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PRIMARY BILIARY CIRRHOSIS*

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"La question de la cirrhose hépatique, si simple autrefois dans sa précision trompeuse, est devenue de plus en plus complexe".—V. Hanot, 1892.

THE term biliary cirrhosis, although often loosely used, is, as has been pointed out by Boyd,[1] a convenient one inasmuch as it indicates that the cause of the cirrhosis in these cases is thought to be associated with an inflammatory reaction in or about the fine intra-hepatic bile ducts rather than with disease of the parenchymal cells of the liver. The presence of such a reaction in this situation is likely to interfere with the free passage of bile through these tiny canaliculi and to cause the laying-down of excessive amounts of fibrous tissue in and about the bile ducts in the portal spaces of the liver. It is these changes which produce both the clinical and anatomical features of biliary cirrhosis.

Such a reaction in the small ducts may be secondary to inflammation or obstruction of the large extra-hepatic bile channels or it may be due to primary disease of these finer bile passages themselves. The various etiological possibilities are given in the following comprehensive classification of biliary cirrhosis which is employed by Karsner.[2]

BILIARY CIRRHOSIS CLASSIFICATION (KARSNER[2])

1. Due to extra-hepatic obstruction of the large bile ducts:
   - (*a*) cholestatic
   - (*b*) cholangitic
2. Due to intra-hepatic obstruction of the finer bile channels:
   - (*a*) cholangitic
   - (*b*) cholangiolitic
   - (*c*) xanthomatous
   - (*d*) zooparasitic

In this communication it is not proposed to discuss the first group nor to enter into the argument about whether or not simple obstruction of the common duct, with or without infection, can lead to cirrhosis of the liver. The cases which are to be described belong rather to the second large group in which the extra-hepatic biliary channels are patent and unobstructed and the mechanical obstruction, if it exists at all, is present, not in the large bile ducts, but in the smallest interlobular branches of the biliary tree. This is generally a diffuse process which involves the whole intra-hepatic biliary tract. It leads to marked enlargement of the liver and spleen and to the occurrence of a persistent jaundice. Because of these findings the resulting clinical condition is often called hypertrophic biliary cirrhosis with chronic jaundice. We have preferred to call it simply *primary biliary cirrhosis.* Although in the later stages the parenchymal cells of the liver may become severely damaged they are relatively unharmed in the early stages. It is not surprising then to find that the functional abnormalities present, in the beginning at least, are those of an obstructive jaundice rather than those of hepato-cellular insufficiency. What must be realized in these patients is, of course, that the obstruction is intra-hepatic and not extra-hepatic and that no beneficial result can be expected from any form of surgical interference. This condition of primary biliary cirrhosis is relatively rare but it is of importance because patients who have it are so frequently thought to be suffering from some form of extra-hepatic obstruction and are therefore subjected to needless and often dangerous surgery.

CASE REPORTS

The clinical and other findings in such patients can best be illustrated by the following case report:

CASE 1

R.G., a male, aged 50, was well until January, 1936, when he suffered from some sharp knife-like pains in the lower chest on both sides. These lasted for four days only and did not return. There were no other symptoms.

In February, 1936, about one month later, his skin and scleræ were noted to be yellow. There had been no

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further pain. There was no nausea, vomiting, loss of appetite or other gastro-intestinal symptoms. He noted some itchiness of the skin. He was a little tired but noticed no other impairment of his general health. There was no history which suggested any previous hepatic or biliary tract disease. His jaundice and itching continued.

On July 20, 1936, he was admitted to hospital. On admission he was found to be moderately jaundiced. There were no telangiectases or xanthomas. The liver was large and firm. There were no enlarged abdominal veins. The spleen was not palpable. There was no evidence of ascites.

On July 28, 1936, because it was felt that he was suffering from an obstructive jaundice, a laparotomy was performed by the surgical staff. No evidence of obstruction in the extra-hepatic bile ducts could be found. The spleen was mildly enlarged. A specimen of the liver taken for biopsy showed the microscopic picture of an inflammatory reaction and increased fibrosis in the portal areas (Fig. 1*) and was diagnosed as showing an early atypical biliary cirrhosis.

He recovered satisfactorily from his operation and he was seen after discharge at regular intervals through the kindness of his family physician, Dr. Hession, of Toronto. His symptoms and signs continued and became somewhat more marked during 1937, 1938 and the early part of 1939, but in spite of his deep jaundice he felt reasonably well and continued at his work. The liver remained about the same but the spleen gradually increased in size finally reaching a hand's breadth below the left costal margin. Ascites was noted for the first time in May, 1939, and his downhill course became definitely more rapid. He finally died in September, 1939, some 3½ years after the onset and following a short period of severe anorexia and loss of weight.

At autopsy the liver was enlarged (2,050 gm.) and firm. The extra-hepatic biliary channels were unobstructed.

Microscopic examination of the liver (Fig. 2) showed that the inflammatory process in the portal areas had continued and had resulted in a diffuse perilobular and intra-lobular fibrosis of the liver of the Hanot type.

* The authors wish to express their grateful thanks to Professor William Boyd, Head of the Department of Pathology in the University of Toronto and to the members of his staff, and particularly to Dr. T. C. Brown, who so kindly re-examined and reported on the microscopic sections of these cases and who prepared the photomicrographs for publication.

During the course of this patient's illness certain laboratory examinations were carried out, the results of which are given in Table I. The serum van den Bergh was found to be persistently and increasingly elevated. Bile in large amounts was constantly in the urine as was also urobilin as long as the exclusion of bile from the

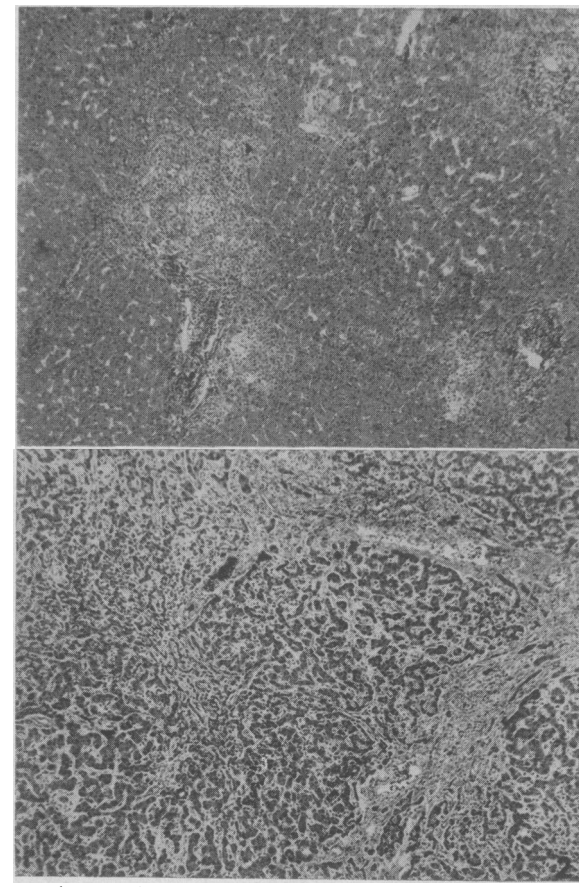

Fig. 1. (Case 1).—Photomicrograph of liver biopsy, taken 6 months after onset of jaundice.

Fig. 2. (Case 1).—Photomicrograph of liver obtained at autopsy, 3½ years after onset of jaundice.

TABLE I.

CASE 1. R.G. (MALE) TORONTO GENERAL HOSPITAL A16003

CLINICAL DIAGNOSIS: PRIMARY BILIARY CIRRHOSIS

BIOCHEMICAL OBSERVATIONS

Date	Serum V.D.B.	Urine		Color of stools	Total serum cholesterol	Serum alk. phosphatase	Serum protein			Oral galactose tolerance test
		Bile	Urob.				Tot.	Alb.	Glob.	
	units				mgm. %	K. J. units	gm. %	gm. %	gm. %	gm. galac. excreted
July 22/36....	16.0	++	Tr.	Normal		68				0.09
July 28/36....	Laparotomy. No obstruction of common bile duct									
August 10/36..	14.0	++	+			92				1.7
January 16/37.	16.0	+++	Tr.	Normal	880	123				
August 14/37..	20.0	++++	++	Pale yellow		70				
April 23/38...	29.0	++	0	Light grey	575		6.8	4.1	2.7	0.34
October 15/38.	36.0	++++	0		425	91				
February 4/39.	40.0	++++	0	Greyish white			6.4	3.9	2.5	
August 12/39..	40.0	++++	0	Greyish white	452	126				
September 19/39.....	Died. Autopsy: Hypertrophic biliary cirrhosis. No extra-hepatic obstruction or inflammation.									

gastro-intestinal tract was not complete. The galactose tolerance test yielded normal results and the serum protein estimations showed no abnormality beyond a mild lowering of the serum albumin. On the other hand both the serum alkaline phosphatase and the total serum cholesterol were grossly elevated to levels which were many times the normal value. The hyperphosphatasæmia persisted during the whole course of the illness but the level of the cholesterol decreased gradually as time went on, reaching, on the last examination 1 month before death, a value which was only twice the normal.

A number of similar cases, which are summarized in Table II, have been studied and followed during the past few years. It is seen from this table that the sexes are equally represented and that the age of onset is remarkably uniform. The total duration of the jaundice has varied from ten months to twelve years, the average (if one excepts the twelve year patient) being just under three years. Three patients are still living. Six, at some time during their illness, have been subjected to surgical exploration and the biopsy specimens taken on such occasions have fortunately been available for study. In three other cases there has not been pathological confirmation of the clinical diagnosis but the clinical course and findings in these have been so characteristic that they undoubtedly belong to this group. In most of the cases the jaundice appeared gradually and in only one was the initial illness felt at the time of onset to have been an acute infective hepatitis. In two cases unexplained itching was the initial symptom. Two other cases had had ulcerative colitis for many years preceding the appearance of jaundice.

The outstanding clinical and biochemical abnormalities of these ten cases are shown in Tables III and IV and are summarized in Table V. Mild to severe visible jaundice was present in all cases as was also itching of varying degrees. True colicky pain was present in only one case and, although mild fever was commonly noted, high fever was uncommon in this group during the time that they were under observation. Multiple xanthomatosis was prominent in three cases and in two others it was present but to a lesser degree. True spidery telangiectases were noted in only two cases. A large firm liver was present in all and the spleen, although never huge, was also readily palpable in all these patients. Ascites was encountered in four of the ten cases but in each instance it was a late phenomenon. Hæmatemesis of severe degree occurred in one case and to a much lesser degree in one other.

Laboratory examinations on these patients have shown an elevation of the direct reacting serum bilirubin in all 10 cases, definite urobilinogenuria in 9 of the 10 cases, hypercholesterolæmia in 7 cases and hyperphosphatasæmia in all 10. A mild lowering of the serum albumin was found in 4 and a moderate or marked elevation of the serum globulin was present in 5 cases. The galactose tolerance test was found to be positive in only 2 cases. The lower level of the serum cholesterol in the 3 cases who showed low or normal values may

TABLE II.
PRIMARY BILIARY CIRRHOSIS
SUMMARY OF CASES

No.	*Pt.*	*Sex*	*Age at onset*	*Present status*	*Duration of jaundice*	*Pathological diagnosis*	*Remarks*
					months		
1	R.G.	M.	50	D	42	Biliary cirrhosis	Gradual onset. Surgical biopsy. Autopsy.
2	A.D.	F.	39	A	31+	Early biliary cirrhosis	Gradual onset. Marked Xanthomatosis. Surgical biopsy.
3	A.S.	M.	40	A	32+	Early biliary cirrhosis	Gradual onset. Initial symptom itching. Surgical biopsy.
4	H.L.	F.	41	D	60	Biliary cirrhosis	Onset with colicky pain. Surgical biopsy. Autopsy.
5	S.W.	M.	40	D	168	Biliary cirrhosis	Ulcerative colitis 28 yrs. Mild jaundice 14 yrs. Xanthomatosis. Autopsy.
6	P.I.	M.	28	A	36+	Biliary cirrhosis	Initial illness diagnosed acute infectious hepatitis. Surgical biopsy.
7	R.S.	M.	46	D	10	.....	Sudden onset deep jaundice. Marked xanthomatosis. No autopsy.
8	J.B.	F.	27	D	13	.....	Ulcerative colitis 18 yrs. Jaundice and large liver 1 yr. No autopsy.
9	S.H.	F.	50	D	18	.....	Gradual onset jaundice. No autopsy.
10	S.E.	F.	38	D	60	Biliary cirrhosis with multilobular cirrhosis	Onset with itching. Moderate xanthomatosis. Surgical biopsy.

be accounted for at least in part by the fact that their condition was far advanced at the time of the examination and with increasing hepato-cellular damage the level of the blood cholesterol tends to fall.

The pathological lesions present in the livers of this group of patients are under review by Professor Boyd and his department in the University of Toronto and will be reported on by them at a later date. In general the microscopic examinations have shown evidence of an inflammatory process, characterized by a round cell infiltration and increasing fibrosis, in and about the portal spaces, and evidence of obstruction and obliteration of the fine interlobular bile capillaries.

TABLE III.
PRIMARY BILIARY CIRRHOSIS
CLINICAL MANIFESTATIONS

No.	Pt.	Jaundice	Pruritus	Colicky pain	Fever	Xanthoma	Spiders	Clubbing of fingers	Large liver	Large spleen	Ascites	Hæmatemesis
1	R.G	++++	+++	0	0	0	0	0	++++	+	+ (Late)	0
2	A.D.	+++	++	0	98-99	++++	0	0	++++	+	0	0
3	A.S.	++	++++	0	0	0	0	0	+	+	0	0
4	H.L.	++	++	++++	99-100	0	++	0	++	++	+ (Late)	++++
5	S.W.	++	++++	0	-	+++	0	0	++++	+	0	0
6	P.I.	++	++	0	0	+	0	0	+++	+	++++ (Late)	+
7	R.S.	++++	++++	0	100-101	++++	0	0	++++	+	0	0
8	J.B.	++	+++	0	-	0	0	0	++++	+	0	0
9	S.H.	++++	++	0	99-100	0	0	0	++++	+	0	0
10	S.E.	++	++++	0	98-100	++	+++	0	++++	+	+++ (Late)	0

TABLE IV.
PRIMARY BILIARY CIRRHOSIS
LABORATORY OBSERVATIONS

No.	Pt.	Serum V.D.B.	Urine urobil.	Color of stools	Serum cholesterol total	Serum alk. phosphatase	Serum proteins (3) (4)				Galactose tolerance (oral)
							Total	Alb.	Glob.		
		units			*mgm. %*	*K.J. units*	*gm. %*	*gm. %*	*gm. %*	*13½% fraction*	
Normal		0.4-1.0	.....	.....	170-250	5-10	6.2-7.8	4.0-5.7	1.6-2.5	0	Negative
Portal cirrhosis		Varies usually low	+++	Normal	Low-normal	10-30	5.3-9.3	2.5-5.4	2.6-6.1	0-2.5	Varies
1	R.G.	16-40	0-++	Norm-Pale	450-880	68-126	6.8	4.2	2.6	—	Negative
2	A.D.	8-16	++	Normal	600-660	49-80	9.4	4.1	5.3	++	Negative
3	A.S.	3-8	+++	Normal	290-330	33-89	7.8	5.0	2.8	0-+	Negative
4	H.L	4-6	+	Normal	128-172	36-80	6.0	3.8	2.2	0	Negative
5	S.W.	3-30	+	Normal	66-180	64	8.5	3.6	4.9	+	Negative
6	P.I.	4-40	+	Normal	180-500	48-99	7.4	3.6	3.8	+	Negative
7	R.S.	40-50	0	Pale	360-1140	27-80	—	—	—	—	Negative
8	J.B.	8-11	++	Normal	226-270	78-100	7.4	4.7	2.7	0	Negative
9	S.H	10-50	0-+	Pale	700-930	35-84	7.2	4.1	3.1	0	Positive
10	S.E.	2-14	++	Normal	254-600	20-37	8.0	3.3	4.7	++	Positive

DISCUSSION

It was this syndrome of chronic jaundice with an enlarged liver and spleen which Hanot[5, 6] described over 70 years ago and for which the name "Hanot's cirrhosis" was later proposed.[7] Since that time many clinical examples of this disease have been reported but evidently the precise microscopic findings which Hanot described have only rarely been encountered.[8] There is considerable confusion as to what should or should not be called Hanot's cirrhosis and various pathological lesions have been found in patients exhibiting this clinical syndrome. In some cases the morphological lesion has been that of an ordinary portal cirrhosis.[9, 10] Klemperer[11] has reported what he calls a *chronic intrahepatic obliterating cholangitis* and Rössle,[12] Karsner,[2] and more recently Watson and his co-workers[13, 14] have described a *cholangiolitic cirrhosis.* Still another variety is the *xanthomatous biliary cirrhosis* described in 1938 by Thannhauser and Magendantz[15] in which the changes in the liver were at first thought to be due to the presence of xanthomatous lesions in the bile ducts, a belief which has recently been abandoned.[16] MacMahon,[17] who has studied some of Thannhauser's patients from a pathological point of view, has reported that the livers of these cases are the site of what he calls a *pericholangiolitic biliary cirrhosis.* He expresses the opinion that in this type of cirrhosis the retention and regurgitation of bile,

the appearance of jaundice, and probably the other manifestations of this syndrome are adequately explained by the destruction of the terminal bile ducts and liver cells and the proliferation of granulation tissue and subsequent fibrosis in the portal areas. Certainly the clinical syndrome of multiple xanthoma, jaundice and hypercholesterolæmia has for many years been known to occur at times in cases of long standing jaundice caused by a variety of forms

TABLE V.
PRIMARY BILIARY CIRRHOSIS
10 CASES

Clinical Manifestations	*Cases*
Jaundice	10
Pruritus	10
Colicky pain	1
Fever	5
Xanthoma	4
Telangiectases	2
Clubbing of fingers	0
Large liver	10
Large spleen	10
Ascites	4
Hæmatemesis	2
Biochemical Abnormalities	*Cases*
Direct reacting V.D.B	10
Urobilinogenuria	9
Hypercholesterolæmia	7
Hyperphosphatasæmia	10
Hypoalbuminæmia	4
Hyperglobulinæmia	5
13½% globulin	5
Positive galactose tolerance test	2

of *extra-hepatic* obstruction.[18, 19] It has been noted even in cases of portal cirrhosis[10] and the opinion of the present writers is that the xanthomatosis exhibited by some of the patients in this present series, is simply due to long standing *intra-hepatic* obstruction and is a secondary and not a primary phenomenon.

In these cases of so-called biliary cirrhosis most agree that the pathological picture is one of periportal inflammation and fibrosis. The etiology of this inflammation is obscure. Watson and his co-workers[13, 14] have related it to an antecedent jaundice—which they consider to have been probably an acute infectious hepatitis—in 5 out of the 9 cases which they have recently described with cholangiolitic cirrhosis. Such an apparent correlation was not seen in our group of which only one case gave a history suggesting a previous infectious hepatitis. Nor has there been any suggestion that alcohol, dietary or lipotropic deficiencies, or exposure to hepato-toxic drugs or chemicals has played any part in the causation of the cirrhosis present in the patients reported in this paper.

The biochemical abnormalities which we have noted—namely the high incidence of hyperphosphatasæmia and hypercholesterolæmia—are similar to those already described by Watson and his group.[13] In the patients which they have reported, however, a constant hyperglobulinæmia was found and there was no significant change in the level of the serum albumin. In our series definite hyperglobulinæmia was found in only 50% of the cases examined and in 4 of the 10 cases there was a definite hypoalbuminæmia.

No treatment is known which favourably influences the course of the disease. Periods of apparently spontaneous improvement may alternate with periods of more rapid progression of the condition. Low cholesterol diets have been advocated for the treatment of those cases in which the serum cholesterol is high but quite marked decreases in serum cholesterol levels have been observed in some of the cases of the present series even though the cholesterol content of the diet was not restricted. We have usually employed a regimen, similar to that used in the treatment of other forms of cirrhosis, which includes a prolonged period of rest, a high carbohydrate high protein diet, and the administration of large amounts of vitamin B complex, but have not observed any striking or sustained benefit.

SUMMARY

The combination of persistent jaundice and itching with hyperphosphatasæmia and hypercholesterolæmia which characterizes primary biliary cirrhosis always suggests an obstructive lesion and unless the possibility of the presence of this form of cirrhosis is considered a diagnosis of extra-hepatic obstruction is likely to be made. The lack of suggestive antecedent history, the relatively low level of the jaundice at the outset, the large liver without gross irregularities, the palpable spleen, and in some instances at least, evidence of parenchymal cell involvement, will suggest however an intra-hepatic lesion and will frequently allow the correct diagnosis to be made on clinical grounds alone.

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A NEW VIEW ON THE USE OF DICOUMAROL IN THE PREGNANT PATIENT*

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THIS is a report of a preliminary study of anticoagulant therapy administered to a number of pregnant women presenting a history and/or evidence of venous disease. As the series developed the procedure of administering dicoumarol earlier and earlier in the puerperium evolved until the present regimen of predelivery administration of dicoumarol was established.

It is admitted that embolic phenomena account for a very small percentage of maternal fatalities. Indeed, they are rare. Everyone has seen the patient, however, who as a reminder of her pregnancy is burdened with a chronically swollen, uncomfortable or even painful leg due to phlebitis. It was the hope in commencing this study that a form of treatment using an anticoagulant might be evolved whereby these morbid conditions might be prevented.

Preliminary discussions with others regarding the advisability of the use of dicoumarol during the last trimester, during labour or in the immediate postpartum period gave considerable concern. One eminent authority gave us to understand that in his considered opinion such use of anticoagulants would be a most dangerous procedure, as blood loss would most likely be quite marked and possibly uncontrollable. There has been a great deal written on the indications for the use of anticoagulants in the treatment of venous disease. However, following a review of a considerable number of articles, one was impressed with the fact that there was almost total absence of any reference to thrombophlebitis or phlebothrombosis or their complications in the pregnant patient. This is in spite of the fact that Allen, Barker and Hines[1] state that in the United States thrombophlebitis occurs after 0.4 to 1% of deliveries.

Fortunately venous thrombosis has its origin most frequently in the leg. In fact 95% of emboli, other than those of cardiac origin, arise in the veins of the lower leg. Many cases remain local and heal, some being recognized and some not. Those that do not heal may progress in one of two ways: (1) The thrombus may spread rapidly through deep venous channels to the groin giving rise to obstruction with acute symptoms of severe pain and swelling; 90% of cases of femoro-iliac thrombophlebitis begin in this way. Because of deep vein thrombosis chronic swelling of the extremity may be expected. (2) Oschner's phlebothrombosis or quiet thrombosis may develop. There may be a minimum of symptoms until pulmonary embolism occurs. Usually, however, if looked for, tenderness of the calf muscle may be elicited; Homan's sign is positive; there may be slight œdema of the ankle, cyanosis of the foot when standing, and dilatation of the superficial veins. There is a slow propagation of the clot which floats free at its proximal end. The longer the floating clot the greater the likelihood of breaking from its mooring.

Thrombophlebitis is more common after difficult delivery, instrumental delivery, Cæsarean section, in cases where puerperal sepsis is or has been present and in the presence of varicose veins. Therefore, in recommending a treatment it is assumed that the usual prophylactic mea-

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