vein Thrombosis: It was suspected clinically that the episode of stupor and back pain, with nitrogen retention, oliguria, albuminuria and hematuria a month before death, might represent a progression of the caval thrombosis to involve the renal veins. At autopsy the patient did indeed have a partial obstruction of the renal veins due to fresh inferior caval thrombosis.

Endocarditis: On the patient's first hospital admission in 1946 he had a high fever, heart murmurs which changed, anemia and a suggestive small embolism. Bacterial endocarditis was suspected but later discounted. At autopsy thrombotic vegetations with fibrin deposits on the surfaces were present on the mitral and aortic valves. The type of endocarditis could not be determined pathologically. It was not the type seen in disseminated lupus erythematosus in which the lesions begin as fibrinoid degeneration within the valve tissue and usually do not ulcerate.[7] The lesions were not typical of rheumatic valvulitis. Although no bacteria could be demonstrated in the vegetations, it seems most likely that they represented a healed bacterial endocarditis. The clinical course suggests this interpretation. The patient had chronic leg ulcers for a long time which certainly gave occasional bacteremia with ample opportunity for valvular implantation. Although he had no evidence of antecedent valvular damage, about 50 per cent of the cases of subacute bacterial endocarditis do not show previous valve damage.[8]

Cirrhosis: Pathologically, the liver showed a combined central and portal cirrhosis. The lesion in the central areas is explained by the hepatic vein occlusion. The portal fibrosis might be a Laennec's type. The patient was a spree drinker but his diet was generally adequate. It is a general impression that periodic alcoholics do not get cirrhosis as frequently as do continuous drinkers. The hepatic cells appeared surprisingly healthy with none of the degenerative changes often seen in Laennec's cirrhosis. It is possible that the portal fibrosis was secondary to the portal vein thrombosis.

Nephritis: In 1947 albuminuria developed which persisted most of that year. This was accompanied by a few white cells but only occasionally by red cells and casts. There was also a slight, perhaps insignificant, rise in the blood urea nitrogen at this time. Obstruction of the inferior vena cava above the renal veins can produce albuminuria if it occurs suddenly enough.[6] This patient's occlusion probably developed rather slowly. Moreover, the albuminuria did not appear until some months after the occlusion began. Active endocarditis is frequently accompanied by focal embolic glomerulonephritis occasionally by the diffuse type. Baehr[9] has pointed out that in healed bacterial endocarditis one-third of the cases present diffuse glomerulonephritis. In this patient evidence of nephritis appeared only after the endocarditis had healed. Pathologically, the kidney lesion was a diffuse glomerulonephritis. It was predominantly of the intercapillary type in contrast to the extracapillary type associated with crescent formation. This nephritis was probably associated with the healed endocarditis and adequately explains the albuminuria seen during 1947. However, the nephritis was not of sufficient severity to account for the terminal uremia which was undoubtedly due to the renal vein thrombosis.

Tuberculosis: At autopsy there was old tuberculosis of the pleura with active lesions

in the thoracic and abdominal lymph nodes and spleen. This was apparently a terminal event.

The underlying disease in this case was apparently a recurrent idiopathic thrombophlebitis.* The patient did not have any of the diseases commonly associated with venous thrombosis, namely, cancer, prior infection, arteriosclerosis or rheumatic heart disease.[10] Polycythemia, an occasional cause of multiple thromboses,[3] was not present nor was thromboangiitis obliterans, which is sometimes accompanied by a migratory phlebitis. The coagulability of the blood was not increased. Baehr, Klemperer and Schifrin[11] have described a syndrome of acute febrile anemia and thrombocytopenic purpura with widespread platelet thromboses. In this syndrome the platelets are low and the capillary fragility is increased as in the patient here presented. However, previous cases have all been in females, the course has been very short and there has been considerable bleeding; while pathologically, the thromboses are composed entirely of platelets and are present in the arterioles and capillaries, not in the veins. None of these factors were present in this patient. The combination of endocarditis and nephritis suggests disseminated lupus erythematosus.[7] The wire-loop glomerular capillaries are seen typically in this disease. However, the patient had no skin rash, pericarditis or pleuritis. The endocarditis did not present the typical lesions described in this disease nor was there pathologic evidence of widespread collagen degeneration. Onion-skin arterioles were not found in the spleen.

SUMMARY

A case is presented of a young man who had thrombophlebitis of the legs for many years. At twenty-four years of age thrombosis of the inferior vena cava suddenly developed involving the hepatic veins with the typical symptomatology of Chiari's syndrome. This disease process was complicated by a concurrent endocarditis which responded to penicillin therapy. Six months after the development of the caval thrombosis he began to show evidence of what proved to be chronic glomerulonephritis. A year after the caval thrombosis the patient's collateral circulation had compensated sufficiently so that the ascites and edema disappeared. After a six-month interval the ascites reappeared due to the development of a portal vein thrombosis. Two years after the first appearance of the caval thrombosis the patient died in uremia following the extension of the thrombosis to the renal veins.

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* A series of six cases of multiple venous thromboses, some similar to this case, has recently been reported. (Gerber, I. E. and Mendlowitz, M. *Ann. Int. Med.*, 30: 560, 1949.)