MEDICAL GRAND ROUNDS

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PRIMARY BILIARY CIRRHOSIS

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Primary biliary cirrhosis (PBC) is a disease of the small bile ducts of the liver (chronic non-suppurative destructive cholangitis). Progressive destruction of these ducts leads to the development of obstructive jaundice on a mechanical basis even though the large bile ducts remain patent. Early in the course of the disease, the lesion is confined largely to the portal and periportal regions of the liver lobule. Cirrhosis, histologically, is a late manifestation.

The disease is unusual in many respects. It is largely a disorder of middle-aged women. It is characterized by a high incidence of abnormal immunological phenomena. Two of these, particularily the presence in serum of antimitochondrial antibodies, and high concentrations of IgM, are of value diagnostically. Etiology is unknown. Treatment is largely symptomatic and aimed at correcting abnormalities induced by progressive intrahepatic biliary tract obstruction.

Pathology

Classification of Intrahepatic Biliary Passages

The following nomenclature is utilized. *Bile canaliculi* are the biliary spaces lined by hepatocytes. *Bile ductules* are passages lined by cuboidal or flat epithelium and are not accompanied by branches of the portal vein, but sometimes by very small branches of the hepatic artery. In the normal liver they appear mainly in the portal tracts and rarely extend far into the lobule.

The *interlobular bile ducts* which are the smallest ducts accompanied by a branch of the portal vein, have a columnar epithelium with nuclei in the center or toward the basal portion of the cell. More than one interlobular duct may appear in a portal tract, and each is accompanied by portal vein branches. *Septal bile ducts*, from which the interlobular ducts branch, are single ducts with high columnar epithelium and basal nuclei; goblet cells are frequent.

Proliferated bile ductules are of two types. Those with cuboidal or plump oval epithelium surrounding a distinct lumen lie within the portal tract or at its immediate periphery and are designated "typical ductules." Other ductules, especially those extending into the parenchyma, have a flat irregular epithelium and a minute lumen; these are termed "atypical ductules."

Hepatic Histology

The disease is essentially one of progressive cholangitis with eventual disappearance of septal and interlobular bile ducts within the liver. Four stages can be recognized:

Stage 1: Florid Duct Lesion

The florid duct lesion is virtually pathognomonic. Septal and larger interlobular bile ducts are damaged and surrounded by a dense infiltrate of lymphocytes,

large histiocytes, or epithelioid cells, plasma cells, and a few eosinophils. Lymphoid aggregates, with or without germinal centers, may be found. Granulomas are often seen as poorly defined collections of histiocytes or as well-organized tuberculoid lesions with giant cells but without central necrosis. They are usually near a damaged duct in the portal tract. This damage is seen as swelling, proliferation, and crowding of epithelial cells and as rupture. The epithelial cells of the bile ducts are swollen and have finely granular eosinophilic cytoplasm with little or no vacuolization. They are in a single layer.

The portal tract is otherwise normal, and the limiting liver cell plates are usually intact. Within the lobules there may be slight mononuclear cell infiltration and regenerative hyperplasia seen as double plates. Centrilobular cholestasis may be seen, but is often absent and rarely severe.

Stage 2: Ductular Proliferation

The lesions are now more widespread throughout the expanded portal tracts, but they are less specific. There is fibrosis, acute and chronic inflammatory infiltration, and ductular proliferation. Ducts are reduced in number and their place is taken by ill-defined lymphoid aggregates that together with the fibrosis and inflammation give a rather characteristic appearance. The appearances are often compatible with or suggestive of PBC rather than diagnostic. Granulomas are less common. Periportal areas show a slight-to-moderate degree of hepatocellular necrosis, swelling, and cholestasis. Lipid-laden histiocytes are sometimes seen.

Stage 3: Scarring

The inflammation subsides and relatively acellular septa extend from the portal tracts into and around the lobules. Lymphoid aggregates are still seen, and periportal cholestasis may be severe. Ducts are reduced in number. Here again, the appearances are not pathognomonic of PBC but can be interpreted as highly suggestive and compatible.

Stage 4: Cirrhosis

Regenerative nodules are seen, and the picture is of end-stage hepatic disease. The diagnosis may still be suggested by paucity of bile ducts or by accumulations of lymphocytes. There is much overlap between the stages, to the extent that stage-1 lesions are occasionally seen in stage-4 livers with well-established cirrhosis.

TABLE 1

Interlobular Bile Ducts in Cirrhosis

(adapted from Baggenstoss et al., Am. J. Clin. Path. 42:259, 1964)

	Number of specimens	Interlobular ducts per portal tract	% of portal tracts without interlobular ducts
Controls			
(no liver disease)	12	1.42	6.5
Cirrhosis			
Alcoholic	12	1.51	8.8
Postnecrotic	12	1.45	10.0
Obstructive	12	1.83	8.2
Primary biliary			
Needle biopsy	18	0.47	65.4
Wedge biopsy	22	0.47	66.5
Necropsy	11	0.33	75.6

Fig. 1. A rate of parallelism of the artery with associated bile duct in each group of arterial size.

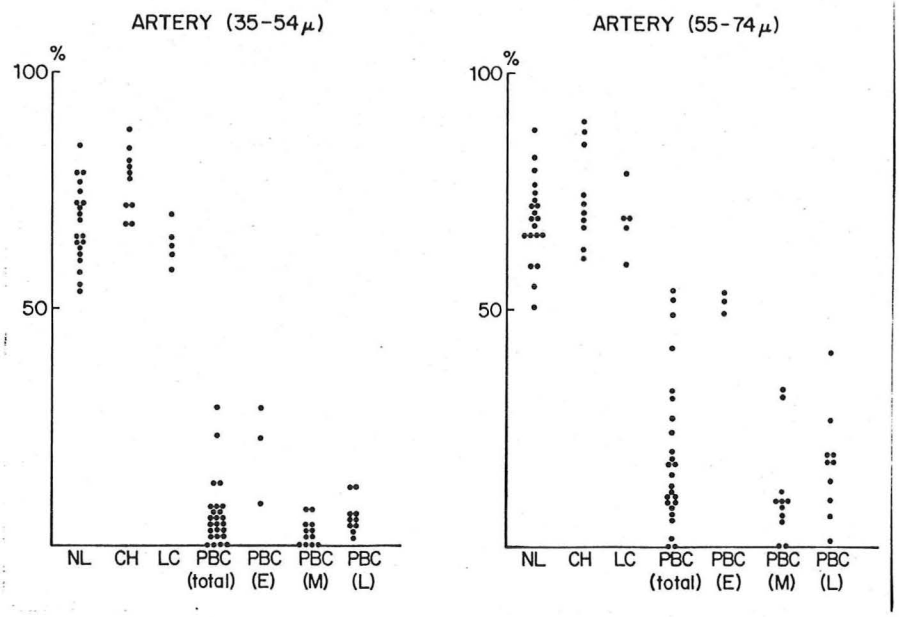

Fig. 1A

Fig. 1B

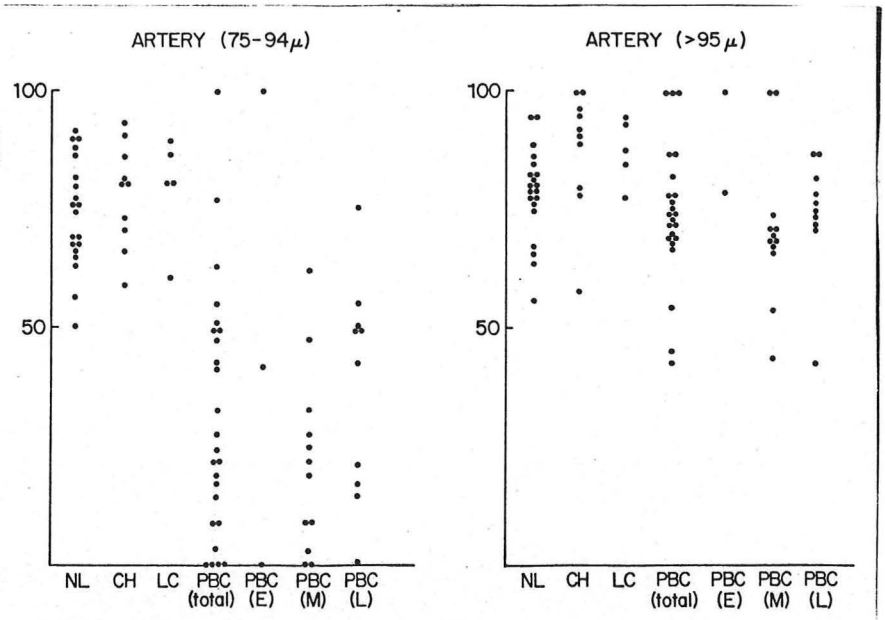

Fig. 1C

Fig. 1D

NL: normal liver (20 cases) CH: chronic hepatitis (10 cases)
LC: liver cirrhosis (5 cases) PBC: primary biliary cirrhosis
E: early stage M: middle stage L: later stage

(unpublished observations of Nakanuma, Y. and Ohta, G., Kanazawa, Japan)

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Hepatocellular Hyalin

Hyalin deposits similar to the Mallory bodies found in liver cells in alcoholic liver disease are found in 25 to 45 per cent of patients with primary biliary cirrhosis. The deposits are usually found in the peripheral portions of the hepatic lobule adjacent to portal tracts and connective-tissue septa. Their presence does not correlate with any clinical or biochemical parameters of the disease. Hyalin is found in other liver diseases too.

TABLE 2

Conditions Associated with Liver Cell Hyalin

Alcoholic hepatitis
Jejuno-ileal bypass liver disease
Primary biliary cirrhosis
Chronic extrahepatic biliary obstruction
Wilson's disease
Cryptogenic cirrhosis
Indian childhood cirrhosis
Hepatoma

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Biopsy Diagnosis

The chances of making a firm histologic diagnosis are greater with a larger operative biopsy than a smaller needle one. Typical lesions considered diagnostic include degenerating or necrotic interlobular ducts, portal granulomata, and dense portal aggregates of mononuclear cells arranged in the form of follicles. Other lesions are considered to be consistent with the diagnosis, but not diagnostic since they often resemble those of chronic active hepatitis. A paucity of interlobular ducts, when an adequate number of portal tracts is available for study, is an essential but not sufficient criterion for the diagnosis of PBC.

The experience with biopsies in 100 consecutive cases at the Royal Free Hospital in London is as follows:

TABLE 3

Hepatic Histology in the Diagnosis of Primary Biliary Cirrhosis

Source of biopsy	No. of Biopsies	Histologic Interpretation		
		Compatible	Diagnostic	Granuloma
Needle	59	42(71%)	17(29%)	3
Operative	41	13(30%)	28(70%)	6

(from Sherlock, S. and Scheuer, P. J. N. Engl. J. Med. 289:674, 1973)

The advantage of the operative biopsy is not sufficiently great to merit surgical exploration of all patients with suspected PBC. Compatible appearances are sufficiently diagnostic if taken in the context of the clinical picture and serological tests.

The Disease

Primary biliary cirrhosis has been reported from all parts of the world. It is predominantly a disease of middle-aged women. Approximately 90 per cent of reported cases are female, and 75 per cent are diagnosed between the ages of 40 and 60.

The disease starts insidiously; dating of onset is virtually impossible. Clinical presentation in 100 consecutive cases seen at the Royal Free Hospital was as follows:

TABLE 4

Clinical Presentation in 100 Cases of
Primary Biliary Cirrhosis

(developed from data of Sherlock, S. and
Scheuer, P. J., N. Engl. J. Med. 289:674, 1973)

Pruritus without jaundice	57		
Pruritus and jaundice	20		
Onset in late pregnancy		5	
Jaundice preceding pruritus	2		
Jaundice without pruritus	6		
Hepatosplenomegaly	3		
Portal hypertension	4		
Bleeding varices		3	
Ascites		1	
Other disease	4		
Duodenal ulcer		1	
Dermatomyositis		1	
Rheumatoid arthritis		1	
Sicca (Sjögren's) syndrome		1	
Abnormal laboratory tests	4		
Antimitochondrial antibody		2	
Arthritis			1
Autoimmune adrenal insufficiency			1
Elevated alkaline phosphatase		2	

Pruritus is the major presenting complaint. Occasionally it develops in the last trimester of pregnancy and is confused with cholestatic liver disease of late pregnancy. After delivery, pruritus may persist, or disappear but reappear at a variable period later. Pruritus may appear when a previously asymptomatic person is given birth control pills or other potentially cholestatic hormones.

Jaundice eventually develops in virtually all patients; is frequently delayed for 6 months to 2 years after the onset of pruritus, but may not appear even as long as 10 years after pruritus is first noted.

TABLE 5

Development of Jaundice in Patients Presenting with Pruritus

		No. Patients	%
Pruritus without jaundice		57	
Jaundice develops	in 6 months	14	25
	in 1-20 years; (majority by 2 years)	27	47
Still not jaundiced (1-10 years)		16	28

(developed from data of Sherlock, S. and Scheuer, P. J., N. Engl. J. Med. 289:674, 1972)

Other prominent clinical findings and laboratory data are as follows:

TABLE 6

Clinical Findings in Primary Biliary Cirrhosis

	%
Pruritus	>90
Jaundice	70 - >90
Hepatomegaly	85 - 100
Splenomegaly	50 - 80
Hyperpigmentation	35 - 50
Xanthomata mainly xanthelasma	30 - 50

TABLE 7

Laboratory Data in Primary Biliary Cirrhosis

	%
Hyperbilirubinemia	80 - >90
Raised alkaline phosphatase	100
Hypercholesterolemia	85 - >90

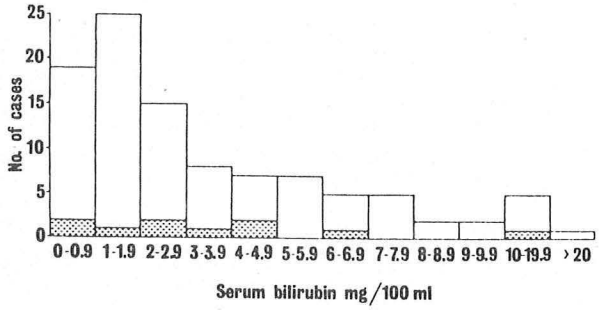


Fig. 2. Serum bilirubin levels at presentation in 100 patients with primary biliary cirrhosis. (from Sherlock, S. and Scheuer, P.J., N. Eng. J. Med. 289:674, 1973)

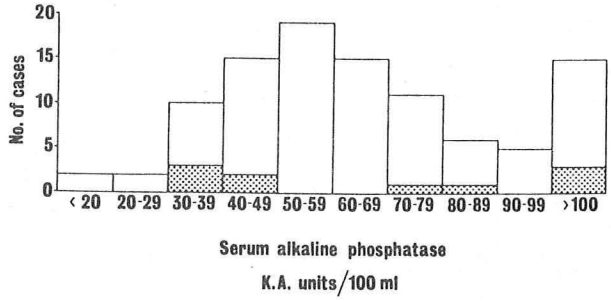
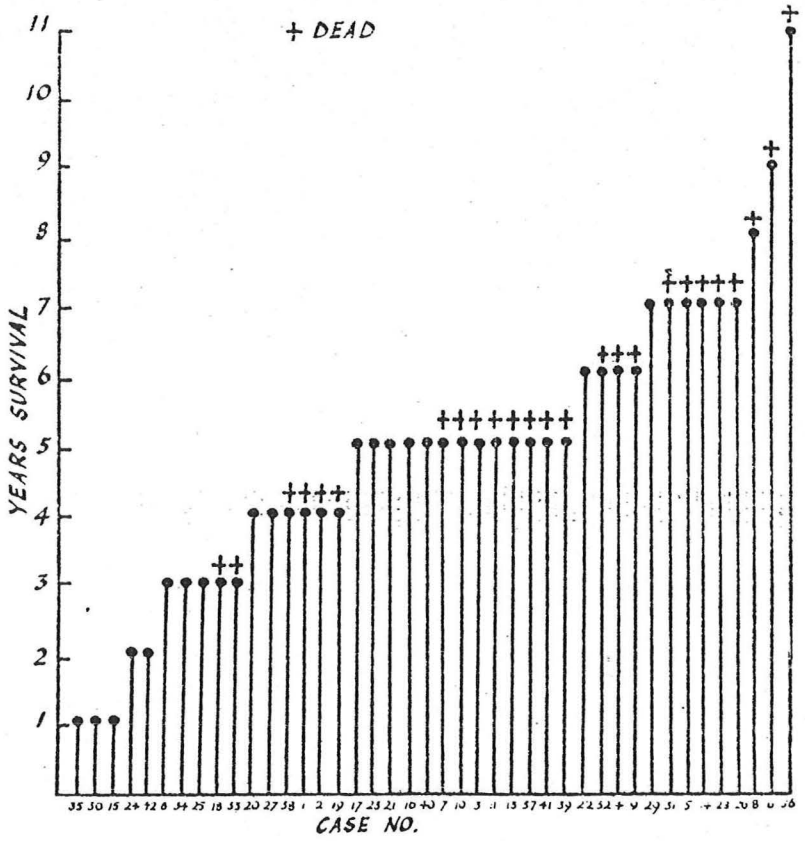


Fig. 3. Serum alkaline phosphatase levels (normal 3-14 K.A. Units) at presentation in 100 patients with primary biliary cirrhosis. (from Sherlock, S. and Scheuer, P.J., N. Eng. J. Med. 289:674, 1973)

Jaundice progresses during the course of the illness but is extremely variable. During the final few months of the disease, icterus deepens precipitately. Patients surviving for longer than 6 years usually have serum bilirubins less than 5 mg per 100 ml until their last few months. In general, those most deeply jaundiced run the shortest course and have the greatest likelihood of developing early hepatocellular failure.

With progression of the disease, serum albumin, cholesterol and alkaline phosphatase tend to fall.

Fig. 4. The duration of disease in fatal cases and followup period in those surviving.



(from Sherlock, S., Gastroenterology 37:574, 1959)

TABLE 8

Changes in Laboratory Tests during the Course of Primary Biliary Cirrhosis

Serum Albumin gm/100 ml		Serum Cholesterol mg/100 ml		Alkaline Phosphatase King-Armstrong units	
Initial	>3 years later	Initial	>3 years later	Initial	>3 years later
3.9	2.7	1052	368	81	39

(adapted from Sherlock, S. Gastroenterology 37:574, 1959)

Portal hypertension formerly believed to be a late and unusual complication is now also known to account for bleeding from esophageal varices as an early presentation.

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Association with Other Diseases

Primary biliary cirrhosis is one of three liver disorders (i.e. PBC; chronic active hepatitis, non-HB$_s$Ag related; cryptogenic cirrhosis) in which evidence of multisystem involvement is common. In one large series, Sjögren's syndrome occurred in 37 per cent, renal tubular acidosis in 32 per cent, pulmonary diffusion defects in 26 per cent and peripheral neuropathy in 10 per cent of patients with these diseases. The incidence of other conditions determined from clinical features alone was as follows: skin lesions in 17, arthropathy in 14, thyroid disorders in 10, and colitis in 5 per cent respectively. In the complete series of 218 patients, 125 (57 per cent) had involvement of at lease one organ other than the liver, such involvement being significantly more common in those with primary biliary cirrhosis (68 per cent) and chronic active hepatitis (63 per cent) than in those with cryptogenic cirrhosis (38 per cent).

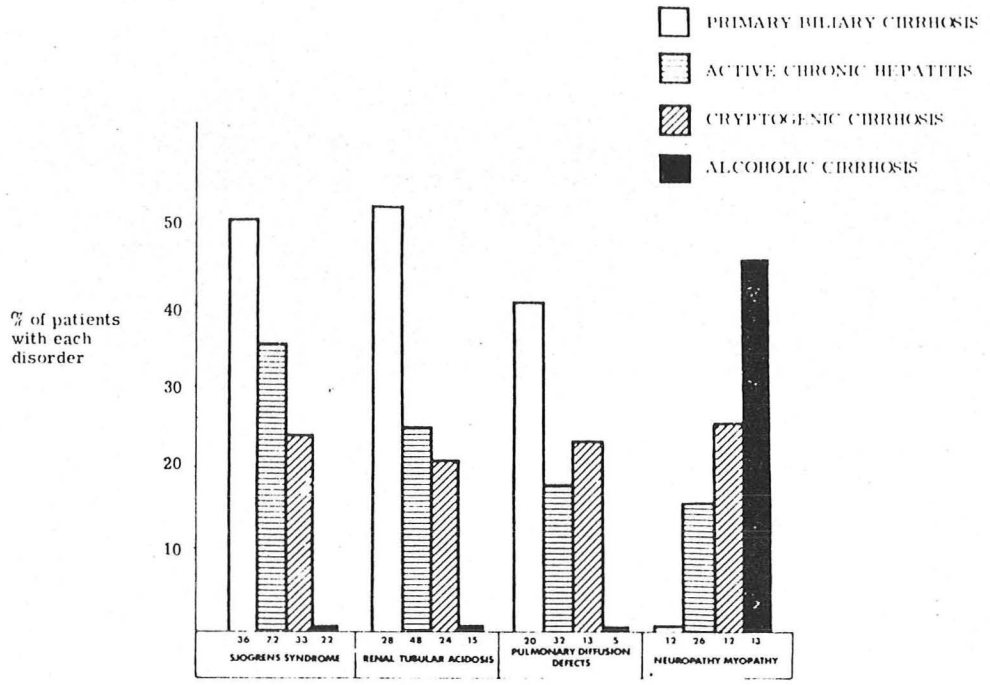

Fig. 5 *The frequency of certain manifestations of multisystem involvement. The figures given under each column refer to the number of patients investigated.*

(from Golding, P.L., et al., Am. J. Med. 55:772, 1973)

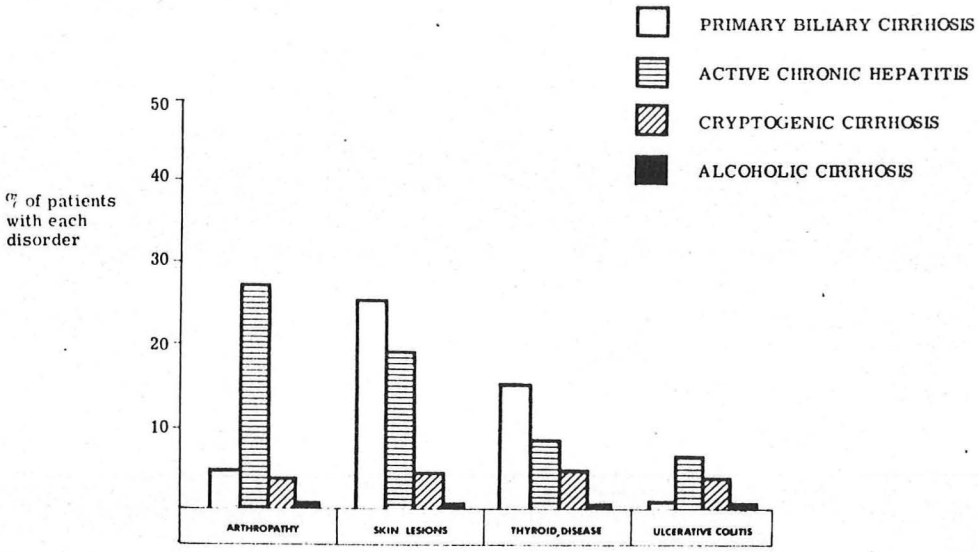

Fig. 6 *The frequency of certain other manifestations of multisystem involvement.*

(from Golding, P.L., et al., Am. J. Med. 55:772, 1973)

An association of PBC with scleroderma and Raynaud's phenomenon, telangiectasia and calcinosis cutis, as well as with rheumatoid arthritis and dermatomyositis, has been reported by several authors.

TABLE 9

Incidence of the Elements of the
CRST Syndrome Found in 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.

(from Reynolds, T., et al., Am. J. Med. 50:302, 1971)

All of these associations provide evidence that PBC is a generalized disease and not simply confined to the liver.

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The Immune Flavor of Primary Biliary Cirrhosis

Antibodies to Tissue Antigens

Antibodies to various tissues are found in sera of a high proportion of patients with PBC. Mitochondrial antibody is of particular interest because it is detected in the serum of most patients. It is also detected in a smaller proportion of patients with chronic active hepatitis, or cryptogenic cirrhosis, but rarely in those with other disorders.

A representative experience is as follows:

TABLE 10

Results of Tests for Mitochondrial Antibody*

Diagnosis	Positive Tests/Total Number of Patients (% Positive)
Primary biliary cirrhosis	158/188 (84)
Chronic active hepatitis	8/77 (11)
Cryptogenic cirrhosis	2/33 (6)
Other forms of cirrhosis	0/244
Viral hepatitis	0/332
Drug-induced hepatitis	3/73 (4)
Other forms of hepatitis	0/87
Extrahepatic biliary obstruction	4/180 (2)
Nonobstructive biliary tract disease	0/66
Hepatic malignancy	0/124
Miscellaneous hepatic lesions	2/230 (1)
Collagen diseases	1/62 (2)

*The serums of 1696 patients were tested.

(from Klatskin, G. and Kantor, F.S., Ann. Int. Med. 77:533, 1972)

The antigen is a component of the inner membrane of mitochondria. It is a lipoprotein with a molecular weight of approximately 200,000 daltons. Antibody is usually detected by an immunofluorescent test with frozen sections of kidney (rat or human) serving as antigen. The staining reaction is neither organ, nor species specific.

The test is positive in 84 to 96 per cent of patients with primary biliary cirrhosis. It is negative in patients with extrahepatic obstruction of the bile duct.

Antibody may be present in the IgG, IgA or IgM fractions of serum. Antibody titers do not correlate with the duration of symptoms, the depth of jaundice, the level of gamma globulin in serum, serum alkaline phosphatase activity, the presence of other autoantibodies (ANA, Anti Smooth Muscle) in serum, or any histological findings in liver biopsies.

The practical diagnostic importance of the antimitochondrial antibody test is twofold. A positive test in an icteric patient is strong evidence against a mechanical block in the main bile ducts; a negative test in a patient with cholestatic jaundice raises suspicion that PBC is not the correct diagnosis.

References

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Other autoantibodies are detected in a significant proportion of patients with PBC, chronic active hepatitis and cryptogenic cirrhosis. Data collected by Golding et al. *Am. J. Med.* 55:772, 1973 is as follows:

TABLE II Data Relating to the Four Clinical Groups

Diagnosis	No.	Sex		Age (yr)	Autoantibodies (% with)				Immunoglobulins (% with abnormal values, mean in brackets)		
		Male	Female	(Mean ± SD)	AMA	SMA	ANA	RF	IgA	IgG	IgM
Active chronic hepatitis	108	29	79	48 ± 17	31	52	62	19	48(461)	64(2,207)	64(329)
Primary biliary cirrhosis	47	2	45	54 ± 11	98	33	33	24	30(398)	50(1,855)	67(474)
Cryptogenic cirrhosis	63	34	29	57 ± 11	18	25	25	15	43(482)	40(1,809)	36(196)
Alcoholic cirrhosis	60	43	17	55 ± 9	2	13	13	17	61(563)	51(2,007)	41(189)

NOTE: AMA = mitochondrial antibody, SMA = smooth muscle antibody, ANA = antinuclear antibody, RF = rheumatoid factor. Normal ranges (mean ± 2 SD) for immunoglobulins by immunodiffusion plates. Partigan: IgA 142 to 434 mg/100 ml, IgG 539 to 1,637 mg/100 ml and IgM 54 to 165 mg/100 ml.

The incidence of detectable autoantibodies in these disorders varies somewhat from one series to another, but in general they are consistent in demonstrating an increased frequency in this subset of liver diseases.

Immunoglobulins

Immunoglobulins in serum (IgG, IgA, IgM) are also elevated in patients with these liver diseases. Disproportionate elevation of IgM was reported for primary biliary cirrhosis by Hobbs, 1967 and confirmed by Feizi, 1968 and Hadziyannis et al, 1970. In a given patient, absolute values of these immunoglobulins is of little differential value. In the setting of obstructive jaundice however, IgM and IgG are elevated more frequently in patients with PBC as compared to extrahepatic bile duct obstruction.

References

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Circulating Immune Complexes

Evidence of immune complexes in serum has been found by a variety of techniques. Thomas et al, 1978 found increased binding of C1q and increased anticomplementary activity in PBC as well as in other forms of chronic liver disease.

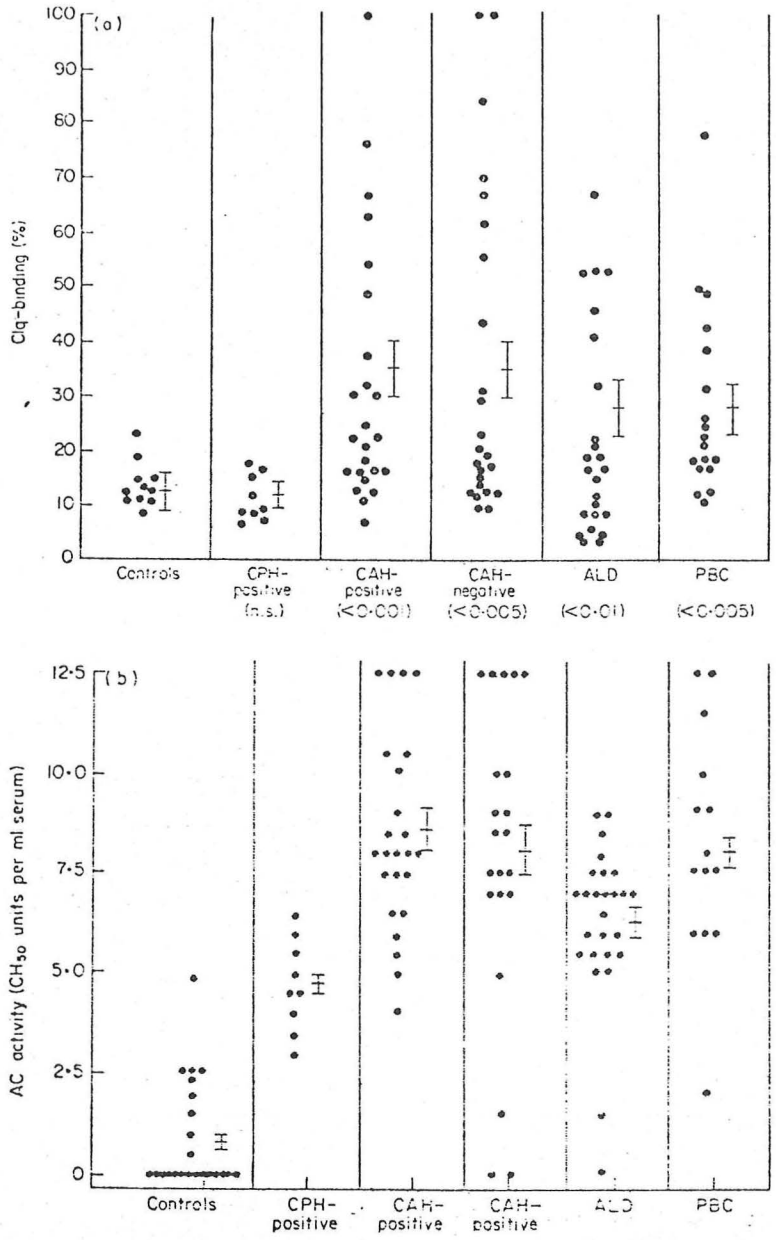

Fig. 7 C1q binding in chronic liver disease. *P* values in parentheses. (b) Anti-complementary activity in chronic liver disease. Means ± s.e.m. are shown by ⊤⊥.

(from Thomas et al., Clin. Exp. Immunol.31:150, 1978)

Increased C1q-binding and anticomplementary activity did not correlate with each other. A highly significant correlation of C1q-binding, but not anticomplementary activity, was found with the serum concentration of IgM and IgA. C1q-binding and anticomplementary activity were seen as frequently in the various histological stages of the disease.

Data from sucrose gradients demonstrate that C1q-binding activity is associated with large (19-22S) and small (8-14S) molecules. The larger complexes were prominent in PBC and in acute hepatitis (A and B); small complexes were found in all types of liver disease.

Wands et al (1978) also found circulating immune complexes to be prevalent in PBC. Their evidence was the presence of cryoproteins in 18 of 20 patients with PBC. The immunoglobulin composition of cryoproteins was striking in that 60 per cent were composed only of IgM. Mixed IgG-IgM were found in 25 per cent, and 1 patient mixed IgA-IgM was present. Complement components were not detected in the cryoprecipitates, perhaps because of the extensive washing they had been subjected to. The cryoprecipitates (11 of 18) were able to fix complement when added to normal serum.

Utilizing the Raji-cell technique, 95 per cent of the PBC patients were demonstrated to have circulating immune complexes.

TABLE 12

Circulating Immune Complexes and Complement Activation in 20 Patients with Primary Biliary Cirrhosis

Cryoprotein Analysis	No. of Cases Positive	Concentration	
		Mean	Range
		mg/dl	
IgM	12/20 (60%)	7.90	0.3-20.0
IgG, IgM	5/20 (25%)	6.24	0.1-18.3 (IgG)
		17.44	5.0-44.0 (IgM)
IgM, IgA	1/20 (5%)	5.0 (IgM)	-
		0.1 (IgA)	-
C1q, C3, C4, C5	0/20 (0%)	-	-
Raji serum titer	19/20 (95%)	474*	16.2-2,192
ACPA†	8/20 (40%)	-	-

*Serum titer of immune complexes measured by Raji-cell radioimmunoassay expressed as μg/ml of aggregated-human-gamma-globulin equivalents bound to 2 X 10^6 Raji cells.

†Alternate-complement-pathway activation.

(from Wands, et al., N. Engl. J. Med. 298:233, 1978)

The concentration of serum complement C3 is usually normal (Wands et al, 1978) or increased (Potter et al, 1973); C4 is either normal (Wands et al, 1978) or low Potter et al, 1973). Activation of the complement system is evident however in that C3 catabolism is markedly increased (Potter et al, 1976) as is the catabolism of C1q (Thomas et al, 1977); and C3 conversion products can be demonstrated in serum (Teisberg and Gjone, 1973).

TABLE 13

Complement (C3) Catabolism in Primary Biliary Cirrhosis

	No. Pts	C3 mg%	Fractional Catabolic Rate % IV pool per hour C3	Albumin
Controls	7	133	2.0	11.5
PBC	9	153	4.2	11.4

(adapted from Potter, et al., J Lab Clin Med. 88:427,1976)

The significance of circulating complexes in PBC is not clear. Extra-hepatic manifestations, i.e. urticaria, serum-sickness like joint findings, membranous glomerulonephritis, are not features of PBC. Complexes associated with these manifestations are usually small and antigen is present in excess. Large complexes, in antigen-antibody equivalence are said to induce granuloma formation. It has been speculated that the large complexes of PBC resulting from interaction of a biliary tract antigen with antibody result in bile duct damage and granuloma formation. The nature of the postulated antigen is uncertain. It is not the mitochondrial antigen however, since the immunoglobulins obtained from the cryo-precipitates had no antimitochondrial activity (Wands et al.,1978).

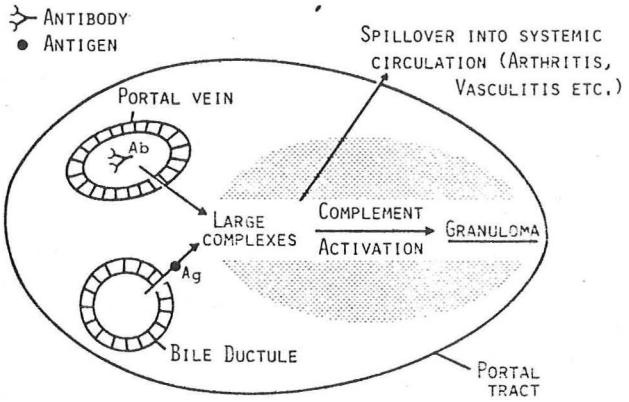

Fig. 8—**Possible mechanism of bile-ductular injury in primary biliary cirrhosis.**

(from Thomas et al., Lancet ii:1261, 1977)

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Cellular Immunity

Delayed hypersensitivity is impaired in primary biliary cirrhosis. Skin testing reveals a high incidence of Mantoux negatives in PBC compared with non-liver and liver disease controls. The incidence of induction of delayed hypersensitivity with dinitrochlorobenzene (DNCB) or Keyhole limpet hemocyanin (KLH) is significantly depressed in patients with PBC. Lymphocytes of PBC patients have an impaired in vitro response to phytohemagglutinin (PHA). Both serum and cellular factors contribute to impaired lymphocyte transformation.

A significant correlation exists between in vitro lymphocyte transformation and in vivo DNCB skin test results but in general the results of multiple tests which assess delayed hypersensitivity correlate poorly with each other.

TABLE 14

Tuberculin Status

Group	Total	Positive		Negative	
		No.	%	No.	%
Control	39	27	69	12	31
Cirrhosis	55	32	58	23	42
Cholestasis	32	20	62	12	38
Primary biliary cirrhosis	42	15	36	27	64

(from Fox, et al., Lancet i:959, 1969)

TABLE 15

Results of Skin Testing with Haemocyanin Following Immunization of the Subjects Studied

Group	Total Number	Positive Number	Positive Percentage
Normal	16	16	100
Cholestasis	10	9	90
Cirrhosis	27	17	63
Primary biliary cirrhosis	22	8	36

(from Fox, et al., Clin. Exp. Immunol. 14:473, 1973)

TABLE 16

Correlation Between In-Vitro Lymphocyte Transformation and In-Vivo D.N.C.B. Skin-Test Sensitisation in 24 Patients with Primary Biliary Cirrhosis in Whom Both Tests Were Done, Compared with 21 Controls

Lymphocyte transformation	D.N.C.B.	Primary biliary cirrhosis	Controls
+	+	6 (25%)	18 (86%)
-	-	14 (58%)	1
+	-	1	0
-	+	3	2

(from Fox, et al., Lancet i:959, 1969)

TABLE 17

Delayed Hypersensitivity in Twenty Patients with Primary Biliary Cirrhosis

Number	Tuberculin (±)	DNCB* (±)	Lymphocyte transformation (+ normal, - impaired)	KLH skin test† (±)
5	+	+	+	+
1	+	+	+	-
1	-	+	+	+
3	-	+	+	-
1	+	-	-	+
2	-	-	-	+
2	+	-	-	-
1	-	-	+	-
4	-	-	-	-
Total number positive	9	10	11	9

*Dinitrochlorbenzene

†Haemocyanin

(from Fox, et al., Clin. Exp. Immunol. 14:473, 1973)

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Cytotoxicity studies using blood mononuclear cells and target cells including autologous liver cells, human Chang liver cells, and mouse sarcoma cells provide evidence for differences between patients with PBC, chronic active hepatitis and normal controls. Differences in experimental techniques, and in data obtained provide no consistencies that permit a meaningful hypothesis as to the role played by T cells and K cells and suppressor cells in the pathogenesis of PBC.

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Inhibition of leukocyte migration in response to bile protein was observed in 30 of 37 patients (81%) with PBC. Seven of 27 patients (26%) with chronic active hepatitis also showed inhibition of leukocyte migration. Inhibition was not observed in patients with other causes of intrahepatic cholestasis; or in most patients with extrahepatic obstruction. A notable exception was that 8 patients with sclerosing cholangitis demonstrated impaired leukocyte migration.

The antigens inducing leukocyte migration inhibition appears to be associated with the cell membranes of interlobular and septal bile ducts and with bile canaliculi.

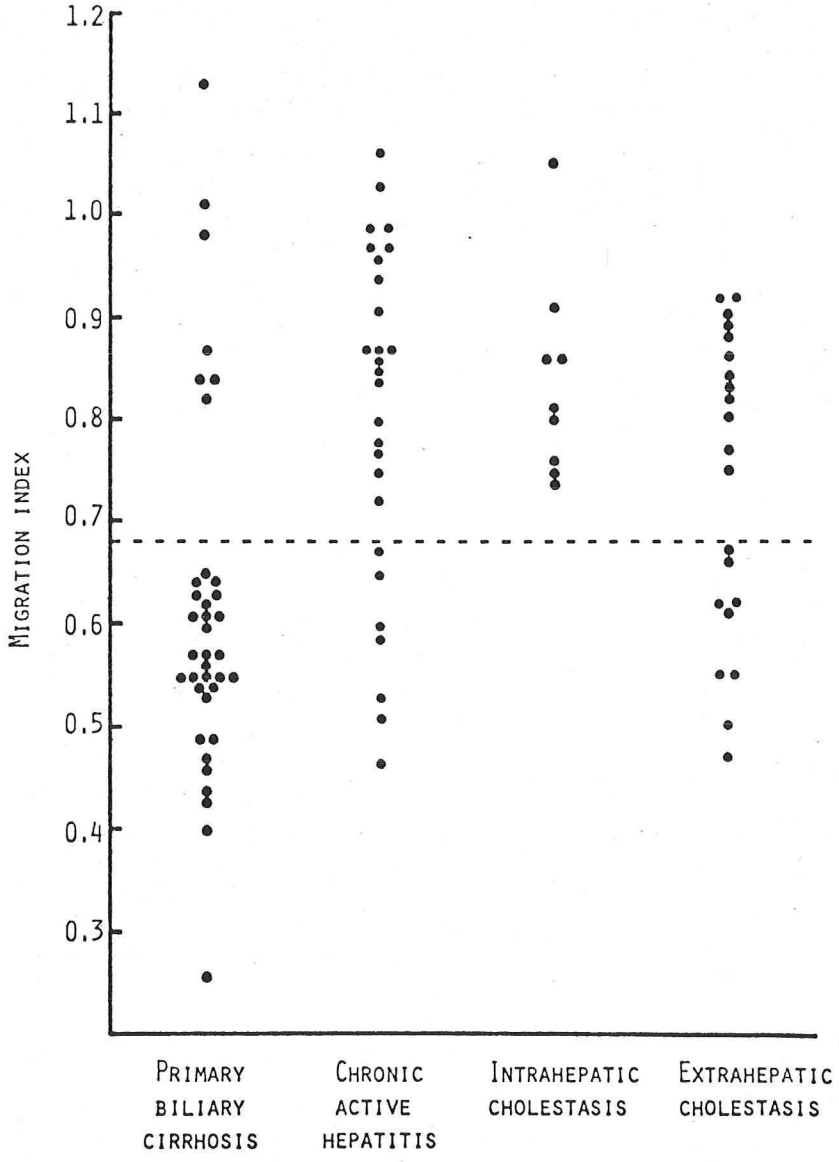

Fig. 9

(from McFarlane et al., unpublished observations)

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Summary of Immunologic Findings in Primary Biliary Cirrhosis

1. Elevated immunoglobulins - particularly IgM.
2. High incidence of autoantibodies, particularly antimitochondrial but increased incidence of ANA, ASMA and others.
3. High incidence of circulating immune complexes that activate complement.
4. Tendency to anergy with impaired lymphocyte response to mitogens.
5. Probable important role for cellular immunity.

   Granuloma formation, marked mononuclear infiltrate in portal tracts.

   Sensitivity to antigen in bile that cross reacts with membranes of bile ducts.

Genetic Aspects

PBC has been observed in sisters, twins, and mother and daughter pairs. A significant increase in the incidence of mitochondrial and other autoantibodies was found in relatives of patients with PBC. The frequency of the histocompatibility antigens HL-A1 and HL-A8 is similar in PBC and controls.

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Therapy

Corticosteroids

Primary biliary cirrhosis is one of three liver conditions in which immunological phenomena are common. The other two are chronic active hepatitis and cryptogenic cirrhosis. Since corticosteroids are of value in patients with severe forms of chronic active hepatitis one would consider their use in PBC. No control trials have been carried out in this latter disease however. Nevertheless, uncontrolled trials do not suggest any beneficial role for corticosteroids in PBC. Indeed it is felt they hasten the development of bone disease and pathological fractures. There is already a tendency for bone disease to develop in PBC. In some instances, it may be difficult to distinguish between PBC and chronic active hepatitis. Use of steroids is said to help distinguish between the two.

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Azathioprine

A controlled trial has been conducted on 45 patients. The aim was to provide immunosuppression but avoid bone complications attendant to the prolonged use of corticosteroids. Forty-five symptomatic patients were randomized (not double blind and no placebo) to azathioprine 2 mg/kg/day or nothing. Patients with ascites, edema, encephalopathy; varices, chronic infection or prior use of immunosuppressive agents were excluded.

No significant lasting therapeutic effects were observed for results of tests, hepatic histology, or survival.

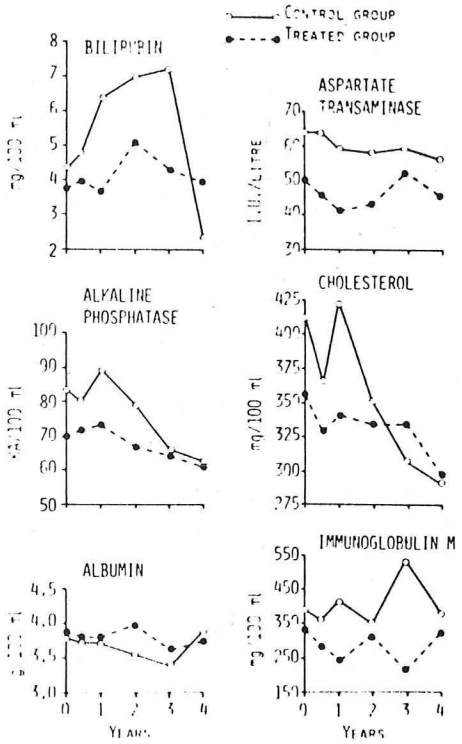

Fig. 10 Mean serum biochemical values during the trial. Serum bilirubin rose in both groups, but did not differ significantly between them. At 1 year, aspartate transaminase values were significantly lower in the treated group ($P < 0.5$), but not at other times. There were no statistically significant differences between alkaline phosphatase, cholesterol, albumin, or immunoglobulin M in the two groups.

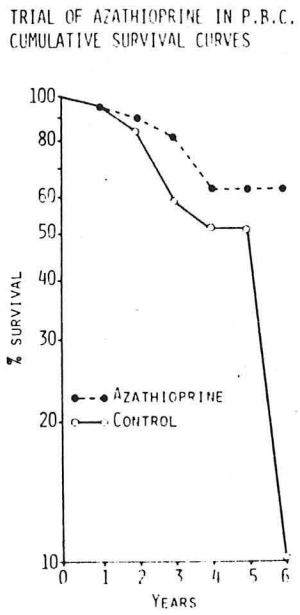

Fig. 11 Cumulative survival curves show no significant difference between treated and control groups except at the 6th year when the number in both groups is very small.

(from Heathcote et al., Gastroenterology 70:656, 1976)

Reference

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d-Penicillamine

The rationale for the use of this compound is based on the observations 1) that tissue copper is increased in liver and other organs of patients with PBC; 2) increased copper in tissues accounts for tissue damage in Wilson's disease; 3) d-penicillamine is an effective chelator of copper and leads to net loss of copper from the body; 4) liver and other tissue injury in Wilson's disease improves with d-penicillamine treatment.

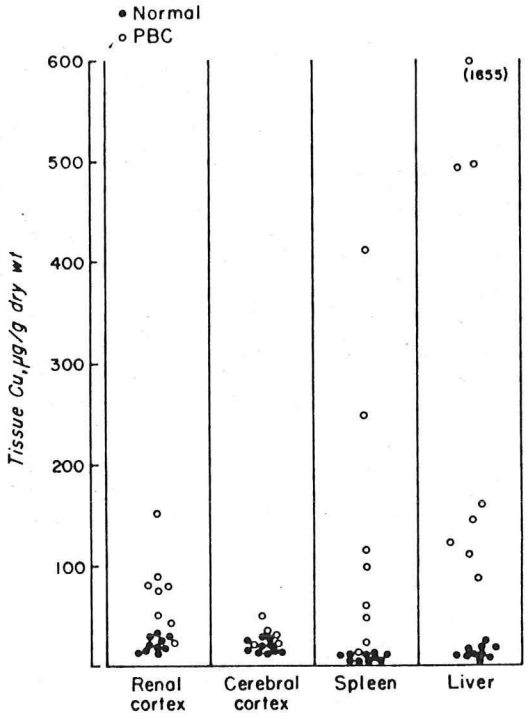

Fig. 12 Tissue copper concentrations in major organs in primary biliary cirrhosis (*PBC*) and in normal organs.

(from Fleming et al., Gastroenterology 67:1182, 1974)

TABLE 18

Hepatic Copper (Cu) Levels in Normal Subjects and in Hepatic Diseases

Group	No.	Hepatic Cu	
		Mean	Range
		μg Cu/g dry wt	
Normal	10	27	15-35
Primary biliary cirrhosis	8	441	99-1655
Extrahepatic obstruction	10	128	15-474
Postnecrotic cirrhosis	15	57	21-134
Alcoholic cirrhosis	13	35	12-96

(from Fleming, C.R., et al., Gastroenterology 67:1182, 1974)

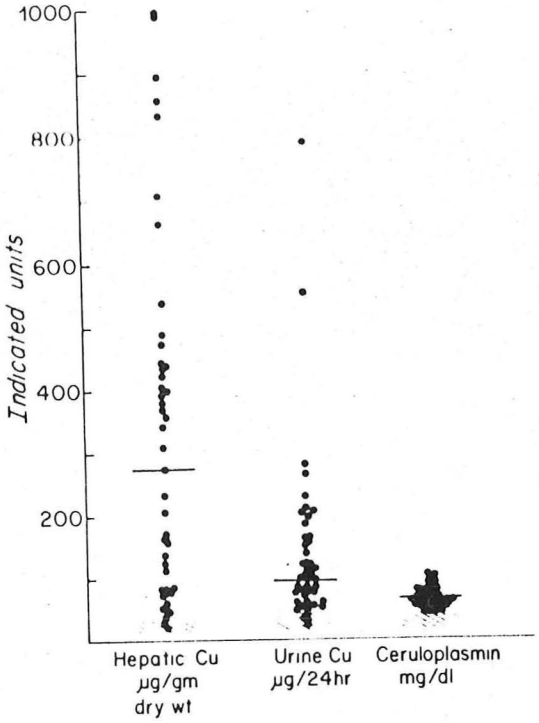

Fig. 13 Pretreatment copper measurements in 46 untreated patients with primary biliary cirrhosis. *Hatched lines*, normal range; *horizontal lines*, median value.

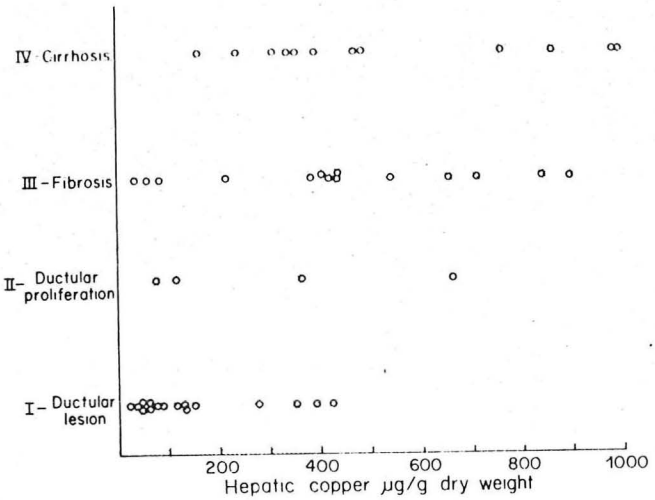

Fig. 14 Histological stage of liver disease plotted against hepatic copper concentration in 46 patients with primary biliary cirrhosis. $P \leq 0.01$ for difference between stages I and II versus stages III and IV.

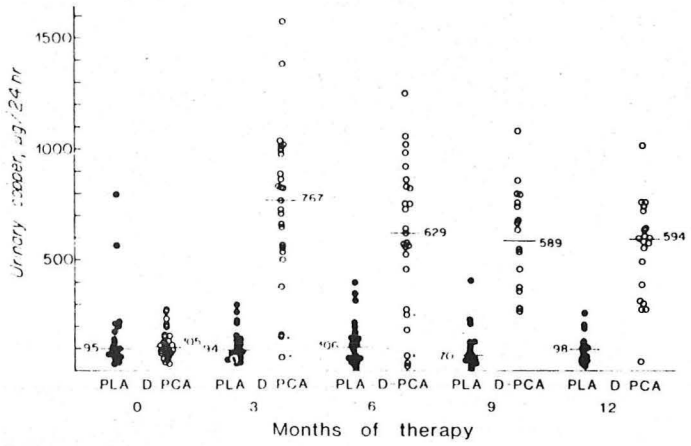

Fig. 15 Effect of D-penicillamine on urinary copper excretion. ○, group that received placebo; ●, group that received D-penicillamine. $P < 0.001$ for difference between groups at 3, 6, 9, and 12 months (*, drug temporarily discontinued).

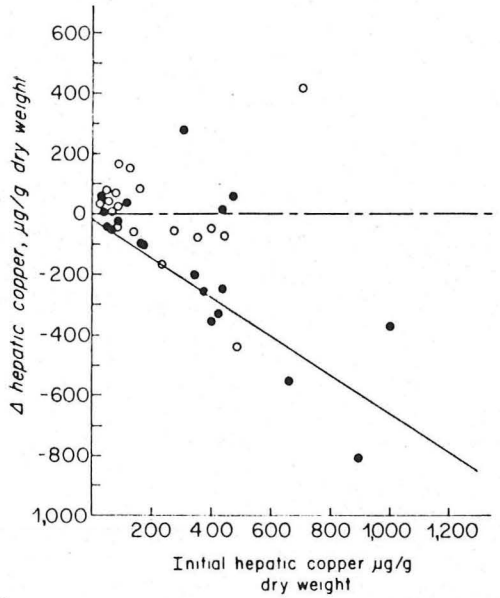

Fig. 16 Change in hepatic copper concentration in 37 patients after 1 year of therapy. $P \leq 0.02$ for difference in change of D-penicillamine group versus placebo group. *Calculated regression line* shows change in hepatic copper on initial hepatic copper of patients in the D-penicillamine group who had a decrease in hepatic copper ($r = 0.86$, $P \leq 0.005$, slope $= -0.64$). *Horizontal broken line* is reference line for no change in hepatic copper. ○, group that received placebo ●, group that received D-penicillamine.

(from Deering, T.B., et al., Gastroenterology 72:1208, 1977)

Therapy in PBC is accompanied by increased urine copper and decreased hepatic copper. It is unclear that potential beneficial effects are related solely to the decoppering effect of d-penicillamine. At this stage in therapy it is too early to tell if d-penicillamine is beneficial or not. The incidence of complications has been significant. It may be that altering dosage schedules similar to those now used in the treatment of rheumatoid arthritis may lower the rate of complications.

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Additional supportive therapy

Cholestyramine is used to control pruritus.

Phenobarbital increases bile flow, and bile acid excretion and may enhance the antipruritic effect of cholestyramine.

Vitamins A, D and K are administered parenterally.