Primary Biliary Cirrhosis with Scleroderma, Raynaud's Phenomenon and Telangiectasia

New Syndrome

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A new syndrome is described consisting of chronic liver disease typical of primary biliary cirrhosis together with scleroderma, Raynaud's phenomenon, calcinosis cutis and telangiectasia. Six female patients had pruritus, jaundice and hepatomegaly with marked elevation of serum alkaline phosphatase activity and a positive test for serum mitochondrial antibody. Extrahepatic bile ducts were normal. In addition, they had telangiectasias, resembling those seen in the Rendu-Osler-Weber syndrome, on the finger pads and lips and occasionally on the mucosa of the upper gastrointestinal tract. The other features of the CRST syndrome (calcinosis, Raynaud's phenomenon and sclerodactyly) were present to a varying degree.

The association of primary biliary cirrhosis with a form of scleroderma suggests an immunologic etiology for the liver disease.

Primary biliary cirrhosis is a chronic liver disease characterized by pruritus, mild or moderate jaundice, melanosis, steatorrhea, hyperlipidemia (occasionally with xanthomatosis), marked elevation of serum alkaline phosphatase levels and ultimately a fatal outcome with progressive liver impairment. Its cause is unknown. Possible clues to pathogenesis are the predominance of women among the recorded cases, the rare development of a similar syndrome in patients after phenothiazine usage [2,3], and an interesting nonspecific serum antibody against mitochondria that is found in about 90 per cent of patients [4–6]. No familial cases have been described to our knowledge.

We describe six patients with a newly recognized syndrome characterized by the association of primary biliary cirrhosis with scleroderma, Raynaud's phenomenon, telangiectasia and, occasionally, calcinosis cutis. The latter four conditions have been described together in the CRST syndrome [7].

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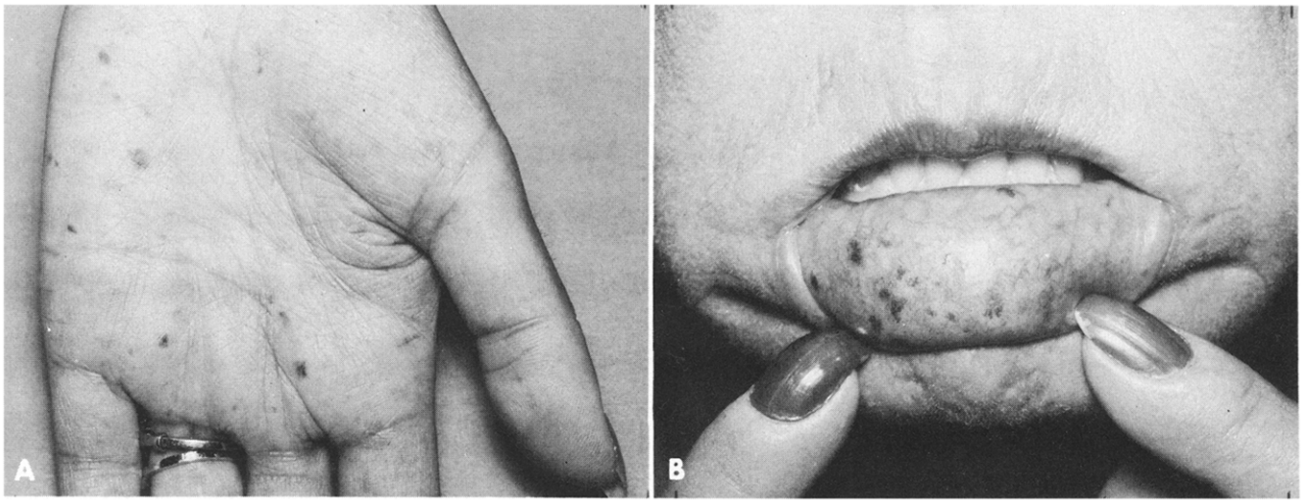

Figure 1. Case 1. Telangiectasias on the palms (A) and on the lower lip (B).

CASE REPORTS

Case 1. When first seen at Los Angeles County-University of Southern California Medical Center (LAC-USCMC), this forty-five year old Mexican-American waitress (G.B.) had had mild jaundice and generalized pruritus for approximately one year. She had originally gone to a dermatologist because of generalized itching, and he had detected jaundice and referred her for medical evaluation. This led to laparotomy in September 1966 with the suspicion of choledocholithiasis. A normal gallbladder and common bile duct were found, and no definite diagnosis was made. Mild jaundice and severe pruritus persisted during the next year. In addition, there was mild fatigue, some anorexia, increase in stool frequency and a gradual weight loss of 30 pounds. Menses ceased after her operation. She was referred to LAC-USCMC in October 1967 for further evaluation.

About 1954 the patient noted the onset of numbness, tingling, coldness and pain in the fingers on exposure to cold. The fingers would turn pale, blue or purple at these times. After two years, cervical sympathectomy was performed, first on one side and then on the other, with partial relief of the symptoms. For about two years there had been slowly progressive tightness of the skin of the hands and forearms with some difficulty in making a fist. There had been a generalized darkening of her skin for about a year and a half. For many years the patient had noticed small red spots on the skin of her palms and finger pads and on the lips and tongue. She occasionally had bleeding from the red lesions on the lips and tongue but did not suffer from nosebleeds.

Findings at LAC-USCMC were mild jaundice, slight hepatomegaly with a firm nontender edge and an easily palpable spleen. There were no spider angiomas or

TABLE I Laboratory Test Results Soon After the First Detection of Liver Disease and on the Last Occasion Measured in Six Patients with Primary Biliary Cirrhosis

Case No.	Date of Tests	Total/Direct Bilirubin (mg %)	Alkaline Phosphatase (B-L units/ml)	Albumin/ Globulin (gm %)	SGOT (Karmen units/ml)	SGPT (Karmen units/ml)	Prothrombin (%)	Serum Cholesterol (mg %)	Serum Phospholipids (mg %)	Mitochondrial Antibody Test
1	9/26/67	3.9/1.6	59	2.8/3.4	97	47	100	356	305	Positive*
	7/24/69	1.7/0.6	59	3.4/3.6	...	79	100	492	...	Positive
2	9/18/64	2.0/...	250†	2.8/4.7	135	...	100	...	...	...
	10/23/69	1.8/0.8	39	3.2/4.1	89	68	100	316	351	Positive
3	6/20/68	2.6/...	...	...	...	60	...	290	...	...
	4/30/69	1.4/0.9	38	2.2/6.2	99	122	100	422	392	Positive
4	6/26/68	5.2/2.7	24	3.2/5.3	110	110	100	...	...	...
	6/24/69	4.4/2.3	30	3.0/5.0	116	62	73	364	652	Positive
5	9/28/67	13.3/6.0	34	3.4/4.0	130	155	100	1,100	...	...
	4/8/68	10.5/6.5	90	2.0/4.6	95	49	75	390	510	Positive*
6	11/10/66	1.5/0.9	190†	...	110	130	100	258	...	...
	9/4/69	7.1/3.9	14	3.9/4.4	118	76	51	269	297	Positive

* Kindly performed for us by the laboratory of Drs. Fred Kantor and Gerald Klatskin, New Haven, Connecticut.
† King-Armstrong units (N 3-13).

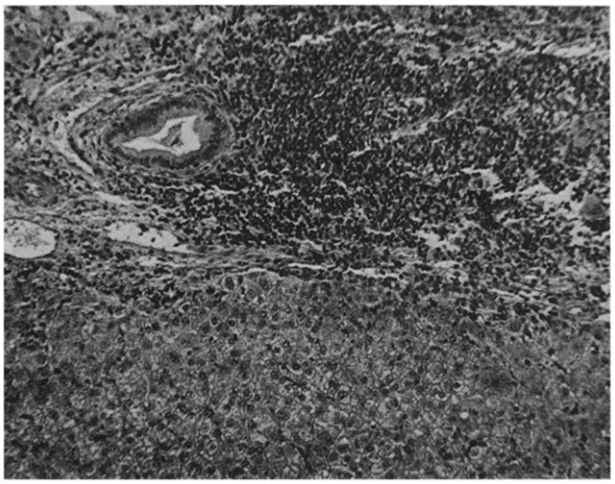

Figure 2. Case 1. Liver biopsy specimen. The larger interlobular bile ducts are surrounded by lymphocytes, cholangioles are reduced in number. (Hematoxylin and eosin stain, original magnification × 225).

xanthomas and no xanthelasma. The skin of the hands and forearms was tight, thickened and shiny, and there was a 7 mm hard nontender subcutaneous nodule on the extensor surface of the left forearm. There was generalized hyperpigmentation, and a few excoriations were noted on the upper trunk. The skin of the face felt normal, and the patient was able to open her mouth widely. There were numerous, round, 1 to 2 mm telangiectasias on the skin of the palms, the soles of the feet, around the mouth, on the lips, on the tongue and on the buccal mucosa (Figure 1A and 1B). They blanched on pressure, did not have radiating branches, were not pulsatile and seemed identical with the lesions seen in Rendu-Osler-Weber (R-O-W) syndrome.

Investigations at LAC-USCMC included a hemoglobin level of 9.9 gm per cent, white blood cell count of 6000/cu mm with 5 per cent band forms, 60 per cent segmented polymorphonuclear leukocytes, 17 per cent lymphocytes, 5 per cent monocytes and 13 per cent eosinophils. Results of representative hepatic tests appear in Table I. Wedged hepatic vein pressure was 10 mm Hg above inferior vena caval pressure (normal 1 to 4 mm Hg), serum bile acid levels were moderately elevated (dihydroxy bile acids 4.1 μg/ml) and the lupus erythematosus cell test was negative. A biopsy specimen of the skin from one finger was interpreted as showing "dermal collagenosis, most consistent with scleroderma." The hard nodule in the forearm skin appeared calcified on roentgenograms. Celiac angiography failed to disclose any of the hepatic vascular lesions considered typical of hereditary hemorrhagic telangiectasia [8]. The test for serum mitochondrial antibody was positive in 1/100 dilution.*

* Kindly performed for us by the laboratory of Drs. Fred Kantor and Gerald Klatskin, New Haven, Connecticut.

Tests for serum smooth muscle antibody and hepatitis-associated ("Australia") antigen were negative. Needle biopsy of the liver was performed on September 26, 1967.

The patient was treated with cholestyramine and supplementary calcium and fat-soluble vitamins. There was complete relief of the pruritus. A second needle biopsy of the liver was undertaken in December 1968 for quantitative copper determination (emission spectrograph), with a finding of 29 mg copper/100 gm dry liver. Normal values by this technic are 2.76 ± 0.12 (SE) mg/100 gm dry liver [9].

The patient's general health has remained fair with moderate fatigue, mild jaundice and occasional pruritus. Eosinophilia of 6 to 14 per cent has persisted, without explanation. In December 1968, January 1969 and February 1969, she had moderate upper gastrointestinal bleeding with hematemesis. There were no peptic ulcer symptoms. Two x-ray series of the upper gastrointestinal tract failed to demonstrate any abnormality. Esophagoscopy and gastroscopy showed small (1+ on a scale of 0 to 4+) esophageal varices and numerous red telangiectasias on the mucosa of both the esophagus and stomach. Repeat wedged hepatic vein pressure in January 1969 was 11 mm Hg above inferior vena caval pressure. Portacaval shunt was considered but not performed because of the mildly elevated wedge pressure, the small size of the esophageal varices and the likelihood that the bleeding came from the telangiectasias in the upper gastrointestinal tract.

Microscopic examination of the liver biopsy specimen obtained on September 26, 1967, showed relatively few portal areas. Those seen contained no cholangioles. One of the larger portal radicles had an interlobular duct partially engulfed by lymphocytes (Figure 2), and at the periphery of the portal region there were large numbers of plasma cells. The limiting plates were irregularly destroyed. There were somewhat dilated angiomatous spaces in the portal regions, and the hepatic arterioles were thickened. The liver cells were not swollen but Kupffer's cells were prominent. There was no cholestasis. There was no nodular regeneration. It was concluded that although the liver biopsy was not sufficiently large to confirm absolutely the diagnosis of primary biliary cirrhosis, it did show the most important features, namely, absence of the cholangioles in the few portal areas obtained, and an infiltrate of lymphocytes and plasma cells that formed a cuff around the interlobular duct.

Case 2. A fifty year old Mexican-American housewife (C.E.) was first thought to have liver disease in 1964. Because of vague symptoms including fatigue and pruritus she was hospitalized for evaluation in March 1964. Gallstones were diagnosed on cholecystogram, and she underwent cholecystectomy. The liver appeared normal; the gallbladder contained 18 small stones; the

common duct seemed normal to palpation. She was told that mild jaundice was noted postoperatively. Vague symptoms continued including fatigue, anorexia, burning epigastric and substernal pain, intermittent generalized pruritus, darkening of the urine and increase in stool frequency to three to four times daily. The patient was first seen at Kaiser Foundation Clinic in August 1964. Laboratory tests showed mild hyperbilirubinemia and an elevated alkaline phosphatase level (Table I). After intravenous cholangiography failed to show any contrast media concentration, laparotomy and common duct exploration were performed on October 8, 1964. The common duct was normal in every respect as was a T tube cholangiogram. There was good visualization of the intrahepatic ducts. The liver appeared normal except for a small venous dilatation, 0.5 cm in diameter, on the inferior surface of the left lobe. The spleen was approximately three times normal in size. During the next fifteen months there was no major change in the symptoms of fatigue and intermittent pruritus. The abnormal hepatic tests remained unchanged. In January 1966 the patient presented with melena and a fall in the hemoglobin value from 13 to 6 gm per cent. Roentgenologic study showed intermittent contractions of the cervical esophagus but poor esophageal peristaltic activity below this level. With the patient in the supine position, barium remained in the esophagus for thirty minutes. No abnormality of stomach, duodenum or small bowel was found. Prior x-ray studies had demonstrated a small hiatal hernia and free reflux, but the motility disorder had not been noted. Inquiry revealed epigastric symptoms compatible with esophagitis since early 1963; she had taken antacids for this intermittently. At esophagoscopy, a superficial ulcer was seen at the gastroesophageal junction; this bled freely when simply touched with the biopsy forceps. Gastroscopy was normal. On therapy directed toward acid neutralization and avoidance of reflux her symptoms diminished. Subsequently, she has had dysphagia for solids which responds well to periodic esophageal dilation, although no stenosis has been shown roentgenographically or by endoscopy. There have been three recurrences of melena since the first episode. Two blood transfusions were given on one of these occasions in 1966. In October 1968 esophagoscopy was repeated, and small esophageal varices were seen.

Since approximately the age of twenty-five years she has had typical Raynaud's phenomenon, the fingers becoming white and painful on exposure to cold. The skin over the backs of her hands has become thicker and tighter in the past three years, and there has been a moderate generalized darkening of her skin. Small telangiectasias typical of R-O-W syndrome were first noted on her fingers and palms in 1966. She was uncertain how long they had been present. Since then additional lesions have appeared on her lower lip and tongue. There is no history of nosebleeds. Telangiectasias were not noted on esophagoscopy or gastroscopy.

At the last evaluation (October 1969) the patient continued to feel reasonably well except for chronic fatigue, intermittent epigastric burning and moderate pruritus that was well controlled with cholestyramine therapy. Physical findings included mild scleral icterus, generalized melanosis and numerous small flat red telangiectasias on the volar surface of the fingers (Figure 3) and the lower lip. The skin over the dorsum of the hands and fingers was moderately tight and thickened. The liver edge was barely palpable at the costal margin on inspiration and was moderately firm. The spleen was not palpable. There were no skin xanthomas.

Laboratory abnormalities (Table I) have consisted of markedly elevated alkaline phosphatase levels (100 to 260 King-Armstrong units/ml), slight hyperbilirubinemia (serum total bilirubin 1.9 to 2.5 mg per cent), moderately elevated serum cholesterol levels (290 to 380 mg per cent), an elevated serum phospholipid level (351 mg per cent), a mild increase in serum transaminase activity (SGOT 100 to 300 units/ml) and some decrease in serum albumin and an increase in serum globulin. There has been little change in these abnormalities since 1964. The serum mitochondrial antibody test was strongly positive; tests for serum smooth muscle antibody and hepatitis-associated ("Australia") antigen were negative.

A needle liver biopsy specimen taken at surgery in October 1964 showed an intact lobular arrangement. The only portal area on the specimen had an inflam-

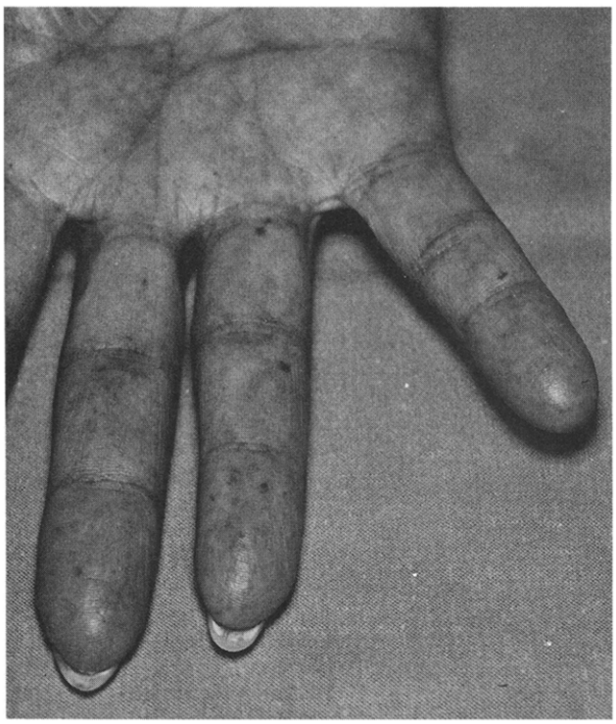

Figure 3. Case 2. Numerous telangiectasias on the hands.

matory exudate of lymphocytes and plasma cells that effaced the cholangiolar structures and limiting plate but spared hepatic arterioles. There were no abnormal vascular structures in the portal regions. There was no cholestasis in the centrolobular portions of the liver. The specimen was not of sufficient size to confirm the diagnosis of primary biliary cirrhosis but the features were consistent with the findings in that disease.

Case 3. A fifty-one year old Jewish housewife (S.L.) was first seen at LAC-USCMC on April 30, 1969, for evaluation of chronic liver disease. In April 1968 a mild generalized pruritus developed followed in May 1968 by slight jaundice. The liver was palpable, the serum bilirubin 2.8 mg per cent and the SGOT activity 60 Karmen units/ml. No definite diagnosis was established. Mild jaundice and pruritus persisted without other symptoms. Oral cholecystography and an x-ray series of the upper gastrointestinal tract were normal in September 1968 at which time the serum bilirubin was 3.1 mg per cent. The patient was admitted to a hospital in January 1969 for further evaluation, including liver biopsy. Intravenous cholangiography showed a normal gallbladder and faint visualization of a common bile duct of normal caliber. Mild jaundice and pruritus continued, leading to hospitalization on the liver service at LAC-USCMC. Throughout the eleven months of jaundice the patient maintained her weight, strength and general health. Medication included an estrogen preparation (Vallestril®) for menopausal symptoms, a uricosuric agent (sulfinpyrazone) for elevated serum urate levels, thyroid tablets, 120 mg daily (since 1953) and a short course of clofibrate in 1967, given for elevated serum cholesterol levels.

The patient gave a history of episodes of coldness and paleness of the hands on exposure to cold since high school. This had been diagnosed as Raynaud's phenomenon, and a left cervical sympathectomy had been performed at age 16.

Physical findings in April 1969 included mild generalized melanosis, slight scleral icterus and firm, nontender hepatic enlargement extending 10 cm below the xiphoid and 5 cm below the right costal margin on inspiration. The spleen tip was easily palpable. There were no xanthomas, spider angiomas or xanthelasma. There was an old sympathectomy scar over the left upper dorsal region, mild ptosis of the left eyelid and meiosis of the left pupil. Small hard subcutaneous masses were felt over the right kneecap and in the skin of the distal right second finger. The skin over the hands and fingers seemed tighter and stiffer than normal. There were numerous small round red telangiectasias on the finger pads, the lower lip and the buccal mucosa. She had noted the lesions on her lip approximately one year earlier.

Laboratory findings included a hemoglobin level of 11.8 gm per cent, white blood cell count of 5900/cu mm with 5 per cent band forms, 61 per cent segmented neutrophils, 28 per cent lymphocytes, 1 per cent monocytes and 5 per cent eosinophils; normal urinalysis except for 20 to 30 white cells/high power field on microscopic exam of a voided specimen; negative lupus erythematosus cell preparation and antinuclear factor; serum dihydroxy bile acids of 6.6 μg/ml (normal 0 to 1.9 μg/ml); serum total lipids of 1,086 mg per cent with triglycerides 83 mg per cent, cholesterol 422 mg per cent and phospholipids 392 mg per cent; a negative test for serum smooth muscle antibody and for hepatitis-associated ("Australia") antigen and a strongly positive test for serum mitochondrial antibody. On roentgenograms the firm subcutaneous nodules appeared calcified. Barium meal showed a marked lack of peristaltic activity in the lower part of the esophagus, although there was no dilatation.

Subsequently the patient has had several episodes of melena and then hematemesis, for which she required approximately 50 transfusions. Ascites has developed, and jaundice has increased. Esophagoscopy at another hospital* has shown both esophageal varices and telangiectasias on the esophageal and gastric mucous membrane. The telangiectasias on the hands are thought to have increased in number.

A needle biopsy specimen of liver taken in January 1969 showed fibrous widening of portal areas with proliferation of cholangioles and pseudocholangioles but with destruction of the limiting plate. There was no cholestasis, there were increased numbers of plasma cells, neutrophils and mesenchymal cells in the portal areas. Because of the presence and even proliferation of cholangioles, prolonged biliary tract obstruction was favored over primary biliary cirrhosis as the histologic diagnosis.

Case 4. A thirty-eight year old Mexican-American housewife (V.Z.) was first seen at LAC-USCMC in June 1968 because of the recent development of jaundice with moderate generalized pruritus. She felt well except for mild fatigue. There was no pain. The liver edge was barely palpable in inspiration just below the costal margin; the spleen was not palpable. Results of representative hepatic tests are listed in Table I. No definite diagnosis was established during a four week hospitalization. She was advised to discontinue birth control pills that she had been taking for a year on the chance that they might be the cause of the jaundice. She was lost to follow-up after discharge. She returned to LAC-USCMC in June 1969 because of moderate increase in jaundice and pruritus. She stated that jaundice and generalized mild pruritus remained after her initial hospitalization, although they fluctuated in intensity. She felt well otherwise except for mild chronic fatigue and did not resume taking the birth control pills.

* Information provided through the courtesy of Dr. Martin Pops, University of California at Los Angeles School of Medicine.

At the time of the second hospitalization there appeared to be some generalized increase in skin pigment. A firm, nontender liver edge was felt 6 cm below the right costal margin and 5 cm below the xiphoid on inspiration. The spleen was not palpable. There were no spider angiomas. Additional history was obtained of episodes of pain and blanching of the hands on exposure to cold during the past three to four years. The skin of the hands and forearms felt tight and smooth, and it was difficult to pick up a fold of skin in these areas. Small round telangiectasias were found on the volar surfaces of several fingers on each hand. She had not noted these. No lesions were found on the tongue or the lips or in the mouth. There was an increase in frequency of bowel movements to two or three times daily during the past year and the stool occasionally floated. Investigations included a normal barium esophagram, a positive test for serum mitochondrial antibody, a negative test for smooth muscle antibody and for hepatitis-associated ("Australia") antigen, total serum lipid of 1,705 mg per cent with phospholipid 656 mg per cent and cholesterol 364 mg per cent, hemoglobin 11.6 gm per cent and white blood cell count 6,600/cu mm with 2 per cent band forms, 53 per cent segmented neutrophils, 38 per cent lymphocytes, 3 per cent monocytes and 4 per cent eosinophils. Needle liver biopsy specimens were taken in June and again in July 1969. Quantitative liver copper content measured 25 mg/100 gm dry liver. Lipid content of a twenty-four hour stool sample was 18 gm. Wedged hepatic vein pressure was 7 mm Hg above vena caval pressure (normal 1 to 4 mm Hg).

The liver biopsy section of June 1969 was quite fragmented. There was cholestasis in centrolobular regions. The portal areas were widened by lymphocytes and fibrous tissue that destroyed the limiting plate and effaced the cholangioles. The biopsy specimen taken in July 1969 showed that the cholestasis had receded. The portal areas had less exudative reaction but modest fibrosis; cholangioles still could not be found.

The histologic pattern was thought to be strongly suggestive of primary biliary cirrhosis. There was no vascular anomaly. The small size of the biopsy specimens prevented an absolute histologic confirmation of the diagnosis.

Case 5. A fifty-one year old Caucasian housewife (H.B.) had seemed well until the gradual onset of jaundice in August 1967, without accompanying symptoms except for mild pruritus and fatigue. Jaundice continued during the next six months and she lost 20 pounds; it was uncertain whether this was due to her illness or to a low fat diet prescribed because of the discovery of marked hypercholesterolemia. At the time of hospitalization in January 1968 the liver and spleen were both enlarged, and there was a mild generalized increase in skin pigment. Tiny linear yellow xanthomas were visible in several of the palmar creases; there was no xanthelasma. There were two or three small, round telangiectasias on the volar aspect of several of the fingers of each hand. No lesions were seen in the mouth or on the lips. The patient was unaware of these lesions and had never had severe nosebleeds. Laparotomy with common duct exploration was performed, disclosing an enlarged smooth liver, an enlarged spleen, a normal gallbladder and a normal common bile duct. Operative cholangiography was normal, with good visualization of the intrahepatic bile ducts. In the next three months there was progressive clinical deterioration with fatigue, further weight loss and weakness. Jaundice continued and stools were bulky and increased in frequency. Ankle edema and then progressive ascites appeared in March 1968 and she was admitted to the liver service at LAC-USCMC for further care. Physical findings were unchanged from January 1968, except for ascites and edema. There was progressive deterioration until her death in hepatic coma with renal failure on May 5, 1968. One week prior to death necrotic lesions developed on the tips of several fingers which were painful despite the patient's semicomatose condition. The hands were cool but not ice-cold; there was no evidence of sepsis or circulatory failure. A test for cryoglobulins was negative. Additional investigations during her terminal illness included hemoglobin 7.7 gm per cent; white blood cell count 7,800/cu mm, with a normal differential; serum total lipids 1,058 mg per cent with phospholipids 510 mg per cent, cholesterol 390 mg per cent and triglycerides 158 mg per cent; serum dihydroxy bile acids 14 μg/ml (normal 0 to 1.9 μg/ml); trihydroxy bile acids 8.7 μg/ml (normal 0 to 3.5 μg/ml); lupus erythematosus cell test negative; ascitic fluid protein 2.2 gm per cent; and a serum mitochondrial antibody test that was strongly positive.*

Segments of liver taken at the time of laparotomy showed an intact lobular arrangement, but the portal areas were widened by heavy lymphocytic and plasma cell exudate with a preponderance of plasma cells. The limiting plate was destroyed by inflammatory cells. Cholangioles were markedly reduced. Some of the interlobular ducts were surrounded by lymphocytes, and in a few portal areas there were epithelioid cells in the centers of lymphoid nodules (Figure 4). The liver cords were intact, and there were no regenerative nodules or fibrous septums. There were striking bile plugs in scattered foci. The histologic pattern, including the epithelioid granulomas in the portal area, was considered to be quite characteristic for primary biliary cirrhosis. There was no suggestion of vascular anomalies in the biopsy specimen.

At autopsy the patient was cachectic, and her tissues were icteric. There were small areas of necrosis

* Kindly performed for us by the laboratory of Drs. Fred Kantor and Gerald Klatskin, New Haven, Connecticut.

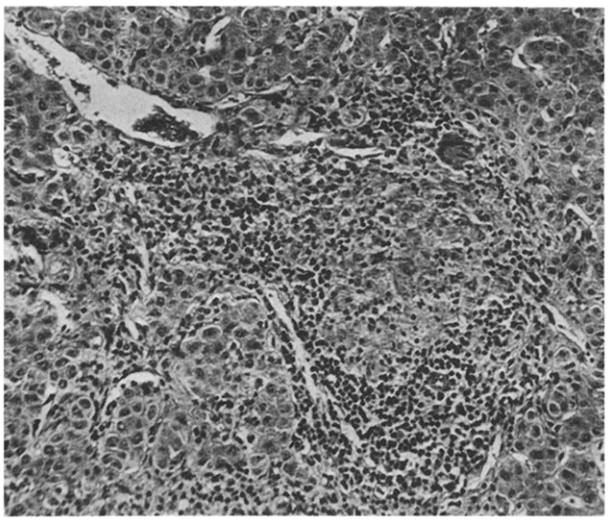

Figure 4. Case 5. Liver biopsy specimen obtained in January 1968 showing a portal area that is widened by lymphocytic and plasma cell infiltrate with destruction of cholangioles and development of an epithelioid granuloma. Note giant cell near top of photograph. (Hematoxylin and each stain, original magnification × 125).

at the fingertips near the nail margins. No vascular skin lesions were recognizable. The liver weighed 1,200 gm, the common bile duct circumference was 1.3 cm. Although the liver was bile-stained, the capsule was smooth. There was scarring around the common bile duct, but the duct was patent throughout, and there were no stones. There was no thickening of the wall of the gastrointestinal tract. The lungs were pale pink and well aerated.

Microscopically the liver had an intact lobular arrangement, but the small portal areas were almost replaced by relatively acellular fibrous scarred areas. Hepatic arterioles and portal veins were recognizable, but cholangioles were generally absent (Figure 5). Larger portal structures did have lymphoid activity and interlobular ducts. There were no granulomas; there was canalicular cholestasis. There were no areas of vascular ectasia in any of the multiple segments of liver examined.

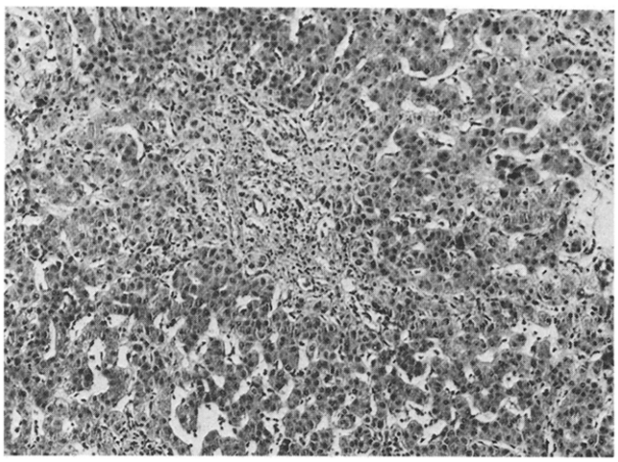

Figure 5. Case 5. Section of liver taken at autopsy shows a portal area in the center of the field with destruction of the limiting plate and cholangioles. Central veins are at the extreme right and left of the photograph. (Hematoxylin and eosin stain, original magnification × 125).

The pulmonary arterioles were slightly thickened, but there was no fibrous thickening of the alveolar septums. The submucosa of the gastrointestinal tract was not thickened or fibrotic. The renal arterioles were not thickened. The skeletal muscle fibers were quite atrophic but the small arteries had no alterations.

The changes on biopsy and at autopsy were those of primary biliary cirrhosis. The granulomas that had been present in the biopsy specimen were no longer found at autopsy, and the destructive lesions of the portal regions had become relatively quiescent in that the inflammatory activity had diminished and there had been no progression of the destructive process.

Case 6. A sixty-seven year old Caucasian housewife (I.B.) was found in November 1966 to have abnormal hepatic tests that included 27 per cent retention of bromsulfalein, marked elevation of alkaline phosphatase levels and moderate increase in transaminase activity (Table I). Complaints were vague malaise and fatigue. These complaints persisted, in addition to mild generalized pruritus, until she was hospitalized for evaluation in February 1968. At this time the liver edge was not palpable. There was some generalized increase in skin pigmentation. Numerous small telangiectasias were found on the finger pads of both hands (Figure 6) and on the lower lip. She was not aware of their presence. The spleen was not palpable, there was no jaundice, there were no spider angiomas and no xanthelasma or skin xanthomas. Investigations included a normal cholecystogram and intravenous cholangiogram, hematocrit of 32 per cent, negative tests for antinuclear antibody and for lupus erythematosus cells and serum leucine aminopeptidase activity of 844 units/ml (normal 80 to 210 units/ml). Needle liver biopsy was performed. No definite diagnosis was made.

During the next year her condition remained about the same, with fatigue, mild pruritus and increasing melanosis. The laboratory abnormalities persisted. Jaundice appeared in July 1969 and gradually increased. The frequency of her bowel movements increased to three or four daily, and the stool sometimes floated. At the time of the last evaluation in August 1969 the liver edge was palpable 1 to 2 cm below the right costal margin on inspiration. The skin of the backs of the fingers and hands was somewhat tight and suggestive of scleroderma, although she was still able to make a fist with ease. She stated that her hands have had a tendency to become cold and pale at times

during the past few years, but she did not describe classic Raynaud's phenomenon. The serum mitochondrial antibody test was positive, the smooth muscle antibody and hepatitis-associated ("Australia") antigen tests were negative.

Microscopic examination of the liver biopsy specimen obtained in February 1968 showed considerable fragmentation. The portal areas were somewhat poorly defined and the limiting plate was infiltrated by lymphocytes and to some extent by plasma cells. Cholangioles were numerically reduced although an occasional ductal structure could be identified. Kupffer's cells were hyperplastic throughout the liver, and there were increased numbers of lymphocytes in sinusoids. The liver cells were shrunken, and the liver cords were quite regular. There was very little fibrosis. Cholestasis was not demonstrable. The histologic impression was that the biopsy specimen was consistent with a primary biliary cirrhosis but not diagnostic of that disease.

SUMMARY OF FINDINGS

Representative hepatic test results, soon after the first recognition of liver disease and again at the time of last evaluation at LAC-USCMC, are listed in Table I. The abnormalities are similar in all patients and consist of mild or moderate hyperbilirubinemia, markedly elevated alkaline phosphatase levels, moderate depression of serum albumin and increase in globulin and slight increase in transaminase activity. Prothrombin time has been normal or nearly normal. Serum cholesterol and phospholipid levels are moderately or markedly elevated. In the patient with the most marked hypercholesterolemia (Case 5), there was a marked decrease in hyperlipidemia with increasing severity of liver disease. The serum mitochondrial antibody test has been positive in all patients.

All the patients have had pruritus to some degree, and all have had symptoms suggesting steatorrhea. Only one patient has had skin xanthoma and, surprisingly, none have had xanthelasma. Absence of biliary tract obstruction was determined at surgery in three patients and by normal intravenous cholangiography in two patients. One patient (Case 4) has not had surgery and is too jaundiced for cholangiography. Known duration of liver disease ranges from nineteen months (Case 4) to five and a half years (Case 2). The total course in one patient (Case 5, twenty-one months) was unusually short for primary biliary cirrhosis.

The features of interest relative to the CRST syndrome are summarized in Table II. All six patients had telangiectasias typical of those seen in the R-O-W syndrome. They were numerous and obvious in four patients (Cases 1, 2, 3, and 6) but were much less numerous and could easily have been overlooked in the remaining two patients (Cases 4 and 5). Three patients (Cases 1, 2, and 3) have had several episodes of upper gastrointestinal tract bleeding. Because of the relatively low wedged hepatic vein pressure and small size of the esophageal varices in one (Case 1), mucosal telangiectasias were considered a more likely source of her bleeding. Only small esophageal varices were seen in another (Case 2), and it is possible that undetected telangiectasias were responsible for her repeated bleeding episodes. In the third patient (Case 3), large varices were present, and there was clinical evidence of portal hypertension so that either the visualized mucosal telangiectasias or the esophageal varices might have been responsible for the severe recurring hemorrhages. The presence of portal hypertension might increase

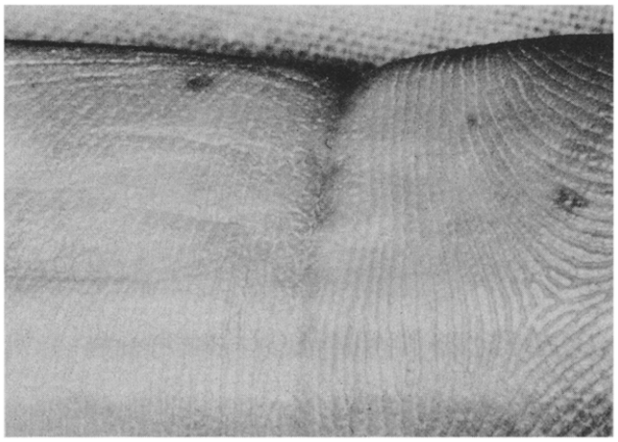

Figure 6. Case 6. Telangiectasias on the fingers.

TABLE II Incidence of the Elements of the CRST Syndrome Found in Our Six Patients with Primary Biliary Cirrhosis

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Raynaud's phenomenon	+	+	+	+	?	±
Sclerodactyly	+	+	+	±	−	+
Calcinosis cutis	+	−	+	+	−	−
Esophageal motility disturbance	−	+	+	−	−	−
Telangiectasias						
Hands	+	+	+	+	+	+
Mouth	+	+	+	−	−	+
Gastrointestinal	+	−	+	?	−	?
Upper gastrointestinal bleeding	+	+	+	−	−	−

NOTE: ? = not determined; ± = uncertain.

the risk of bleeding from gastrointestinal telangiectasias.

Raynaud's phenomenon was prominent in four of our patients. Two had had sympathectomy performed for this many years previously with considerable relief, and the operation had been considered in a third. In one patient (Case 6) the history was suggestive of Raynaud's phenomenon but not definite. In the patient who died before we were fully aware of the syndrome we are describing (Case 5), there is no record of Raynaud's phenomenon on her hospital chart, but it is possible that the proper questions were not asked. Unexplained necrosis of the finger tips developed terminally. The skin changes of sclerodactyly were present in five of our six patients but were severe in only one (Case 1). Three patients had areas of calcinosis cutis. Two had decreased esophageal motility characteristic of that seen in scleroderma. None of the patients had evidence of other visceral involvement with systemic sclerosis, with one possible exception (Case 5) in which minor pulmonary vascular changes were found at autopsy.

FAMILY STUDIES

Twenty-nine immediate relatives of our six patients were examined for evidence of telangiectasias or liver disease. These included seven siblings, five parents, eleven children and six nieces and nephews. None had a history or obvious evidence of liver disease with the exception of the mother of one patient (Case 4) who was recovering from surgery for removal of a common duct stone. There was no history of excessive bleeding in the immediate family of any of our patients. Several relatives had tiny telangiectatic lesions on the fingers or lips that were visible only to careful inspection and were not considered to be typical of those seen in R-O-W syndrome. Similar nonspecific lesions were found in thirteen of seventy-six control subjects (unselected female hospital patients between the ages of twenty and eighty-six). In nine close relatives of our patients the serum was examined for mitochondrial antibody, and all had a negative reaction. Serum from ten patients with typical R-O-W syndrome and from nine patients with typical CRST syndrome gave a negative test for mitochondrial antibody.

COMMENTS

The term CRST syndrome was coined by Winterbauer in 1964 [7]. As he pointed out, the occurrence of telangiectasias in patients with scleroderma had been recorded previously [10–12] but the similarity of the vascular lesions to those seen in the R-O-W syndrome does not seem to have been recognized. Despite the similar appearance and location of the lesions, it was uncertain whether patients with the CRST syndrome had the same hereditary disorder as patients with the R-O-W syndrome. Winterbauer and others [7,13–15] have pointed out that a history of bleeding from the vascular lesions is usually lacking in patients with CRST. Winterbauer [7] examined 129 relatives of his seven patients without finding any typical skin lesions and obtained a negative history for hemorrhagic phenomena and skin lesions in an additional 253 relatives. Most family surveys of patients with R-O-W syndrome show large numbers with skin lesions and hemorrhagic phenomena [16–20]. However, this difference between CRST syndrome and R-O-W syndrome seems relative rather than absolute. Winterbauer [7] mentions one patient with CRST syndrome, known to him but not included in his report, who had hematuria and hematemesis and telangiectatic lesions in the bladder and the stomach. One of his seven patients had recurrent epistaxis, and another had visible telangiectasias in the rectum and in the stomach. At least two of the patients included in our report (Cases 1 and 3) have mucosal telangiectasias which may well have bled on several occasions. We know of another patient with typical CRST syndrome whose father has typical R-O-W syndrome with recurrent epistaxis and gastrointestinal bleeding. In all probability, therefore, the CRST and R-O-W syndromes are intimately related although it is not clear why bleeding is infrequent and family history is usually negative in the former.

There seems to be no valid reason to question the relationship of the CRST syndrome to systemic sclerosis (scleroderma). A few patients with typical CRST syndrome have had evidence of systemic sclerosis [13,14] and a few have had family members with systemic sclerosis [14,22]. Disturbed esophageal motility has been a common finding in the CRST syndrome [7,13,14]. Sclerodermatous changes in the hands ("acrosclerosis") seem to be relatively benign and may remain as the only expression of systemic sclerosis for many years. In only three of seventy-one patients with acrosclerosis described by Farmer et al. [21] did signs of systemic sclerosis develop in a follow-up period averaging ten years.

The liver is generally not considered to be one of the organs involved in progressive systemic sclerosis, and there are only a few reports in the literature of coincident liver disease and scleroderma. D'Angelo et al. [23] found more instances of cirrhosis in fifty-eight control patients than they

did in fifty-eight patients with systemic sclerosis. Bartholomew et al. [24] found eight examples of chronic liver disease in 727 cases of scleroderma and concluded that there was no relationship between the two disorders. None of the case descriptions suggests primary biliary cirrhosis, but many are incomplete. Other articles [25–29] mention occasional patients with liver disease. Copeman and Medd [30] describe a patient very much like ours with pruritus, Raynaud's phenomenon, melanosis, sclerodermatous changes of the hands and arms, facial and palmar telangiectasias, marked elevation of alkaline phosphatase, a normal biliary tree and a nodular liver with portal fibrosis. The gallbladder was thick walled; they considered the changes in the gallbladder and liver to be due to systemic sclerosis. This patient had anemia and melena which was ascribed to bleeding from a hiatus hernia. Calvert and co-workers [31] describe two patients with scleroderma and portal hypertension. One of these resembles our cases. This was a fifty-three year old woman with Raynaud's phenomenon, steatorrhea, telangiectasias of the face and tongue, sclerodactyly, marked elevation of alkaline phosphatase levels and a granular "cirrhotic" liver. Slight jaundice (serum bilirubin 2.1 mg per cent) appeared after six months of observation. There was bleeding in the upper gastrointestinal tract. At autopsy, no gastrointestinal telangiectasias were described, and there were said to be "several varices" in the lower part of the esophagus. The liver "showed a fine cirrhosis with a smooth capsular surface and varying degrees of nodularity. The degree of basic hepatic fibrosis was neither uniform nor intense." The records of our liver unit include a total of six patients with a diagnosis of scleroderma and some type of liver disease. The hepatic diagnoses were alcoholic liver disease (three patients), "lupoid" hepatitis (one patient) and cryptogenic cirrhosis (two patients). One of the latter had evidence of long-standing chronic liver disease with hepatosplenomegaly, ascites and slight jaundice. Serum alkaline phosphatase was unusually high (113 King-Armstrong units/ml). No telangiectasias were noted. This patient died in 1967.

R-O-W syndrome can be associated with liver disease. Hales [32], Michaeli et al. [33], Zelman [34] and Halpern et al. [8] have described multiple telangiectasias in the liver that can act as hepatic artery-hepatic venous shunts. These may be surrounded by fibrosis and apparently can lead to a liver disorder that Martini [35] has characterized as a type of "cirrhosis." The liver disease in our patients does not appear to resemble this liver lesion, and in one patient (Case 1) a celiac angiogram showed no evidence of vascular shunts in the liver.

Since the syndrome we are describing seems rather common, judging from our experience (six of a total of forty-one cases with primary biliary cirrhosis), it is surprising that so few patients fitting this description have been mentioned in the literature. It is inconceivable that the telangiectasias in these patients could be confused with the spider angiomas of chronic liver disease. Neither their location nor their appearance is similar. In four of our patients the vascular lesions were numerous and obvious, and could hardly have been overlooked. In the other two cases they could easily have been missed in an examination that was less than searching, and they could be passed off as unimportant by someone not familiar with the syndrome of R-O-W. Nineteen of our total of forty-one patients with primary biliary cirrhosis are not available for re-examination either because they are dead or have moved away from this area, so the true incidence of this syndrome may be greater than our report indicates.

It is interesting to speculate whether the gastrointestinal bleeding episodes in our Cases 1, 2 and 3 are due to gastrointestinal telangiectasias. Variceal hemorrhage is not considered to be frequent except as a terminal event in primary biliary cirrhosis [36]. Zeegen et al. [37] reported, however, that twenty-three of their total of 250 patients with portal decompression operations for intrahepatic portal hypertension had primary biliary cirrhosis. Interestingly, fifteen of these twenty-three patients seemed to have bleeding as the first manifestation of their disease. One wonders if undetected gastrointestinal telangiectasias could have been responsible for bleeding in some of these patients. Relief of portal hypertension might decrease the tendency to bleed from such lesions.

Scleroderma appears to be a collagen disease; the R-O-W syndrome is clearly a hereditary angiodysplasia whereas primary biliary cirrhosis is neither hereditary nor does it resemble a collagen disease. The association of these disorders in our material is too frequent to be due to chance alone and might provide a clue to the pathogenesis of primary biliary cirrhosis.

ADDENDUM

Since this paper was submitted for publication, two similar patients have been described by Murray-Lyon et al. [38].

REFERENCES

1. Reynolds TB, Denison EK, Frankl HD, Lieberman FL, Peters RL: New syndrome: combination of primary biliary cirrhosis, scleroderma and hereditary hemorrhagic telangiectasia (abstract). Gastroenterology 58: 290, 1970.
2. Myers JD: Xanthomatous biliary cirrhosis following chlorpromazine with observations indicating overproduction of cholesterol, hyperprothrombinemia and the development of portal hypertension. Trans Ass Amer Physicians 70: 243, 1957.
3. Kohn NN, Myerson RM: Xanthomatous biliary cirrhosis following chlorpromazine. Amer J Med 31: 665, 1961.
4. Walker JG, Doniach D, Roitt IM, Sherlock S: Serological tests in diagnosis of primary biliary cirrhosis. Lancet 1: 827, 1965.
5. Goudie RB, MacSween RNM, Goldberg DM: Serological and histological diagnosis of primary biliary cirrhosis. J Clin Path 19: 527, 1966.
6. Kantor FS, Klatskin G: Serological diagnosis of primary biliary cirrhosis: a potential clue to pathogenesis. Trans Ass Amer Physicians 80: 267, 1967.
7. Winterbauer RH: Multiple telangiectasia, Raynaud's phenomenon, sclerodactyly and subcutaneous calcinosis: a syndrome mimicking hereditary hemorrhagic telangiectasia. Bull Johns Hopkins Hosp 114: 361, 1964.
8. Halpern M, Turner AF, Citron BP: Hereditary hemorrhagic telangiectasia. Radiology 90: 1143, 1968.
9. Butt EM, Nusbaum RE, Gilmour TC, DiDio SL: Trace metal patterns in disease states. Amer J Clin Path 42: 437, 1964.
10. Prosser Thomas EW: Calcinosis cutis and scleroderma: Thibierge-Weissenbach syndrome. Lancet 243: 389, 1942.
11. Verel D: Telangiectasia in Raynaud's disease. Lancet 271: 914, 1956.
12. Tuffanelli DL, Winkelmann RK: Systemic scleroderma. Arch Derm (Chicago) 84: 359, 1961.
13. Carr RD, Heisal EB, Stevenson TD: CRST syndrome: a benign variant of scleroderma. Arch Derm (Chicago) 92: 519, 1965.
14. Schimke RN, Kirkpatrick CH, Delp MH: Calcinosis, Raynaud's phenomenon, sclerodactyly and telangiectasia. Arch Intern Med (Chicago) 119: 365, 1967.
15. Duperrat B: Deux cas de sclérodactylie avec télaniectasis du visage. Bull Soc Franc Derm Syph 72: 126, 1965.
16. Steiner WR: Hereditary hemorrhagic telangiectasia: with report of three families and a review of those previously recorded. Arch Intern Med (Chicago) 19: 194, 1917.
17. Garland HG, Anning TT: Hereditary hemorrhagic telangiectasia: a genetic and bibliographic study. Brit J Derm 62: 289, 1950.
18. Dolowitz DA, Rambo ON Jr, Stephens FE: Hereditary hemorrhagic telangiectasia. Ann Otol 62: 642, 1953.
19. Bean WB: Vascular Spiders and Related Lesions of the Skin, Springfield, Ill, Charles C Thomas, 1958.
20. Hodgson CH, Burchell HB, Good AC, Clagett OT: Hereditary hemorrhagic telangiectasia and pulmonary arterio-venous fistula. New Eng J Med 261: 625, 1959.
21. Farmer RG, Gifford RW, Hines EA: Raynaud's disease with sclerodactylia: a follow-up study of 71 patients. Circulation 23: 13, 1961.
22. McAndrew GM, Barnes EG: Familial scleroderma. Ann Phys Med 8: 128, 1965.
23. D'Angelo WA, Fries JF, Masi AT, Shulman LE: Pathologic observations in systemic sclerosis (scleroderma). Amer J Med 46: 428, 1969.
24. Bartholomew LG, Cain JC, Winkelman RK, Baggenstoss AH: Chronic disease of the liver associated with systemic scleroderma. Amer J Dig Dis 9: 43, 1964.
25. Goetz RH, Berne MB: The pathology of progressive systemic sclerosis (generalized scleroderma): with special reference to changes in the viscera. Clin Proc 4: 337, 1945.
26. Beigelman PM, Goldner F, Bayles TB: Progressive systemic sclerosis (scleroderma). New Eng J Med 249: 45, 1953.
27. Piper WN, Helwig EB: Progressive systemic sclerosis; visceral manifestations in generalized scleroderma. Arch Derm (Chicago) 72: 535, 1955.
28. Batsakis JG, Johnson HA: Generalized scleroderma involving lungs and liver with pulmonary adenocarcinoma. Arch Path 69: 633, 1960.
29. Treacy WL: Scleroderma of the gastrointestinal tract: a clinical-pathological study. Thesis, Graduate School, University of Minnesota, 1960.
30. Copeman PWM, Medd WE: Diffuse systemic sclerosis with abnormal liver and gallbladder. Brit Med J 3: 353, 1967.
31. Calvert RJ, Barling B, Sopher M, Feiwel M: Systemic scleroderma with portal hypertension. Brit Med J 1: 22, 1958.
32. Hales MR: Multiple small arteriovenous fistulae of the lungs. Amer J Path 32: 927, 1956.
33. Michaeli D, Ben-Bassat I, Miller HI, Deutsch V: Hepatic telangiectasias and portosystemic encephalopathy in Osler-Weber-Rendu disease. Gastroenterology 54: 929, 1968.
34. Zelman S: Liver fibrosis in hereditary hemorrhagic telangiectasia. Arch Path 74: 66, 1962.
35. Martini GA: Cirrhosis of the liver in hereditary hemorrhagic telangiectasia. Proceedings of the Third World Congress of Gastroenterology, vol II, Baltimore, The Williams and Wilkins Co, 1959, p 857.
36. Ahrens EH Jr, Payne MA, Kunkel HG, Eisenmenger WJ, Blondheim SH: Primary biliary cirrhosis. Medicine (Balt) 29: 299, 1950.
37. Zeegen R, Stansfeld AG, Dawson AM, Hunt AH: Bleeding esophageal varices as the presenting feature in primary biliary cirrhosis. Lancet 2: 9, 1969.
38. Murray-Lyon IM, Thompson RPM, Ansell ID, Williams R: Brit Med J 3: 258, 1970.