Case Reports

THROMBOSIS OF THE VENA CAVA AND HEPATIC VEINS (CHIARI'S SYNDROME) IN A PATIENT WITH NEPHROSIS

Report of a Case and Observation on Serum Phosphatase and Prothrombin Time of Plasma

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A CASE of Chiari's syndrome is reported, with autopsy and observations on the serum phosphatase level and the prothrombin time of the plasma.

REPORT OF CASE

M. T., a 3½ year old white boy, was admitted to the Children's Hospital on June 2, 1945, with a history of a "cold" followed by swelling of the face and extremities, oliguria and anorexia. Examination revealed generalized edema and a moderate amount of fluid in the peritoneal cavity. The blood pressure was 98 mm. of mercury systolic and 60 mm. diastolic. The nonprotein nitrogen of the serum measured 34 mg., the total protein 3.8 Gm. and the albumin 1.5 Gm., per hundred cubic centimeters. The serum cholesterol was 572 mg. per hundred cubic centimeters one month after admission and 1,088 mg. two weeks later. His urine contained albumin, a few white blood cells and granular casts. A diagnosis of lipid nephrosis (nephrotic syndrome) was made. Except for short visits home, he remained in the hospital until his death, on July 6, 1946. During the entire period results of analyses of his urine remained practically unchanged except for a few red blood cells observed at intervals. The nonprotein nitrogen of the serum usually ranged from 35 to 50 mg. per hundred cubic centimeters. The blood pressure rose slightly at times but was usually within normal limits. The serum protein was always low; the albumin was often less than 1 Gm. per hundred cubic centimeters. The temperature reached 99 to 100 F. almost every day; occasionally it rose to 101 or 102 F.

He gained weight steadily during the first few weeks in the hospital, and by August 1, two months after admission, so much fluid had accumulated in the peritoneal cavity that abdominal paracentesis was necessary for relief of the distention. During the remaining eleven months of his life sixteen more abdominal paracenteses were performed. By September 6 it was noted that the superficial veins over the lower part of the chest and the upper portion of the abdomen were becoming prominent. No acute episode of fever, vomiting or abdominal pain

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had occurred. The venous distention increased steadily until his death, but it was not until June 1946 that enlargement of the liver was noted. At that time the liver was found to extend 2½ fingerbreadths below the costal margin. The edge felt firm and the surface slightly nodular.

There was an unexplained episode of slight jaundice in October 1945. Another brief episode of jaundice occurred in January 1946 after a reaction to transfusion with fever.

By December 1945 the patient began to complain of abdominal pain and vomited occasionally. In April 1946 it seemed certain that portal obstruction must have occurred. Although the legs and abdomen were always greatly swollen, the face and arms appeared free of edema, and even emaciated. The veins were greatly dilated on the chest and abdomen and were visible over the neck, the back and both inguinal regions, the inner aspect of the thighs and the ankles. During the first few days of April the child became irritable, cried a great deal, complained of pain in the abdomen and vomited several times. He was capricious about his food and demanded salt constantly. The patient then contracted measles, modified by the administration of human immune globulin U.S.P. He had Koplik spots and slight fever, but no rash. He was sent to the hospital for contagious diseases. After this episode he seemed weaker, but he did not vomit or complain of any pain for some time.

In June 1946, while at home, the patient suddenly began to vomit all food and drink, and diarrhea developed. Since he was dehydrated when readmitted to the hospital, an intravenous infusion was given. The dehydration and the diarrhea were promptly relieved. With improvement in hydration the abdomen rapidly filled with fluid, and another paracentesis became necessary on July 2. Severe vomiting recurred; his condition rapidly deteriorated, and he was discovered cold and almost pulseless on July 6. He died before fluid therapy could be started.

Laboratory Studies.—The cephalin flocculation test gave a 3 plus reaction in October and a negative reaction in November; it again gave a 3 plus reaction in June and a 4 plus reaction on the day of death, in July. During the first episode of jaundice the total serum bilirubin was 3.2 mg. per hundred cubic centimeters, of which 1.1 mg. gave a direct reaction. During the second episode of jaundice the bilirubin was 4.2 mg. per hundred cubic centimeters, all of which reacted indirectly.

In October the value for serum phosphatase was 4 Bodansky units. On April 4, during the episode of abdominal pain, it was 85 Bodansky units; the value had fallen to 65 units by April 9, to 35 units on April 18 and to 15 units on June 24.

The nonprotein nitrogen level generally ranged from 35 to 50 mg. per hundred cubic centimeters. On April 4 it rose to 97 mg. It was still 87 mg. on April 9 and reached 64 mg. on April 18, but gradually fell to 36 mg. per hundred cubic centimeters. On the sample obtained on the patient's readmission to the hospital, in June 1946, the nonprotein nitrogen measured 42 mg. per hundred cubic centimeters. It was 127 mg. in a sample obtained immediately after death. The value for inorganic phosphorus was normal at all times; the cholesterol was always increased and measured 853 mg. per hundred cubic centimeters at the time of death.

Prothrombin times were obtained only during the first episode of jaundice. In the first sample, the prothrombin time of the undiluted plasma was prolonged to 30.0 seconds (by the method using Russell viper venom, the normal mean value is 19.9 seconds, with a standard deviation of 1.2 seconds); the dilution constant, expressing the increase in seconds per unit increment of reciprocal dilution, was 0.3 second (the normal mean value is 3.8 seconds, with a standard deviation of 0.8 second). Another sample taken two weeks later gave a clotting time of 19.4 seconds

for undiluted plasma and a dilution constant of 0.9 second. A further test in the middle of November showed a clotting time of 23.2 seconds for the undiluted plasma, with a dilution constant of —0.3 second; that is, plasma dilution up to a 1:5 clotted more rapidly than the undiluted plasma.

Necropsy Report.—Gross Examination: Numerous large, dilated, blue veins were visible in the skin of the neck, the anterior portion of the chest, the upper part of the abdomen and the back, and over the inguinal regions, the inner surfaces of the thighs and the ankles. The inferior vena cava was distended and occluded by a firm, dark red and yellow, laminated thrombus, which was adherent to the intimal surface and extended from the level of the renal veins into the right atrium. The renal veins, bilaterally, and the right hepatic vein also were filled with a similar thrombus. A firm, dry thrombus, which was composed principally of dark red, clotted blood, distended and occluded the portal vein and its mesenteric tributaries. This thrombus was laminated in portions and was firmly adherent to the

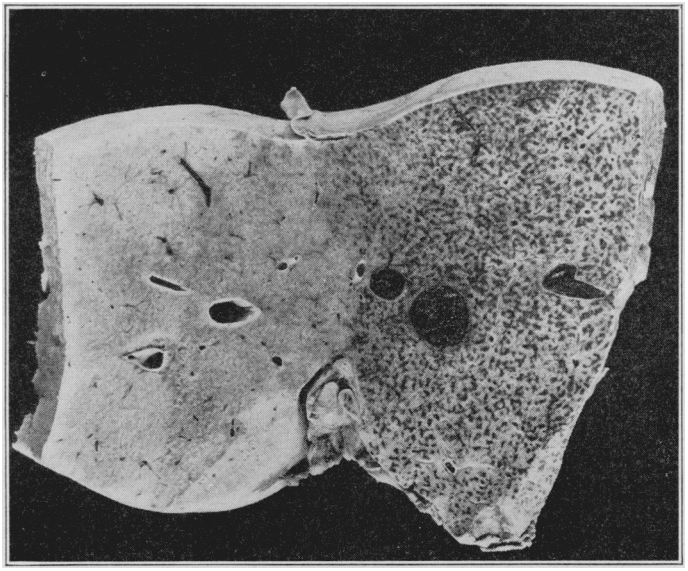

Fig. 1.—Cross section of the liver showing the relatively noncongested left lobe and the extremely congested right lobe, with thrombosis of the hepatic veins.

intima of the vessel just below the point of entrance of the splenic vein. It extended to, but not into, the large intrahepatic radicles of the portal vein and at this site was detached easily from the wall of the vessel. The splenic vein also was filled with, but not distended by, a soft clot of blood, which had retracted slightly from the wall of the vessel. The peritoneal cavity contained approximately 300 cc. of slightly turbid fluid. The surfaces of the peritoneum were congested, and there was moderate fibrous thickening of the parietal portion.

The liver was slightly enlarged and weighed 615 Gm. The smooth capsular surface was dark red over the right and caudate lobes and light tan over the left lobe. The cut surface of the right and caudate lobes revealed light yellow tissue, mottled with prominent dark red markings, which imparted to it a nutmeg appearance. Numerous large veins in these lobes were thrombosed. The left lobe was

pale yellowish tan, with only slight evidence of congestion. A sharp line of demarcation existed between the congested and the relatively noncongested portions of the liver. The gallbladder was normal.

The spleen, approximately two to three times normal size, weighed 108 Gm. and was composed of a dark red, moderately soft pulp.

There were no esophageal varices and no abnormalities of the gastroenteric tract except for moderate congestion of the small intestine.

The kidneys were about twice normal size and together weighed 215 Gm. The capsules were thin, and the external surfaces were smooth. The swollen cortices were mottled with light yellowish tan and reddened areas. The medullas were moderately congested. The calyxes, pelves, ureters and urinary bladder were normal.

The heart was of average weight but slightly increased in size. The chambers on the right side were dilated, and a pale yellowish pink thrombus, extending from the inferior vena cava, hung in the right atrium.

The lungs appeared normal, and no free fluid was present in the pleural cavities.

Microscopic Examination: Some of the veins emerging at the hilus of the kidneys had a slight lymphocytic reaction throughout all the layers of their walls and contained organized and recanalized thrombi. Other veins, with similar signs of inflammation, were distended by more recently formed thrombi, which were only beginning to be organized in their peripheral zones. Some of the veins appeared normal.

Only a slight and patchy inflammatory reaction, consisting chiefly of lymphocytes, was present in the intima and media of the inferior vena cava. The vessel was occluded by a thrombus, which was well organized in the outer zone but unorganized in the central zone.

The pathologic changes in the liver consisted of pronounced chronic passive congestion in the right lobe, with central necrosis, and early portal cirrhosis throughout all lobes. In the right lobe there were degeneration, necrosis and even absence of hepatic cords in the central portions of the lobules. The central veins and sinusoids were distended with blood, and the framework was relatively increased in amount. The peripheral portion of the hepatic lobules was fairly well preserved, there being only slight fatty infiltration of some of the hepatic cells. However, the sinusoids in the peripheral portion were moderately congested, and the Kupffer cells were slightly swollen. Several of the larger hepatic veins of the right lobe contained thrombi, in which organization was less advanced than in the thrombus of the inferior vena cava. None of the smaller hepatic veins or the interlobular branches of the portal vein were thrombosed. In the left lobe, the central veins and the sinusoids of the central portion of the lobules were distended with blood, and there was attenuation of some of the hepatic cords. None of the extensive degenerative changes present in the right lobe were seen. In the portal areas of all lobes there was a cellular inflammatory reaction, composed chiefly of lymphocytes, with fewer histiocytes and eosinophils, and accompanied with an increase in connective tissue and slight proliferation of the bile ducts.

The media and, to a greater extent, the adventitia of the splenic vein were infiltrated with lymphocytes, histiocytes and eosinophils. A thin layer of organized thrombus was adherent to the intimal surface. Overlying this layer was a fresh thrombus, the central portion of which consisted of a postmortem clot.

The mesenteric veins were distended with unorganized thrombi. Inflammatory reaction in these veins was slight.

There were degeneration and karyorrhexis of the central portions of the splenic follicles. The sinusoids of the pulp were distended and engorged with

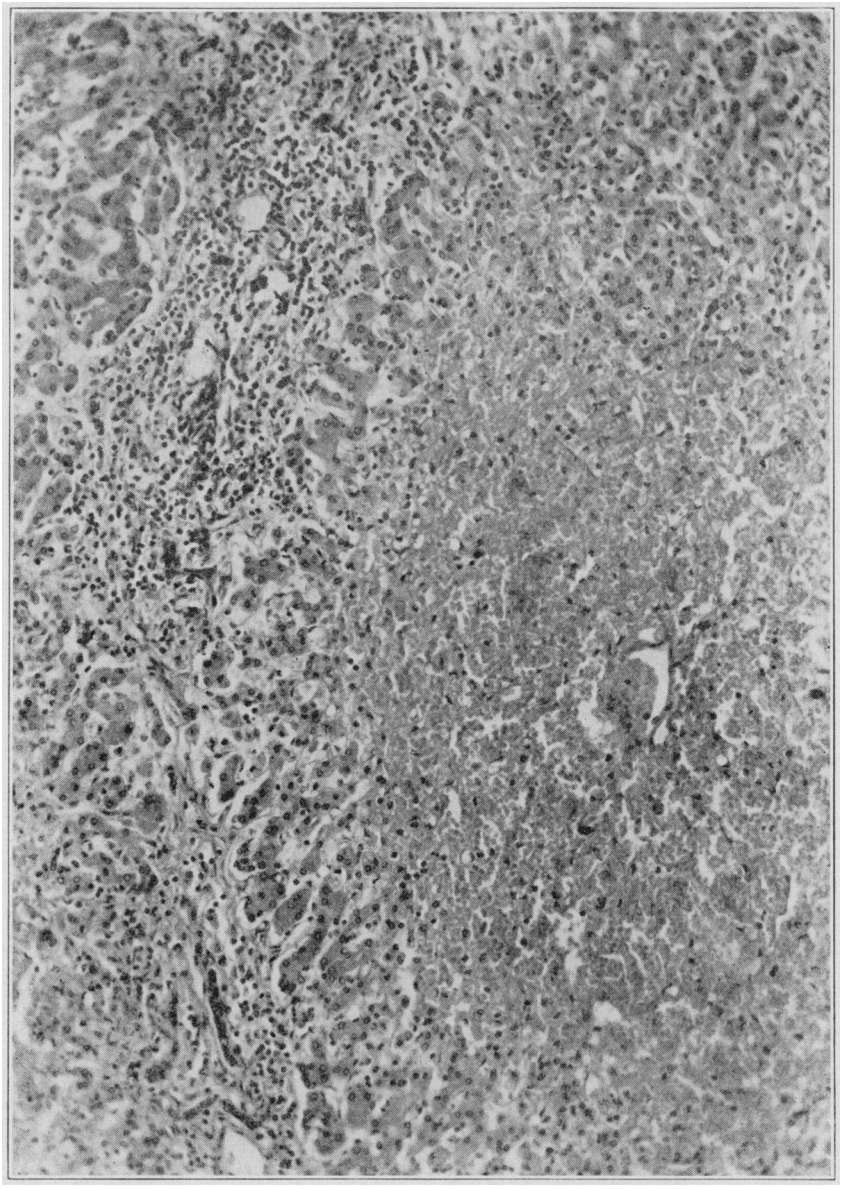

Fig. 2.—Microscopic appearance of a representative lobule of the right lobe of the liver. There are conspicuous congestion of the sinusoids and necrosis and disappearance of the hepatic cords in the central and middle zones. Lymphocytic infiltration, fibrosis and reduplication of bile ducts are evident in the portal canals.

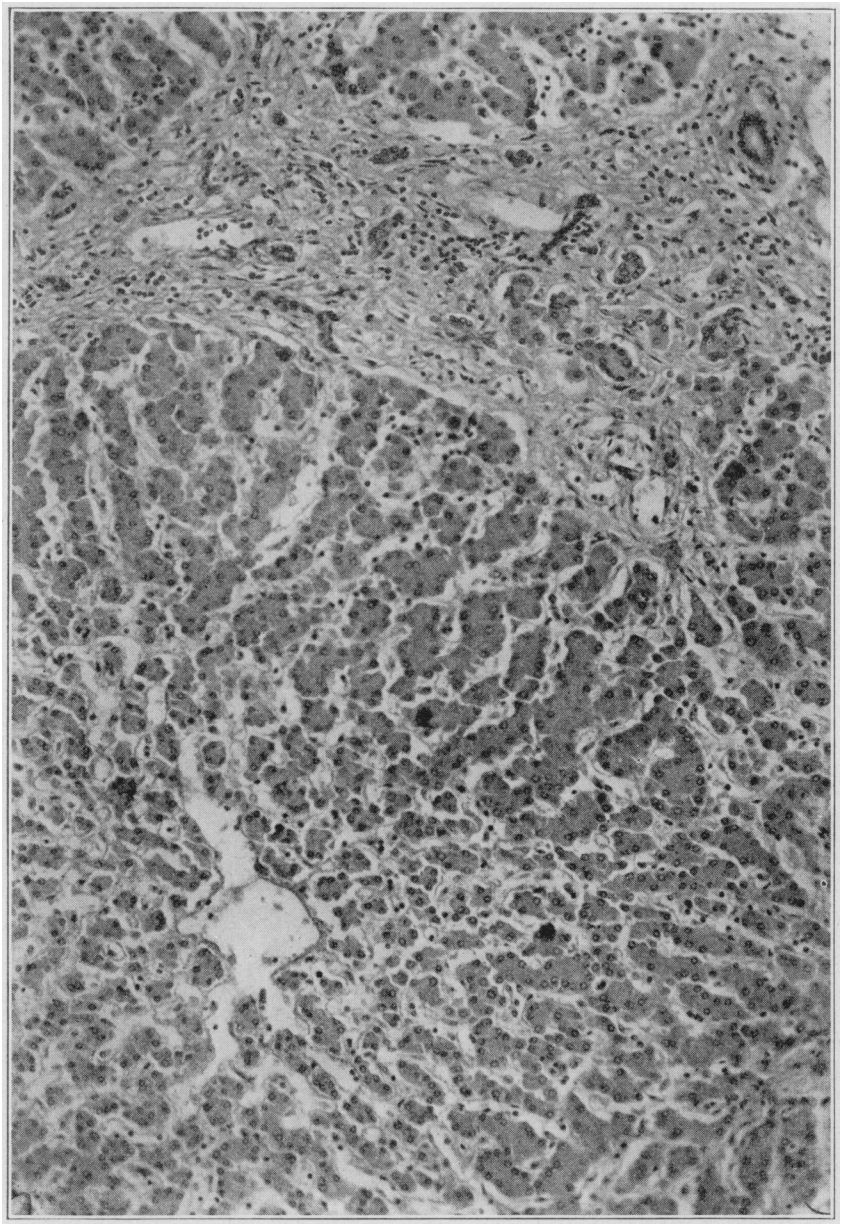

Fig. 3.—Microscopic appearance of a representative lobule of the left lobe of the liver. The sinusoids draining into the central veins are slightly dilated; the hepatic cords are essentially normal and portal cirrhosis is evident.

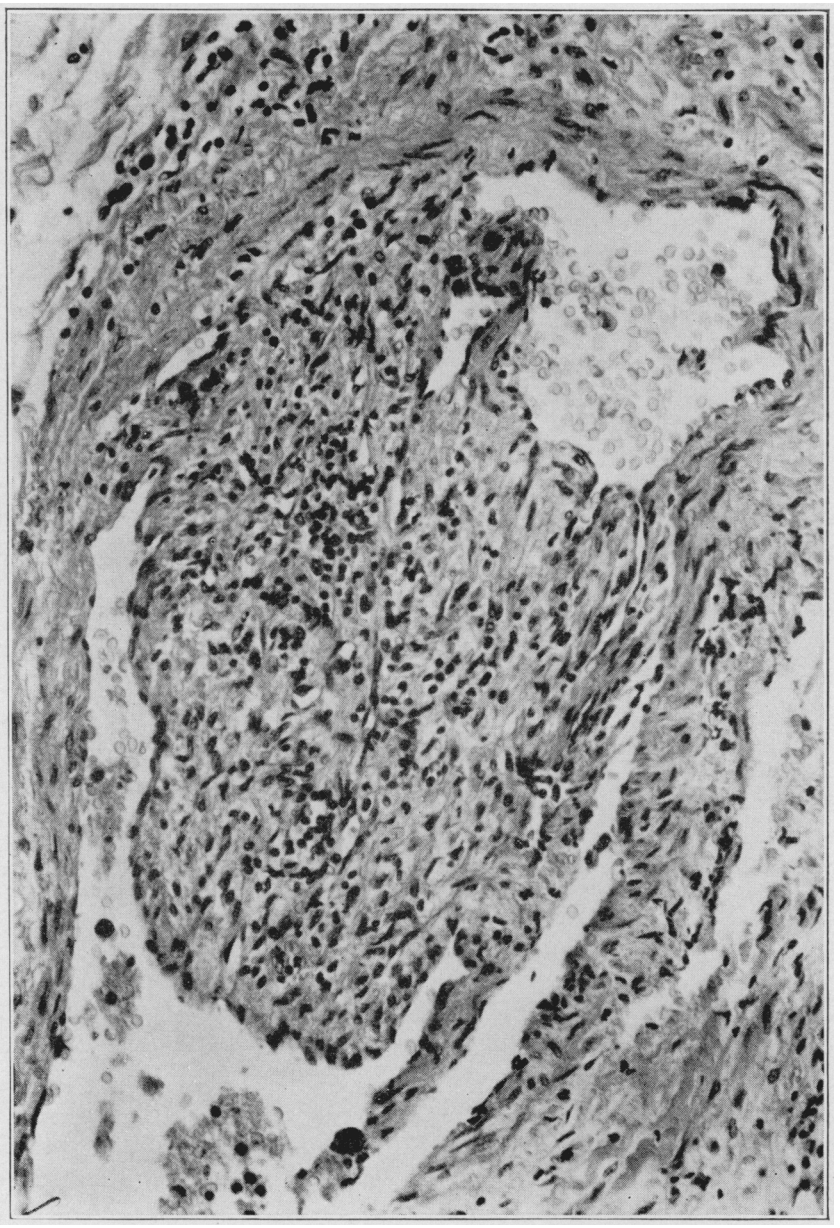

Fig. 4.—Microscopic appearance of a well organized thrombus in a small vein of a renal hilus.

blood, and there was a moderate amount of blood pigment in the reticuloendothelial cells of the pulp. There were no thrombi.

The pathologic changes in the kidney were characteristic of the nephrotic syndrome. Whereas many glomeruli appeared normal, some showed slight endothelial proliferation and thickening of the capillary basement membrane, which were best demonstrated in sections prepared with Mallory's aniline blue stain. Some capsular membranes were adherent to the glomeruli with obliteration of the subcapsular space. A few glomeruli were completely hyalinized. Many of the convoluted tubules were distended and filled with precipitate, and most of them were lined with a swollen, granular epithelium, filled with tiny vacuoles. In many areas where glomeruli showed evidence of glomerulitis there was atrophy of the convoluted tubules, accompanied with inflammatory reaction and fibrosis in the interstitial tissue. The small arteries and arterioles appeared normal. The small veins were moderately congested.

COMMENT

This case is an example of a rare and little understood pathologic entity, thrombosis of the hepatic veins. By 1945 about 70 instances of this condition, which is known as Chiari's syndrome, had been reported in the literature.[1] In the majority of cases, as in the present one, local thrombosis of the vena cava was present. The etiology of the syndrome is obscure. The condition may occur alone or in association with other disorders. Of these disorders, primary polycythemia, cirrhosis, infections and neoplasms of the liver are the most frequent.

Only 7 cases of the syndrome in children[2] have been reported. The disease in each instance was insidious in onset. Abdominal distention, ascites and dilatation of the superficial veins over the upper part of the abdomen and the chest wall were noted, and usually some degree of edema of the legs was seen. Jaundice was not observed. The symptoms were indefinite, but in every instance the occurrence of abdominal pain and vomiting during the course of the disease was described. One patient died of carcinoma of the liver at least twenty-three years after the onset of his illness. The other patients died three months to four years after the occurrence of symptoms, apparently of chronic obstruction of the hepatic veins. The thrombosis in each child appeared to be a primary occurrence and not a complication of another disorder, such as has often been described in adults. Extensive thrombosis of the vena cava was not present in any of the children.

Although Chiari's syndrome in a patient with nephrosis has not previously been reported, thrombosis of blood vessels has been noted as a complication of the disease. Two of 9 patients of Aldrich[3] on whom postmortem examinations were made had thrombi, 1 of the renal vein and the other of the iliac veins. Both children died with infection of the

1. Kelsey, M. P., and Comfort, M. W.: Occlusion of Hepatic Veins: Review of Twenty Cases, Arch. Int. Med. **75**:175-183 (March) 1945. Hirsh, H. L., and Manchester, B.: Chiari's Syndrome, New England J. Med. **235**:507-511 (Oct. 3) 1946.

2. Hutchison, R., and Levy Simpson, S.: Occlusion of Hepatic Veins with Cirrhosis of Liver, Arch. Dis. Childhood **5**:167-186 (June) 1930.

3. Aldrich, C. A.: Nephritis, in Brennemann, J.: Practice of Pediatrics, Hagerstown, Md., W. F. Prior Company, Inc., 1945, vol. 3, chap. 28, p. 24.

blood stream. The thrombosis was ascribed to sepsis. Schwarz and Kohn[4] discovered thrombosis of the right middle cerebral artery in 1 of 9 children who died with nephrosis. The other 8 patients had peritonitis, but no mention was made of infection in the child with thrombosis. No evidence of sepsis was present in the patient reported on here. He was given prophylactic sulfonamide medication throughout his illness.

The question arises whether in patients with nephrosis a tendency to thrombosis may be related to derangements in the humoral balance, more specifically, to changes in the composition of the plasma.

The prothrombin time of patients with nephrosis is characterized by a greatly decreased dilution constant, an expression of a reduced slope of the dilution curve, whereas the clotting time of the undiluted plasma is variable. The data on 6 patients with nephrosis, including the 1 reported on here, are summarized in the table and illustrate the point. It may be seen that the prothrombin time ranged beyond the normal

Prothrombin Time in the Plasma of Patients with Nephrosis

Case No.	Plasma Prothrombin Time	
	Undiluted Plasma,* Seconds	Dilution Constant,* Seconds
1	30.0 19.4 23.2	0.3 0.9 —0.3
2	18.3 19.9 19.8 17.6	2.3 0.6 1.3 1.4
3	22.5 14.1 20.6 23.4	0.4 1.0 2.4 1.2
4	20.1 22.8	1.4 2.4
5	20.8	2.0
6	18.3	1.7

*The mean normal value of undiluted plasma is 19.9 seconds, with a standard deviation of 1.2 seconds; that of the dilution constant is 3.8 seconds with a standard deviation of 0.8 second.

limits in both directions but that the dilution constant was always less than normal. The plasma in case 1 showed wider fluctuation of the prothrombin time and perhaps greater reduction in the dilution constant than that of any other patient. It is regrettable that no samples of plasma were examined during the latter period of his illness.

The interpretation of the behavior of plasma in nephrosis is hypothetic as yet. It is thought that the reduced slope of the dilution curve, with the correspondingly short clotting time of plasma dilutions, is an expression of an increased prothrombin content of the plasma, which is masked to a variable extent in undiluted plasma by the presence of clot-

4. Schwarz, H., and Kohn, J. L.: Lipoid Nephrosis: A Clinical and Pathologic Study Based on Fifteen Years' Observation, with Special Reference to Prognosis, Am. J. Dis. Child. **49**:579-593 (March) 1935.

ting inhibitors. According to an alternate hypothesis, the observations may be explained by the activity of accelerators which, supposedly, is increased in diluted plasma, while the underlying prothrombin level varies widely. Such a hypothesis is less in keeping with the known behavior of secondary factors affecting the clotting mechanism, factors which in general are more active in undiluted than in diluted plasma. One would also have to assume a completely erratic behavior of the prothrombin level in nephrosis, varying from extreme hypoprothrombinemia to hyperprothrombinemia.

As to the character of secondary factors influencing the prothrombin time, the possible role of alterations in the distribution of plasma proteins may be mentioned. Among these variations, a great increase in the plasma fibrinogen, which sometimes exceeds 1 Gm. per hundred cubic centimeters, is prominent. A portion of the globulins, that belonging to the β-globulins, is likewise increased, while other proteins, albumin in particular, are greatly diminished. The relation of these changes to the mechanism of clotting is obscure. There is no indication that an increase in plasma fibrinogen per se can affect the prothrombin time. Another factor, equally undetermined, with a possible effect on the clotting mechanism may be related to the great increase in lipid constituents of the plasma of patients with nephrosis.

The frequency of the changes in the prothrombin time as compared with the rarity of published reports on the incidence of thrombosis in patients with nephrosis may indicate that other factors, about which it would be idle to speculate, are of determining importance in the development of the tendency to thrombosis.

The changes in the phosphatase level observed in this patient appear of theoretic, as well as of practical, interest. At present there is considerable uncertainty as to the mechanism and the significance of increases in serum phosphatase in hepatic disease. According to one point of view, the liver is concerned only with the excretion of the serum phosphatase via the biliary passages; consequently, to proponents of this theory, increase in serum phosphatase in itself signifies biliary obstruction. According to another view, hepatic cells are capable of producing phosphatase. Increase in phosphatase, while of greater extent in persons with obstructive lesions, is thought to represent a specific response of hepatic cells to injury. The great increase in phosphatase, exceeding 85 Bodansky units, in our patient, in whom the hepatic veins of one portion of the liver only were occluded, without any evidence of biliary obstruction, would appear as strong evidence for the view that hepatic cells may respond to certain stimuli with production of phosphatase.

SUMMARY

A case of thrombosis of the vena cava and hepatic veins (Chiari's syndrome) in a child with nephrosis is reported. Thrombi were also present in the renal veins and in the portal area. Great increase in the serum phosphatase occurred in the course of the disease. Observations on the prothrombin time of 6 patients with nephrosis are recorded. The clotting time of undiluted plasma was observed to be variable, but the slope of the dilution curve was always reduced.

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