

Noncirrhotic Portal Fibrosis

S. K. SAMA, M.D.
S. BHARGAVA, M.D., D.M.R.D.
N. GOPI NATH, M.S.
J. R. TALWAR, M.S.
N. C. NAYAK, M.D.
B. N. TANDON, M.D.
K. L. WIG, F.R.C.P.

New Delhi, India

In India noncirrhotic portal fibrosis (portal hypertension without demonstrable intrahepatic or extrahepatic obstruction) accounted for seventy-five (25 per cent) of 300 cases of portal hypertension studied by us. The majority of patients presented with marked splenomegaly of long duration and recurrent hemorrhage from esophageal varices (usually well tolerated), with minimal features of hepatocellular failure. There was an increase of alpha₂ globulin, beta globulins and immunoglobulin G (IgG). Hemodynamically, two significant findings were a marked gradient between the splenic pressure and wedged hepatic vein pressure, and a normal hepatic blood flow; in some patients wedged hepatic vein pressure was high. Roentgenologically, there was dilatation and tortuosity of the portal and splenic veins, with massive varices and hepatofugal collaterals. The intrahepatic vascular pattern was not much distorted, in contrast to cirrhosis. At shunt surgery the gross appearance of the liver varied from near normal to irregular nodularity resembling cirrhosis. There was at times shrinkage of the left lobe and hypertrophy of the right lobe. A needle biopsy specimen of the liver showed nonspecific changes, i.e., small focal areas of necrosis and regeneration, focal infiltrates, Kupffer cell hyperplasia and portal scars of varying size. Wedge biopsy and autopsy specimens revealed focal occlusive changes in the medium-sized radicals of the portal vein, changes considered specific for this disease. Electron microscopy revealed widening and collagenization of the space of Disse, with laying down of large collagen bundles in and around the sinusoids.

Shunt surgery was performed in twenty-six patients. The operative mortality was 10.7 per cent. Splenorenal shunt was better tolerated than portocaval shunt but was associated with postoperative bleeding in 18.75 per cent of the cases.

The syndrome of portal hypertension without demonstrable intrahepatic or extrahepatic obstruction, first described in India by Ramalingaswami, Wig and Sama [1], is now a well recognized entity [2]. A similar disease has been reported in the literature under various names [3-11], but investigators in India have decided to designate this entity noncirrhotic portal fibrosis [12].

Since its first description in 1962, seventy-five cases of noncirrhotic portal fibrosis have been studied in detail at the All-India Institute of Medical Sciences. We report on the clinical, biochemical, roentgenologic, hemodynamic, immunologic, his-

From the Departments of Medicine, Radiology, Thoracic Surgery and Pathology, All-India Institute of Medical Sciences, New Delhi 16, India. Requests for reprints should be addressed to Dr. S. K. Sama, Department of Medicine, All-India Institute of Medical Sciences, Ansari-Nagar, New Delhi 16, India. Manuscript received September 1, 1970.

tologic and ultrastructural features of this disease.

MATERIAL AND METHODS

The diagnosis of noncirrhotic portal fibrosis was established in seventy-five of a total of 300 cases of portal hypertension studied on the basis of the following criteria: (1) definite clinical and/or roentgenologic evidence of portal hypertension; (2) patent extrahepatic portal venous system on splenoportovenogram; (3) adequate liver biopsy specimen showing no evidence of cirrhosis of the liver [13].

A detailed history and physical examination were obtained in each case. Special attention was given to mode of onset, history of malaria, umbilical sepsis, dietary habits, alcoholism, ingestion of hepatotoxins and herbal medicines, presenting symptoms, and size of the liver and spleen. Liver function studies including serum bilirubin, albumin, globulins, alkaline phosphatase, thymol turbidity and serum glutamic pyruvic acid transaminase (SGPT) were carried out in all cases. A standard bromsulfalein test and ^{131}I rose bengal hepatogram before and after stress with bromsulfalein [14] were obtained in twenty cases.

A barium swallow roentgenogram for the detection of esophageal varices and a splenoportovenogram were available in all cases.

Wedge hepatic vein pressure was measured in forty-four cases and splenic pressure in forty-six cases. Both pressures were recorded in twenty-seven cases. The mid-thoracic line was taken as the zero line of reference for all pressure measurements. Estimated hepatic blood flow was determined with indocyanine green by single injection technic [15] in twenty-seven cases and with radioactive gold [16] in twenty cases.

Percutaneous needle biopsy of the liver was performed with the Vim-Silverman's needle. Adequate biopsy material was obtained at least once in each case. In twenty cases, wedge biopsy was carried out at operation. During the period of study seven cases came to autopsy. Ultrastructural studies were made in nine patients. The standard technic for electron microscopic study was used [17].

In twenty patients, serum protein fractions were studied by cellulose-acetate paper electrophoresis [18] and immunoglobulins by Sephadex® G 200 column chromatography [19].

RESULTS

Noncirrhotic portal fibrosis constituted 25 per cent of the total cases of portal hypertension in this series. The maximum incidence of the disease was noted in the second, third and fourth decades (Table I). The mean age was 32.5 years at the time of first presentation and 25.2 years at the onset. The majority of the patients were male.

TABLE I Age Distribution in Seventy-Five Cases of Noncirrhotic Portal Fibrosis

Age Group (yr)	Sex (no.)		Total
	Male	Female	
<10	1	1	2
11-20	12	3	15
21-30	17	1	18
31-40	12	4	16
41-50	10	3	13
50+	8	3	11

This may have been due to the lesser number of beds for female patients in the hospital and does not indicate true predilection for the male sex. The male:female patient ratio in the hospital is 7:2.

Most of the patients were from northern India, a few were from other parts of the country. The disease affected the poor and the middle class. The very poor who came to the hospital with severe malnutrition were not affected. Only three patients had been addicted to alcohol, thirty had been taking indigenous drugs. A past history of jaundice was elicited in nine cases (12 per cent); the interval between the onset of symptoms and the history of jaundice varied from one to twenty-five years, with a mean of seven and a half years. A history suggestive of malaria was present in twelve cases, and of diarrhea and dysentery in ten. Associated pulmonary tuberculosis was present in three and recurrent thrombophlebitis in one case.

Clinical Features. Forty of seventy-five patients (53.3 per cent) had splenomegaly as their first symptom. Splenic enlargement was either observed by the patients or pointed out by the doctor during examination for minor ailments, usually years before the appearance of other symptoms. In nineteen patients (25.3 per cent) sudden hematemesis without any previous symptoms marked the onset of their illness. Gradual abdominal dis-

TABLE II Clinical Features

Clinical Features	Cases	
	No.	%
Splenomegaly (average enlargement 8.57 cm)	75	100
Hematemesis (average 2.3 episodes)	39	52.0
Ascites	31	41.3
Palpable liver (average 3.40 cm)	48	64.0
Pain in splenic area	24	32.0
Engorged abdominal veins	18	24.0
Gynecomastia	4	5.3
Palmer erythema	2	2.6
Scanty pubic and axillary hair	2	2.6
Clubbing	2	2.6

TABLE III Liver Function Tests

Liver Function Tests	No. Cases	Mean $\pm$ S.D.
Serum total proteins (gm %)	75	6.3 $\pm$ 0.84
Serum albumin (gm %)	75	3.2 $\pm$ 0.43
Normal (>3.75 gm %)	36	...
Mild hypoalbuminemia (between 3.1 and 3.75 gm %)	20	...
Moderate hypoalbuminemia (between 2 and 3 gm %)	19	...
Severe hypoalbuminemia (<2 gm %)	0	...
Serum globulins (gm %)	75	3.1 $\pm$ 0.63
Alkaline phosphatase (King-Armstrong units)	75	12.9 $\pm$ 6.5
Thymol turbidity	75	5.7 $\pm$ 3.6
SGPT (μ M/ml/hr/40°C)	75	1.9 $\pm$ 1.2
Serum bilirubin (mg %)	75	0.78 $\pm$ 0.43

tention due to ascites initiated the illness in ten cases (13.3 per cent). The onset of illness in the remaining six cases (8 per cent) was with vague abdominal symptoms, pallor or weakness. Among those whose illness started with hematemesis, ascites or other symptoms, a large spleen was invariably found on examination.

The mean duration of illness at the time of first observation was 7.15 years. The clinical features at the time of first presentation are shown in Table II. Splenomegaly was noted in all patients. The size of the spleen varied from 2 to 27 cm with a mean of 8.57 cm. Recurrent pain in the region of the splenic mass was a complaint of twenty-four patients (32.0 per cent). Severe hematemesis occurred in thirty-nine patients (52 per cent); it was recurrent in a majority of the patients, with an average of 2.3 episodes and a maximum of twelve episodes. Gastrointestinal hemorrhage was usually well tolerated and did not lead to encephalopathy. Engorged abdominal veins were present in eighteen cases (24 per cent).

Ascites was present in thirty-one cases (41.3 per cent); it was mild in seventeen, moderate in

eleven and severe in three. Ascites was considered mild when only shifting dullness was elicited, moderate when a fluid wave could also be demonstrated, and severe when the patient had abdominal or respiratory discomfort. The liver was palpable in forty-eight cases (64 per cent) and varied in size from 1 to 10 cm, with an average of 3.40 cm. It was smooth, firm and nontender. Signs and symptoms of hepatocellular failure and endocrine disturbances were uncommon. Gynecomastia was seen in four cases (5.3 per cent), palmar erythema in two (2.6 per cent), scanty pubic and axillary hair in two (2.6 per cent); jaundice and spider angioma were not observed. Clubbing of the fingers was present in two cases (2.6 per cent). Hematologic Data. Most of the patients were anemic. Anemia was mild in fifteen patients, moderate in forty-four and severe in nine [20]. It was usually normocytic, normochromic or normocytic hypochromic. No case of macrocytic anemia was seen. Bone marrow examination carried out in fifteen cases disclosed hypercellular marrow with relative erythroid hyperplasia in all. Leukopenia was present in fifteen cases, thrombocytopenia in twenty-four and pancytopenia in nine.

Routine liver function tests in the majority of the patients disclosed only minor alterations. The mean serum albumin was 3.2 ± 0.43 , the mean serum globulin was 3.1 ± 0.63 gm per cent. Mild to moderate hypoalbuminemia was seen in thirty-nine of seventy-five patients (52 per cent). Thymol turbidity, alkaline phosphatase and SGPT levels were not significantly altered (Table III). No patient had a serum bilirubin level above 2 mg at the time of first presentation. Bromsulfalein retention was normal (less than 8 per cent) in forty per cent of the cases, mildly increased (between 8 and 16 per cent) in another 40 per cent and markedly increased (retention above 16 per cent) in only 20 per cent. 131 I rose bengal hepatogram showed a

TABLE IV 131 I Rose Bengal Hepatograms With and Without Stress

Subjects	No. of Cases	T 1/2 (min)		Rate of Liver Uptake/Minute*		Maximum Uptake (%)		Time of Peak Liver Activity in Minutes	
		Mean	S.E.	Mean	S.E.	Mean	S.E.	Mean	S.E.
131I Rose Bengal Hepatogram									
Normal	21	4.185	0.31	15.2	0.616	17.04	0.828	22.38	1.44
Noncirrhotic portal fibrosis	20	6.25	0.49	10.95	0.94	10.71	0.54	30.5	1.11
		P < 0.01		P < 0.001		P < 0.001		P < 0.001	
Mean Difference in 131I Rose Bengal and Stress Hepatograms									
Normal	11	0.45	0.16	0.8	0.72	-0.39	0.09	2.5	1.33
Noncirrhotic portal fibrosis	20	2.16	0.43	-2.93	0.72	-2.21	0.69	9.5	2.21
		P < 0.001		P < 0.001		P < 0.02		P < 0.01	

* Expressed as per cent increase over initial counts.

TABLE V Serum Protein Fractions in Cases of Noncirrhotic Portal Fibrosis

Subjects	Sephadex G-200 Gravitational Method			Cellulose Acetate Paper Electrophoresis			
	1st Fraction Mean $\pm$ S.D.	2nd Fraction Mean $\pm$ S.D.	3rd Fraction Mean $\pm$ S.D.	Alpha ₁ Globulin Mean $\pm$ S.D.	Alpha ₂ Globulin Mean $\pm$ S.D.	Beta Globulin Mean $\pm$ S.D.	Gamma Globulin Mean $\pm$ S.D.
Normal	12.8 $\pm$ 0.25	39.9 $\pm$ 0.29	47.0 $\pm$ 0.29	4.1 $\pm$ 0.29	8.2 $\pm$ 0.45	10.5 $\pm$ 0.48	21 $\pm$ 0.74
Noncirrhotic portal fibrosis	10.0 $\pm$ 0.90 P = 0.01	46.0 $\pm$ 1.20 P < 0.001	45.0 $\pm$ 1.10 ...	4.5 $\pm$ 0.13 ...	9.3 $\pm$ 0.34 P = 0.06	13.3 $\pm$ 0.36 P < 0.001	23 $\pm$ 0.75 ...

NOTE: All results are given in percentages.

significant alteration of hepatocellular function in 75 per cent of cases. The hepatogram was entirely normal in five cases. The mean value for all the parameters of hepatocellular function, i.e., T 1/2, rate of liver uptake per minute, maximum uptake expressed as percentage of the injected dose and time of peak liver activity was significantly abnormal as compared to the controls (Table IV). Stress hepatogram was abnormal in all the cases studied. This included five patients with normal rose bengal hepatogram and eight patients with normal bromsulfalein excretion. Further, the abnormality of the ¹²⁵I rose bengal hepatogram was significantly accentuated after stress with bromsulfalein. Bromsulfalein stress did produce slight alteration in the parameters of hepatocellular function in the control group also, but this was relatively insignificant.

Cellulose acetate paper electrophoresis revealed a significant elevation of alpha₂ and beta globulins. Relative increase of IgG (second fraction) and decrease of IgM (first fraction) was observed in Sephadex G 200 column chromatography (Table V).

Roentgenologic Investigations. Esophageal varices were demonstrated in fifty-one cases (68 per cent). The varices were usually marked and extended to the lower and middle third of the esophagus in the majority. Splenoportovenogram revealed varices and collaterals in the gastro-esophageal area. There was dilatation of the main portal vein and portal vein radicles (Figure 1). The splenic vein was dilated and tortuous. Extensive collaterals made interpretation of the state of the major intrahepatic vessels difficult. Small portal vein branches showed gentle curves in some patients. There was no kinking or deformity. The normal complement of small branch filling was present, and the sinusoidal phase was usually dense compared to the patchy sinusoidal phase seen in cirrhosis.

Hemodynamic Studies. Mean wedged hepatic vein pressure was 12.74 ± 6.16 mm Hg, which is significantly higher than in the controls (P

<0.001). It was, however, not increased in all the patients (Figure 2). The splenic pressure was markedly increased in almost all the patients, with a mean value of 20.2 ± 6.80 mm Hg (Figure 2). In twenty-seven patients in whom both wedged hepatic vein pressure and splenic pressure were recorded, the gradient between the two was determined. The pressure gradient of each patient is represented in Figure 3. The mean gradient was 8.84 ± 4.8 mm Hg which indicates a significant increase in presinusoidal resistance. The results of hepatic blood flow studies are shown in Table VI. The mean estimated hepatic blood flow for the group was 1,433 ml/minute/M² of the body surface area, by the indocyanine green method. Expressed as percentage of cardiac output the mean value was 31.8 ± 3.94 per cent. These values are slightly, not significantly, higher than normal. There was a wide variation in hepatic blood flow among individual patients. Estimated hepatic blood flow was above 1,500 ml/minute/M² body surface area in thirteen cases (48 per cent), 1,000 to 1,499 in eight cases (30 per cent) and less than 1,000 in six cases (22 per cent). Hepatic blood flow was also estimated by radioactive gold (Table VII) in twenty patients and twenty-one controls.



Figure 1. Splenoportovenogram of a patient with non-cirrhotic portal fibrosis showing marked collaterals and dilatation of portal and splenic veins.

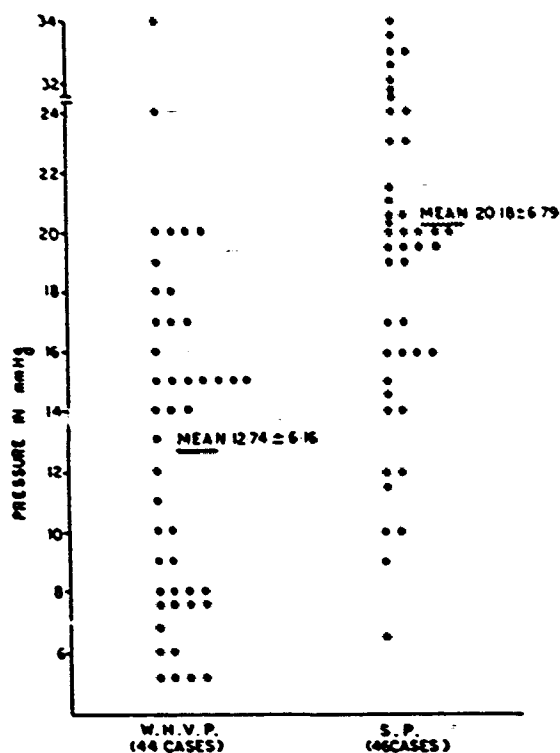


Figure 2. Wedge hepatic vein and splenic pressure in noncirrhotic portal fibrosis.

TABLE VI Estimated Hepatic Blood Flow (EHBF) in Normal Subjects and in Patients with Noncirrhotic Portal Fibrosis

Subjects	Mean EHBF (ml/min/M ²)	Standard Error of Mean	Mean EHBF as % of Cardiac Output	Standard Error of Mean
Normal	1,211 (5)	42.69	32.5 (5)	1.89
Noncirrhotic portal fibrosis	1,433.6 (27)	107.94	31.85 (15)	3.94

P > 0.05

P > 0.10

NOTE: Figures in parentheses represent number of cases.

TABLE VII Hepatic Blood Flow—Au¹⁹⁸ Liver "K" Values in Normal Subjects and in Patients with Noncirrhotic Portal Fibrosis

Subjects	No. Cases	Mean "K"	Standard Deviation	Mean Error
Normal	21	0.357	0.048	0.010
Noncirrhotic portal fibrosis	20	0.374	0.147	0.017

NOTE: Normal versus noncirrhotic portal fibrosis, P not significant.

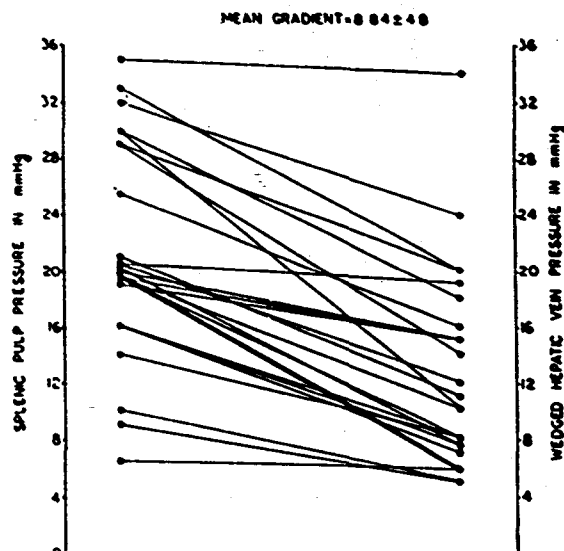


Figure 3. Gradient between splenic pressure and wedged hepatic vein pressure.



Figure 4. Liver specimen from a patient with noncirrhotic portal hypertension. Note the extensive and marked fibrosis, predominantly confined to portal areas. The left lobe is atrophic and the surface presents a scarred appearance reminiscent of cirrhosis.



Figure 5. Characteristic change in large intrahepatic portal vein radicle. The intima shows irregular thickening. Compare with artery on the right. Masson trichrome stain, original magnification × 120.

The results are expressed as disappearance rate constant "K" which represents the fraction of the total blood volume perfusing the liver [16]. The mean "K" in control subjects was 0.357 ± 0.048 ; in noncirrhotic portal fibrosis it was 0.374 ± 0.147 , which is not significantly different from that in control subjects.

Histopathologic Studies. The gross appearance of the liver was noted in thirty-one patients either at the time of operation or at autopsy. In general, the normal luster of the liver was lost, it felt firm and had linear pale scars in some areas due to mild thickening of the capsule. The surface varied from normal to distinctly nodular, resembling cirrhosis (Figure 4). It was smooth in fourteen patients, granular in seven and nodular in ten. The nodularity was more often seen on the under surface and left lobe of the liver. In one patient there was a large hump-like elevation of one lobe with atrophy of the other.

In patients who came to autopsy, inspection of the cut surface of the liver showed that the nodularity was more in the subcapsular regions. Deep inside, the cut surface appeared normal in some and showed thin irregular scars in others. The larger portal tracts were thickened by fibrosis. Nodular transformation of the entire liver was seen in only one case.

Microscopically, in the needle biopsy specimens, the normal architecture of the liver was fairly well preserved except for variably increased fibrosis in the portal tract and small focal areas of necrosis and regeneration in the liver parenchyma. In some there was focal infiltration with inflammatory cells in the lobule or in the portal tracts. Varying degrees of portal scarring were seen in a majority of the cases. The fibrosis was mostly confined to the portal areas, sometimes linking them up. The wedge biopsy specimens showed thickened capsules with prominent portal fibrosis in the subcapsular region. The subcapsular fibrosis at times was so prominent that differentiation from cirrhosis became difficult. Needle biopsy specimens from deeper regions in such cases helped to exclude cirrhosis. The small portal veins were inconspicuous and often replaced by several small vascular channels embedded in the scar tissue. In a few of the wedge biopsy specimens and in all the autopsy material, in addition to these relatively nonspecific lesions, occlusive changes in the portal vein radicles were seen. Large and medium-sized portal vein branches showed thickening of the wall due to subendothelial increase of collagen tissue, reducing the lumen to approximately half

of its normal size (Figure 5). This thickening was so striking that in the routinely stained sections it was frequently difficult to differentiate the vein from the artery. In some livers removed at autopsy large intrahepatic portal veins showed definite evidence of thrombosis and recanalization. These changes were focal in distribution and were seen in deep wedge biopsy specimens and autopsy specimens but not in the needle biopsy specimens.

Examination of the ultrastructure of the liver consistently showed abnormalities in the space of Disse, perisinusoidal space and the cell membranes in all the nine cases. There was widening of the space of Disse and the intercellular space. The widening in the space of Disse was essentially due to the laying down of collagen bundles which were prominent in the parasinusoidal space and in some areas also spread to the intercellular spaces (Figure 6A). Well developed mesenchymal cells were seen close to the collagen bundles. In some areas an attempt at capillarization of sinusoids by the development of endothelial lining was noticed. The microvilli at the cell membranes facing the sinusoids were abundant. The cell membrane between the hepatocytes showed development of microvilli (Figure 6B). The nuclear and all the intracytoplasmic components of the hepatocytes were normal.

Response to Treatment. In general, it was possible to control the ascites and to improve the general condition and anemia by symptomatic treatment. Hematemesis was recurrent, and while in the hospital the patients stood the bleeding well. However, two patients showed gradual but persistent deterioration. In these the ascites gradually became less amenable to diuretic therapy. Ultimately, five years and eight years after the onset of their illness, both had severe ascites, mild icterus and a marked deterioration in liver function tests. Both died in the hospital of hepatic coma precipitated in one by hematemesis.

Surgical Management. In all, twenty-eight patients were operated on for gastrointestinal bleeding. Splenorenal shunt was performed in sixteen cases. There was only one death during the immediate postoperative period, giving an operative mortality of 6.25 per cent. This patient had hematemesis on the third postoperative day and died of peripheral circulatory failure and hepatic coma. In the remaining fifteen patients the operative procedure was uneventful. In two patients serum hepatitis developed three months after the operation. One of them died of hepatic coma, the other recovered completely. Three patients (18.75 per

Figure 6. Electronmicrograph of liver in noncirrhotic portal fibrosis. Original magnification X 30,000. A, collagen bundles (Co) in space of Disse (S) extending into intercellular space. B, widened intercellular space (ICS) with development of microvilli.



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cent) had severe hematemesis five months, three years and four years after the operation; two of these died of bleeding in the hospital. Hematemesis precipitated hepatic coma in one, the other died of peripheral circulatory failure. One patient had grade II encephalopathy and is being maintained on antibiotics. The remaining twelve patients are well, with a follow-up of six months to four years.

Portocaval shunt was performed in nine patients. Two died (22.2 per cent) during the immediate postoperative period due to hepatic coma. Autopsy was performed in one of these patients. The liver showed extensive ischemic necrosis. During follow-up one patient had serum hepatitis, with complete recovery. One had severe encephalopathy and died of hepatic coma one year after the operation. The six surviving patients have been followed up for one to ten years and are asymptomatic.

Splenectomy with transgastric resection of varices was performed in three patients. Huge splenomegaly and hypersplenism were the main indications. There was no operative death. One died one and a half months after the operation, due to severe hematemesis.

COMMENTS

Noncirrhotic portal fibrosis has been described in the literature under various names from all over the world. A series of seventy cases has been reported from Japan [8], twenty-four from Uganda [21] and seventeen from the United States [9]. Iber [2] considers that 3 to 5 per cent of the patients with portal hypertension in the West may have this disease. In India, Ramalingaswami, Wig and Sama [1], while describing the clinicopathologic classification of intrahepatic portal hypertension, reported sixteen cases of this syndrome. Later, noncirrhotic portal fibrosis was recorded by others in India [4-7,12].

The clinical picture of noncirrhotic portal fibrosis is characterized by a long history of splenomegaly, which marks the onset of illness in many cases. Recurrent hematemesis is frequent and is usually well tolerated. Mild to moderate ascites occurs in 41 per cent of the cases and is easily amenable to diuretic therapy. The lower incidence of ascites reported earlier from this center is due to the fact that patients with histologically non-specific changes and ascites as the predominant symptom (type II) were not included in the description of the splenomegalic type of portal hypertension (type III), which is now recognized as non-

cirrhotic portal fibrosis. Mild to moderate anemia and hypersplenism are common. A comparatively higher incidence of hematemesis (90 per cent) and a low incidence of ascites reported by Basu et al. [5] and Boyer et al. [7] may be related to selected material referred for surgery. Other features of hepatocellular failure are uncommon. Jaundice does not occur except during the terminal stages or transiently following hematemesis in some patients. The course of the disease is relatively benign and is compatible with long life in most patients.

There is mild hypoalbuminemia, but other routine liver function tests are within normal limits. The bromsulfalein test helps to differentiate cases of noncirrhotic portal fibrosis from cirrhosis. In noncirrhotic portal fibrosis the bromsulfalein test is either normal or shows retention of less than 16 per cent in a majority of the patients; in cirrhosis retention in most of the patients is above 16 per cent. Other investigators have also reported preservation of liver function tests in this disease [7]. ¹³¹I rose bengal hepatogram after stress with bromsulfalein is a more sensitive liver function test and was found to be uniformly abnormal in noncirrhotic portal fibrosis. There is a rise in alpha₂ and beta globulin levels, but a similar increase is observed in cirrhosis of the liver. IgG was found to be increased in noncirrhotic portal fibrosis but usually normal in cirrhosis and extrahepatic obstruction.

Splenoportovenograms show dilatation of the portal and splenic veins. Similar findings have been reported by Boyer et al. [7] and Williams et al. [10]. Narrowing and constriction of the main branches and poor visualization of peripheral vessels reported by Boyer et al. [7] and Williams et al. [10] was not consistently seen in this study. Bhardwaj et al. [12] reported additional changes in the intrahepatic portal vein radicals viz. selective dilatation of the left main branch of the portal vein, sudden narrowing (cut-off sign) of major intrahepatic branches, truncated peripheral terminals and a granular pattern in place of secondary branching with occasional pooling of dye in the distended portal vein branches.

Hemodynamic studies have indicated normal estimated hepatic blood flow, increased splenic pressure and significant presinusoidal resistance. However, there was marked variation in the estimated hepatic blood flow and the gradient between the splenic pressure and wedged hepatic vein pressure among different patients. Similar hemodynamic findings have been reported by other investi-

gators [7,12]. However, Williams et al. [10] found increased blood flow in their patients; wedged hepatic vein pressure was above 10 mm Hg in twenty-three of forty-four patients. The clinical features of patients with and without raised wedged hepatic vein pressure were similar. Histologically there is a varying degree of portal fibrosis, with focal areas of necrosis and cellular infiltration with chronic inflammatory cells. These changes are all nonspecific. The specific anatomic lesions of this disease not observed in cirrhosis or extrahepatic obstruction are (1) occlusive changes in the intrahepatic portal vein radicals, which are focal in distribution, and (2) diffuse collagenization of the space of Disse and perisinusoidal space on electron microscopy. Obliterative portovenopathy can explain the presinusoidal resistance but fails to account for raised wedged hepatic vein pressure and normal estimated hepatic blood flow. Similar findings of raised wedged hepatic vein pressure and normal estimated hepatic blood flow have been reported in portal hypertension due to schistosomiasis in which the anatomic lesion is certainly presinusoidal [22]. It has been argued that when the obstruction is presinusoidal the increased hepatic arterial flow compensates for diminished portal venous flow, and as the disease progresses secondary changes occur in the sinusoids and space of Disse which may be responsible for raised wedged hepatic vein pressure [23]. However, the obliterative portovenopathy is a patchy lesion most often missed in a needle biopsy specimen, whereas the perisinusoidal fibrosis, easily observed in 600 to 700 Å thick sections of needle biopsy specimens, is a more diffuse change. It is possible that the primary lesion in this disease is collagenization in the perisinusoidal regions and space of Disse. Obliterative venopathy may be secondary to portal hypertension produced by perisinusoidal fibrosis. Alternatively, the same etiologic factor simultaneously produces changes in the intrahepatic radicals of the portal vein and perisinusoidal area. The variation in the severity of changes at these two sites explains the variation in hemodynamic findings.

Splenorenal shunt seems to give better results than portocaval shunt. On correlating the results of shunt operation with estimated hepatic blood flow, interesting observations were made. There were three deaths in the immediate postoperative period. Estimated hepatic blood flow was measured in two of these three patients and was one and a half to two times the normal. Such increase in hepatic blood flow was not observed in any

other patient operated upon. It is possible that sudden cessation of portal blood was not tolerated by the liver in these patients with higher blood flow. Autopsy performed on one of them demonstrated extensive ischemic necrosis of the liver. Even in cases of cirrhosis Warren et al. [24] reported poor results of surgery in patients when the blood flow was relatively high. When evaluating the results of shunt surgery in noncirrhotic portal fibrosis it is therefore important to take into consideration the initial estimated hepatic blood flow and the fall in estimated hepatic blood flow after the operation. Three patients had hematemesis after operation. Two of them died despite conservative treatment in the hospital. Such high mortality due to bleeding was not seen in this disease before surgery. An operative mortality of 10.7 per cent, high risk of serum hepatitis and high mortality due to postshunt bleeding in a relatively benign condition makes one wonder whether the accepted indications for surgery in cirrhosis can be applied to this group. To evaluate the role of surgery in this disease it is necessary to have a control group of patients on conservative management.

The natural history of noncirrhotic portal fibrosis is not known. The disease seems to have a protracted benign course, but progressive hepatic fibrosis may lead to severe impairment of liver functions with fatal results in a few patients, as was observed in four cases in the present series.

The pathogenesis of noncirrhotic portal fibrosis is unknown. It may be the result of abdominal sepsis with thrombophlebitis and repeated embolization into the portal circulation. This process may have been initiated in childhood with sepsis. It is extremely difficult to obtain an accurate history of umbilical sepsis from adult patients. Alternatively, these lesions may be due to some unknown toxin with a specific action on the portal vein radicles and space of Disse. The toxin may be bacterial or parasitic, or may be ingested by the patients as indigenous drugs or as adulterants in food, similar to the specific herbal toxins for hepatic venous system in veno-occlusive disease.

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REFERENCES

1. Ramalingaswami V, Wig KL, Sama SK: Cirrhosis of liver in Northern India. *Arch Intern Med* (Chicago) 110: 350, 1962.
2. Iber FL: Obliterative portal venopathy of the liver and idiopathic portal hypertension. *Ann Intern Med* 71: 660, 1969.
3. Wig KL, Tandon BN, Bhargava S, Sama SK, Nayak NC: Portal hypertension with particular reference to the non-cirrhotic type. *Bull AIIMS* 2: 152, 1968.
4. Nayak NC, Ramalingaswami V: Obliterative porto-venopathy of the liver associated with so-called idiopathic portal hypertension in tropical splenomegaly. *Arch Path* (Chicago) 87: 359, 1969.
5. Basu AK, Boyer J, Basu Mullick KC, Sen Gupta KP: Noncirrhotic portal fibrosis with portal hypertension. Clinical and functional studies with results of operation. Part I. *Indian J Med Res* 55: 336, 1967.
6. Basu Mullick KC, Sen Gupta KP, Basu AK, Biswas SK, Pal NC, Boyer J: Noncirrhotic portal fibrosis with portal hypertension. Part II. Histological studies. *Indian J Med Res* 55: 351, 1967.
7. Boyer JL, Sen Gupta KP, Biswas SK, Pal NC, Basu Mullick KC, Iber FL, Basu AK: Idiopathic portal hypertension. Comparison with portal hypertension of cirrhosis and extrahepatic portal vein obstruction. *Ann Intern Med* 66: 41, 1967.
8. Imanaga H, Yamamoto S, Kuroyanagi Y: Surgical treatment of portal hypertension according to the state of intrahepatic circulation. *Ann Surg* 155: 42, 1962.
9. Mikkelsen WP, Eimondson HA, Peters RL, Redekar AG, Reynolds TB: Extra and intrahepatic portal hypertension without cirrhosis (hepatoportal sclerosis). *Ann Surg* 162: 602, 1965.
10. Williams R, Parsonson A, Somers K, Hamilton PJS: Portal hypertension in idiopathic tropical splenomegaly. *Lancet* 1: 329, 1966.
11. Wig KL, Ramalingaswami V, Sama SK: Clinicopathological classification of intrahepatic portal hypertension (cirrhotic and non-cirrhotic). *J Ass Physicians India* 14: 411, 1966.
12. Proceedings of the workshop on non-cirrhotic portal fibrosis. Indian Council of Medical Research 1969.
13. Havana Conference: Fifth Pan-American Congress of Gastroenterology, Havana, Cuba. Report of the Board of Classification and Nomenclature of Cirrhosis of the Liver. *Gastroenterology* 31: 213, 1956.
14. Taplin GV, Meredith OM Jr, Kade H, Winter CC, Johnson D: New radiodiagnostic techniques for investigating parenchymal and obstructive liver and kidney diseases. Proceedings of 2nd International Conference on Peaceful Uses of Atomic Energy, Geneva 26: 128, 1958.
15. Dobson EL, Warner GF, Finney GR, Johnston ME: The measurement of liver circulation by means of the colloid disappearance rate. Liver blood flow in normal young men. *Circulation* 7: 690, 1953.
16. Fellingner K, Hofer R, Vetter H: Radiocolloids in the study of hepatic circulation in man. Proceedings of 2nd International Conference on Peaceful Uses of Atomic Energy, Geneva 26: 153, 1958.
17. Tandon BN, Lakshminarayanan R, Bhargava S, Nayak NC, Sama SK: Ultrastructure of liver in non-cirrhotic portal fibrosis with portal hypertension. *Gut* 11: 905, 1970.
18. Zweig C, Whitaker JR: Paper Chromatography and Electrophoresis, New York, Academic Press, 1967.
19. Flodin P, Killander J: Fractionation of human serum proteins by gel filtration. *Biochim Biophys Acta* 63: 403, 1962.
20. W.H.O. Technical Report Series 405, 1968.
21. Leather HM: Portal hypertension and gross splenomegaly in Uganda. *Brit Med J* 1: 15, 1961.
22. Ramos OL, Saad F, Leser WP: Haemodynamic and liver function in hepatic schistosomiasis. *Gastroenterology* 47: 241, 1964.
23. Iber FL: Cause of portal hypertension. *Amer J Med Sci* 255: 217, 1968.
24. Warren WD, Restrap JE, Respass JC, Mullee WH: The importance of haemodynamic studies in the management of portal hypertension. *Ann Surg* 158: 387, 1963.



Fig. 1—Radiography of the abdomen, showing thorium dioxide deposits in the liver, spleen and tributary lymph nodes.

ascertain their present state of health and determine whether or not a thorotrast induced lesion could be demonstrated. Satisfactory follow-up examination has been possible in 1,171 (48 per cent) of the patients 882 of which were systemically injected.

The multiple pathologies encountered in this group have been the subject of previous communications.¹⁻⁴ This paper reports the laboratory findings and gastrointestinal complaints in a group of 155 unselected patients.

MATERIAL AND METHODS

Of the 155 patients studied, 76 were men and 79 were women, ranging in age from 22 to 80 years. Every patient had received thorium dioxide, in dosage from 4 to 70 ml. (Fig. 2); in 18 cases, however, the exact dosage was not known. The period of time elapsed between the injection of Thorotrast and examination ranged from 10 to 37 years (Fig. 3).

Table I lists the laboratory tests performed, the methods used, and the normal ranges for the parameters studied.

In 15 cases material was available for histological examination (11 from liver biopsies and four from necropsies).

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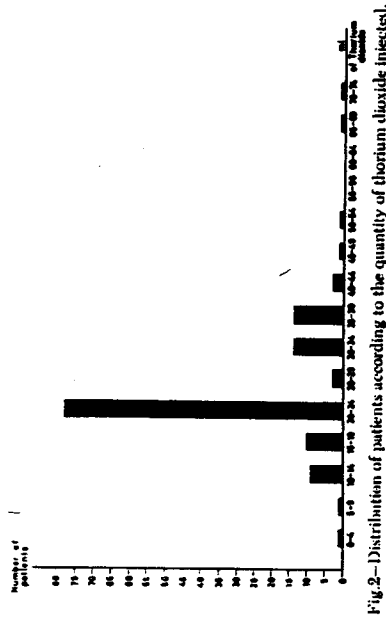


Fig. 2—Distribution of patients according to the quantity of thorium dioxide injected.

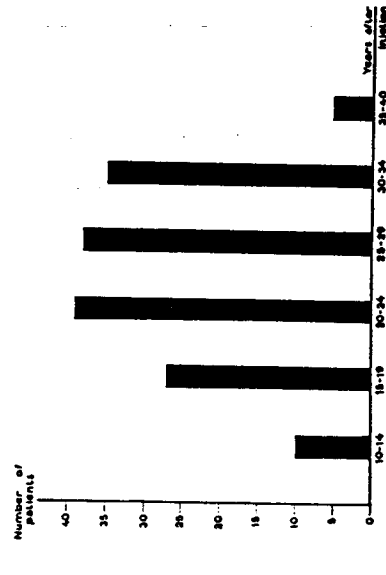


Fig. 3—Distribution of patients according to the number of years elapsed between the injection of thorium dioxide and our examination.

CLINICAL FINDINGS

In the Thorotrast population, two kinds of symptoms can be found: 1. Symptoms related to the location of injection, and 2. general symptoms.

At the site of the injection, an extravasation of the drug outside of the blood vessel occurred frequently and, in some of these cases, "local granuloma" developed. Among these 155 cases, 41 presented "local granulomata", of which 34 were cervical. The general symptoms were mainly of the gastrointestinal type and

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TABLE I
LABORATORY TESTS PERFORMED, METHODS USED AND NORMAL VALUES

Test	Method	Normal values
Total serum protein	Wolfsen, Cohn, Calvary and Ichiba (with changes)	6.5-8 gm./100 ml. of serum
Protein electrophoresis	Grassman and Hanna	55-65%
albumin		3-6%
globulin		6-9%
α ₁		12-14%
α ₂		14-18%
β		
γ		
Cephalin flocculation	Hanger	Negative and ++
Thymol turbidity	La Huerga	0-5 U
Cadmium flocculation	Whurmann and Wunderly	Negative
Glutamic oxalacetic transaminase (GOT)	Karmen	under 40 U/ml./min.
Glutamic pyruvic transaminase (GPT)	Wróblewski and LatDue	under 40 U/ml./min.
Aldolase (ALD)	Bruns*	3.3-6.1 U/ml.
Alkaline phosphatase (AP)	Bodanski and Shinowara	2-4 U Bodansky
Leucine-amino-peptidase (LAP)	Green, Brum and Falcoff	260-520 U/ml.
Serum bilirubin	Mallory and Evelyn with changes by Duclot and Watson	Conjugated—less than 0.24 mg./100 ml. Total—less than 1.5 mg./100 ml.
Bromsulphalein	Mattee, et al.	0-5% of retention after 45 min.

* In some cases, TC-D combinations supplied by C. F. Boehringer & Söhne GMBH (Art. No. 15,974) were used; *Upper Limit of Normal*: 8 milli U/ml. in accordance with recent information from the Biochemical Department.

† In some cases, due to the modifications introduced by C. F. Boehringer & Söhne GMBH, TC-LAP combinations (Art. No. 15,952) were used; *Normal Values*: 8-22 milli U/ml.

were found with the following frequencies: Eighty-one patients had general dyspeptic complaints, such as flatulence, dyspepsia, nausea, vomiting. Some also complained of pain in the right or left upper abdomen, and a few had increased intestinal transit. In eight of these patients, hepatic pathology from liver biopsy disclosed hepatic fibrosis (Fig. 4). Fourteen patients had jaundice and ascites, marked loss of weight and weakness. The clinical course of these patients led rapidly to death, always in a period of three to nine months from the onset of symptoms. In the seven cases with liver biopsy or necropsy, a malignant liver tumor was always found, four hemangioendotheliomata (Figs. 5 and 6) and three cholangiocarcinomata (Fig. 7). The encountered neoplasm was always associated with hepatic fibrosis. In the remaining seven cases without histological



Fig. 4—Hepatic fibrosis. Medium power (H and E).



Fig. 5—Hemangioendothelioma of the liver. Macroscopic aspect.

examination, no other obvious pathologies were encountered which might account for the gastrointestinal symptoms and presumably represent liver fibrosis with developing tumors. These cases are summarized in Table II. In the cases with available histological examination of the liver, spleen, and tributary lymph nodes, liver fibrosis was always accompanied by spleen and lymph node fibrosis.

LABORATORY RESULTS

Table III presents the laboratory data. The greatest frequency of abnormal results was found in the protein electrophoresis, with low serum albumin (65, 3 per cent) and increased alpha 2 and gamma serum-globulins (64, 8 per cent), alterations which, of course, influence the seroflocculation tests. Increased levels of alkaline phosphatase was the more frequently found abnormality in enzymatic activities (66, 6 per cent); the other enzyme values showed abnormal values in only a small number of cases. Bromsulphalein was performed in less than half



Fig. 6

Fig. 6—Hemangioendothelioma of the liver. Medium power (H and E).

Fig. 7—Cholangiocarcinoma. Medium power (H and E).

of the cases, but it was abnormal in 44.6 per cent of all cases. It was never done in patients with jaundice or congestive cardiac failure.

Figure 8 shows the distribution, in relation to the time elapsed after Thorotrast injection, of the laboratory tests which presented the highest percentage of abnormal results. It is obvious that the incidence of abnormal values increases with the time following Thorotrast injection, and the more abnormal values were always found in the patients that had been injected quite some time before.

Figure 9 shows the distribution of the same data analyzed in accordance with the dose of Thorotrast injected. The largest number of patients received 20 ml., and in that group we found more abnormal than normal values. For all the remaining doses, there is a similar incidence of abnormality, apparently independent of the amount of drug injected. Moreover, the degree of alteration in the laboratory tests was not correlated with the dose injected.

COMMENT

The general symptoms of the gastrointestinal type found in 81 patients are probably caused by the deposits of the drug in the liver, spleen, and tributary lymph nodes. The drug probably acts in two ways: 1. induction of fibrosis with the consequent loss of function, and 2. induction of radiation injury with possible subsequent development of neoplasia.

Jaundice, ascites and loss of weight always led to death between three to nine months after the onset of symptoms. Fourteen patients of this study presented this clinical picture: in seven cases, in which pathological examinations were performed, diagnoses of hemangioendothelioma in four cases and of cholangiocarcinoma in three cases were established. We believe that these tumors have been induced by Thorotrast, even though all of them appeared 29 or more years after reception of the drug. Therefore, every patient who has received Thorotrast should be subjected to periodic examination. It must be pointed out that the

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TABLE II
DECEASED PATIENTS WITH MALIGNANT TUMORS OF THE LIVER

Case	Sex	Age at death (years)	Time elapsed between Thorotrast injection and death (years)	Quantity of Thorotrast injected (ml.)	Time elapsed between the onset of symptoms and death (months)	Diagnosis
1	♀	46	31	36	3	Liver hemangioendothelioma (histological)
2	♀	46	34	36	5	Liver hemangioendothelioma (histological)
3	♂	56	36	33	5	Liver hemangioendothelioma (histological)
4	♀	54	37	18	3	Liver hemangioendothelioma (histological)
5	♀	50	30	20	4	Cholangiocarcinoma (histological)
6	♂	56	33	36	4	Cholangiocarcinoma (histological)
7	♂	54	34	?	7	Cholangiocarcinoma (histological)
8	♂	54	29	20	6	Liver tumor (clinical)
9	♂	55	31	40	6	Liver tumor (clinical)
10	♂	48	33	36	6	Liver tumor (clinical)
11	♀	77	34	40	4	Liver tumor (clinical)
12	♀	48	34	30	4	Liver tumor (clinical)
13	♀	61	35	18	8	Liver tumor (clinical)
14	♂	38	?	20	5	Liver tumor (clinical)

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TABLE III

TIMES REPORTED FOR EACH LABORATORY TEST AND PER CENT OF ABNORMAL RESULTS

Test		Times reported	Normal	Abnormal	Per cent of abnormal results
Total serum proteins		132	127	5	3.7
Protein electrophoresis	albumin	147	51	96	65.3
	α 1	145	128	17	11.7
	α 2	145	51	94	64.8
	β	145	96	49	33.7
Sero-flocculation tests	γ	145	51	94	64.8
	Cephalin flocculation	142	117	25	17.6
	Thymol turbidity	142	92	50	35.2
Cadmium flocculation		130	60	70	53.8
Glutamic oxaloacetic transaminase (GOT)		125	108	19	15.2
Glutamic pyruvic transaminase (GPT)		125	113	12	9.6
Aldolase (ALD)		68	55	13	19.1
Alkaline phosphatase (AP)		135	45	90	66.6
Leucine aminopeptidase (LAP)		70	53	17	24.2
Bilirubin	conjugated	85	75	10	11.7
	total	88	81	7	8.0
Bromsulphalein		65	36	29	44.6

hemangioendothelioma of the liver and of the RE organs is an almost "Thorotrast specific" tumor, because only Thorotrast recipients show this kind of tumor. In fact, among 11,300 autopsies performed in the Institute of Pathology of the Lisbon Medical Faculty, 16 hemangioendotheliomas have been found, all but one in Thorotrast recipients.

The most important findings among the laboratory tests have been a serum-disproteinemia consisting of low albumin and increased alpha 2 and gamma globulin values, as well as increased alkaline phosphatase values, very high indeed, in the cases of malignant liver tumors. The other enzymatic abnormalities have not been striking.

Finally, we would stress the fact that the clinical and laboratory alterations found in this group of patients are related not only to the doses of Thorotrast received, but also to the time elapsed since reception of the drug.

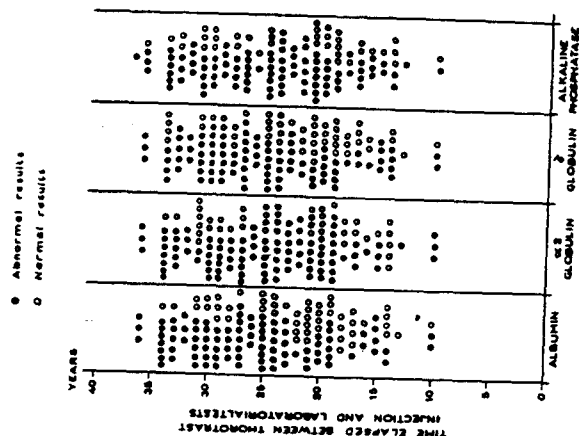


Fig. 8—Distribution of some of the laboratory test results according to the time elapsed after thorium dioxide injection.

SUMMARY

One hundred and fifty-five patients injected years ago with a colloidal suspension of thorium dioxide have been clinically investigated for gastrointestinal pathology and biochemical aberration. Fifteen cases had material available for histological examination.

General dyspeptic complaints were encountered in 81 patients, eight of them with a histological diagnosis of hepatic fibrosis. A malignant tumor of the liver caused death in 14 patients, seven of which had histological corroboration, e.g. four hemangioendotheliomas and three cholangiocarcinomas.

An interesting abnormality of the laboratory tests, disclosed by this investigation, is increased levels of alkaline phosphatase and of alpha 2 and gamma globulins and low serum albumin.

Av. Joaquim Antonio de Aguiar
45-3° E
Lisbon I, Portugal

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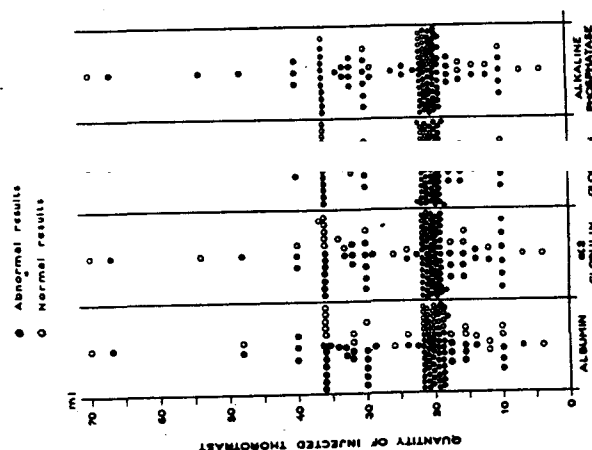


Fig. 9—Distribution of some of the laboratory test results according to the quantity of thorium dioxide injected.

REFERENCES

1. da Silva Horta J: Reação dos tecidos ao tiorotast. *Rev Med Portuguesa* 4:665-711, 1951.
2. da Silva Horta J: As formas anatomo-clínicas resultantes da acção do tiorotast. *Colectânea de Trabalhos Médicos de Discipulos de Pulido Valente*, pp. 17-44, 1954.
3. da Silva Horta J: Late lesions in man caused by thorotrast. *Arch Pathol* 63:403-415, 1959.
4. da Silva Horta J: Reactions of the RES to colloidal thorium dioxide in man. *RES Bull* 4:10-19, 1959.
5. da Silva Horta J, Collette J, Roriz ML: Circulation of thorium dioxide in the liver. *Visualisation du thorotrast par la technique de la radioautographie*. *Arch de Vecchi* 5, 1955.
6. da Silva Horta J, Abbott JD, Cayolla da Motta L, following administration of thorotrast. *Lancet* 2:20, 1955.
7. da Silva Horta J: Late effects of thorotrast on the lymph nodes. *Ann NY Acad Sci* 145:676-689, 1967.
8. da Silva Horta J, Cayolla da Motta L: Follow-up of thorium dioxide patients in Portugal. *Ann NY Acad Sci* 145:830-849, 1967.

Comparison of Pentagastrin and Augmented Histamine Stimulation as Tests of Gastric Acid Secretion

JAHANGIR KHODADOOST, M.D.*

Tehran, Iran

OLIVAL LEITAO, M.D.*

Curitiba, Brazil

and

GEORGE B. JERZY GLASS, M.D.

New York, N. Y.

Following isolation of gastrin I and II* and determination of their composition and complete sequence of the amino acids,* including the C-terminal portion where its secretory activity resides,* a synthetic preparation was developed (ICI 50,123) under the name of pentagastrin (Peptavlon®). This contains a similar sequence of 4 amino acids to that present in the terminal portion of the gastrin molecule, namely tryptophan, methionine, asparagine, phenylalanine-NH₂. Pentagastrin** as well as another synthetic preparation called tetragastrin* have been successfully applied to testing the gastric acid secretion in humans.

Subsequently, pentagastrin has been submitted to rigid evaluation in several investigational centers of the United States. This report presents results obtained by our group with this material as a part of this multicenter study. It compares the gastric acid output following pentagastrin and augmented histamine stimulation, evaluates the side-effects of pentagastrin, and describes the gastroscopic findings following pentagastrin stimulation.

MATERIALS AND METHODS

Twenty patients, 12 males and eight females ranging in age from 21 to 66 years and hospitalized at Metropolitan Hospital in New York City for various gastrointestinal disorders were selected at random for this study. An informed consent was obtained from each of the patients. Of the 20 cases, four had duodenal ulcer; 10 had functional gastrointestinal disorders with a normal upper gastrointestinal series; three had atrophic gastritis as proven by gastric suction biopsy, and three had miscellaneous disorders (Table I).

Each patient had upper gastrointestinal x-ray series just prior to the test. All drugs including anticholinergics and sedatives were withheld 48 hours before the study.

From the Gastroenterology Section and Gastroenterology Research Laboratory, New York Medical College.

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* Formerly, Fellow in Gastroenterology, Department of Medicine, New York Medical College and Metropolitan Hospital.