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The False-Positive Hepatic Scan[1,2,3]

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INTRODUCTION

Twelve years have passed since scintillation scanning of the liver was introduced by Stirret, Yuhl and Cassen (1). During this period, the hepatic scan has been employed primarily to screen patients for possible intrahepatic neoplasia. The extent of its clinical utilization is indicated by the fact that about 1,000 hepatic scans are performed annually at the authors' institution. This is attributable to the safety, simplicity and sensitivity of the procedure, a combination not yet attained by alternate methods.

A substantial literature, summarized recently (2,3), attests the clinical value of hepatic scanning. Gollin *et al* (4) found it more sensitive than the serum alkaline phosphatase and other tests of liver function in detecting localized lesions and differentiating these from diffuse hepatic disease. However, it is well established that a normal scan does not exclude space-occupying disease within the liver. The false-negative rate is variously reported as 7% to 27% (2,4,5). Factors contributing to this failure rate include the liver's unique geometrical configuration, its respiratory excursions (6), limited resolution of collimators and random fluctuations in counting rates. The introduction of new radiopharmaceuticals and advances in instrumentation promise to minimize the false-negative rate.

The false-positive hepatic scintillation scan.

It is less well known that the hepatic scan may falsely suggest a space-occupying intra-hepatic lesion. Although false-positive rates of 2.5% (4, 5) to 12.5% have been reported by some investigators, others appear to have encountered this problem infrequently (7) or not at all; Achaval *et al* found no false-positives in their series (8).

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We have periodically been confronted by patients whose scans contained a focal area of low or no radioactivity clearly compatible with space-occupying hepatic disease. However, subsequent clinical courses effectively excluded this possibility in each case. The histories of four such patients are summarized.

CASE REPORTS

Case 1.

(W.A., #154-07-95) A 62-yr-old male was admitted for intermittent diarrhea and progressive hepatosplenomegaly. A scan following administration of ^{198}Au colloid (Fig. 1A) disclosed enlargement of the spleen & liver and an ill-defined area of low radioactivity in the right hepatic lobe. Biopsy of the liver revealed healed granulomata, but cultures of the specimen and of gastric washings were negative for *M. tuberculosis.* There was transient response to anti-tuberculosis drugs, but hepatomegaly progressed and icterus supervened. On re-admission eight months later, the patient's liver and spleen lay 8 cm and 5 cm below the costal margin respectively. The serum bilirubin was 6.0 mg/100 cc. alkaline phosphatase was 18 King-Armstrong (KA) units, cephalin flocculation and thymol turbidity were 3+. A repeat scan (Fig. 1B) disclosed greater radioactivity in the spleen than in the liver, which was smaller than before and now contained a large discrete area of virtually absent radioactivity in the right lobe. Repeat biopsy revealed active post-necrotic cirrhosis. Hepatic insufficiency progressed rapidly to frank decompensation and death.

At post-mortem examination the liver weighed 1350 gm and contained multiple 2-3 mm yellow nodules. Histological examination showed severe active Laennec's cirrhosis with microscopic foci of necrosis. No neoplastic or granulomatous tissue was present.

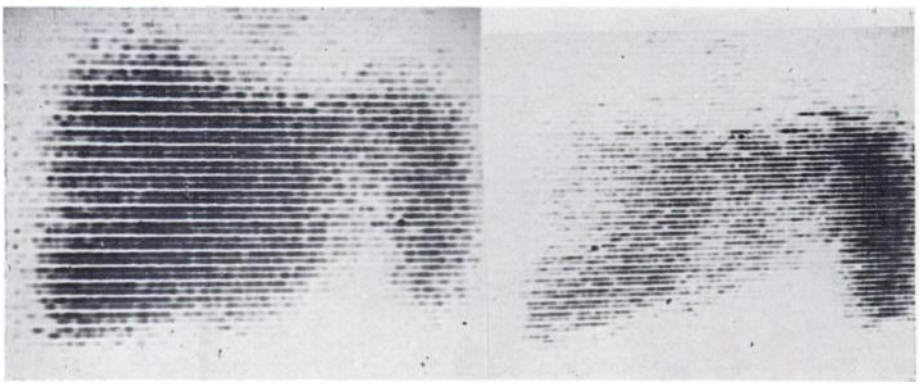

Fig. 1. Case 1: *Hepatic pseudo-mass in Laennec's cirrhosis.* (a) left. Initial scan discloses hepatosplenomegaly and slightly reduced radioactivity laterally in the right hepatic lobe. (b) right. Eight months later, scan suggests extensive hepatic replacement by space-occupying tissue, particularly in the right lobe. The liver is slightly smaller and splenic radioactivity is greater. There was no neoplasm at postmortem examination.

SUMMARY

In this patient serial scans suggested an expanding mass lesion in the right hepatic lobe but post-mortem examination revealed only severe Laennec's cirrhosis.

Case 2.

(J.W., #173-15-43) A 47-yr-old male was admitted for evaluation of probable cirrhosis. There was scleral icterus, a firm, nodular liver extending 6 cm below the costal margin and a spleen tip 3 cm below the costal margin. The serum bilirubin was 1.05 mg/100 cc, the alkaline phosphatase was 18 KA units, the cephalin flocculation was negative. Following administration of ^{198}Au colloid, a scan (Fig. 2) revealed massive hepatomegaly with two large areas of virtually absent radioactivity. Closed biopsy disclosed advanced Laennec's cirrhosis. At laparotomy for possible hepatoma the liver was greatly enlarged, uniformly firm and finely nodular. Deep wedge biopsy of the anterior surface of the right lobe, in an area of firm, yellowish tissue, disclosed advanced Laennec's cirrhosis. There was no evidence of neoplasm. Despite appropriate treatment, hepatic insufficiency progressed and the patient expired eight months later. Post-mortem examination was not obtained.

SUMMARY

Localized, discrete areas of absent radioactivity, strongly suggestive of intrahepatic masses, were present on the hepatic scan. Exploration and biopsy of these areas revealed cirrhosis without evidence of neoplasia.

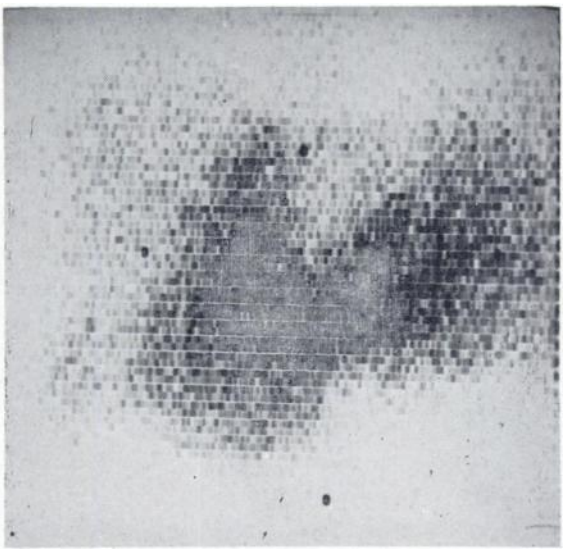

Fig. 2. Case 2: *Hepatic pseudo-masses in cirrhosis.* Frontal scan demonstrates marked hepatomegaly with apparent space-occupying lesions in the central and right lateral portions of the liver. Exploration and biopsy established the absence of masses in these areas.

SUMMARY

Two scans of the liver in a 25-month period demonstrated an apparent mass replacing the left lobe and imprinting the right. At operation there was contraction and rotation of the left lobe secondary to cirrhosis; no mass was present.

Case 3.

(A.L., #160-06-61) A 50-yr-old male was admitted for recurrent hematemesis. The liver extended 10 cm below the costal margin; the spleen was not palpable. The serum bilirubin level was normal, the alkaline phosphatase was 15 KA units and the sulfobromophthalien retention was 21% at 30 minutes. Esophageal varices were demonstrated radiographically. Following administration of ^{198}Au colloid a scan (Fig. 3A) disclosed marked hepatomegaly with greatly reduced radioactivity in the right lobe superiorly and absence of radioactivity in the region of the left lobe. The medial hepatic margin was sharply indented and there was slight splenomegaly. On the 20th day an end-to-end portacaval anastomosis was performed. The right hepatic lobe was massively enlarged and coarsely nodular. The left lobe was shrunken and rotated cephalically. Wedge biopsy disclosed Laennec's cirrhosis.

The patient subsequently did well. Two years later a repeat scan (Fig. 3B) again disclosed hepatomegaly; radioactivity was now present superiorly in the right lobe. Again there was no radioactivity in the usual region of the left lobe, and the sharp indentation of the medial hepatic margin was unchanged.

Case 4.

(C.D. #167-17-91) A 35-yr-old male was admitted for evaluation of an

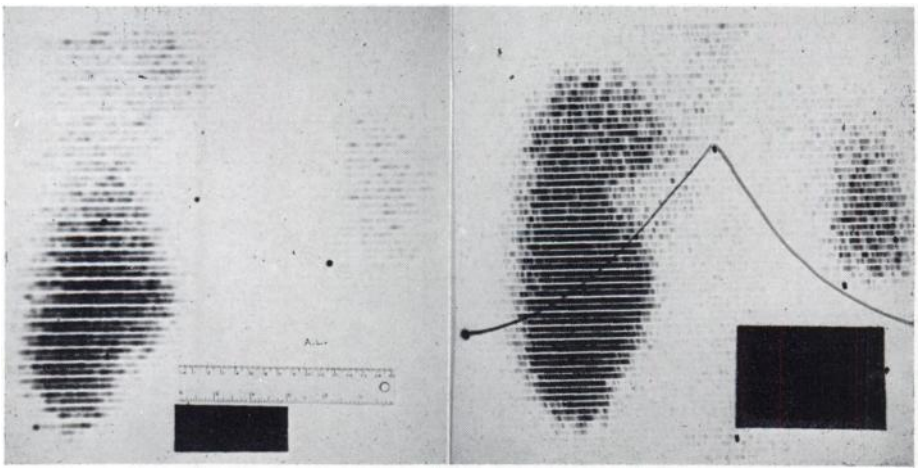

Fig. 3. Case 3: *Hepatic pseudo-mass in cirrhosis.* (a) left. Initial scan reveals virtually absent radioactivity in the right lobe superiorly and in the left lobe. These findings, together with an apparent imprint on the medial hepatic margin, suggest a space-occupying lesion replacing the left lobe and invading the right. (b) right. Twenty-five months later the configuration of the liver is unchanged; there is now increased radioactivity in the right lobe superiorly. No mass was found during direct exploration of the liver, but the left lobe was markedly contracted and rotated.

abdominal mass. Past history included admissions elsewhere for hepatic decompensation and gastrointestinal bleeding; 6 years earlier a portacaval shunt had been performed. Pertinent physical findings included a 9 cm mass in the right upper quadrant, confluent with the liver, and a palpable spleen tip. Laboratory examinations included serum bilirubin 1.0 mg/100 cc, alkaline phosphatase 42 KA units and sulfobromophathalien retention 36% at 30 minutes. Splenoportogram revealed a patent portacaval anastomosis. A scan (Fig. 4) following administration of ^{198}Au colloid disclosed hepatosplenomegaly with greatly increased splenic radioactivity. There were multiple localized areas of diminished or absent radioactivity in the liver.

At laparotomy the liver was enlarged, firm and nodular. No mass was palpable; the left lobe was contracted and shrunken. Deep wedge biopsy disclosed Laennec's cirrhosis. The immediate postoperative course was benign; the patient was subsequently lost to followup.

SUMMARY

Direct visualization and biopsy of the liver failed to verify the presence of intrahepatic mass lesions suggested by scintillation scanning. There was atrophy and contraction of the left hepatic lobe.

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Each of our encounters with the false-positive hepatic scan had occurred in the presence of cirrhosis. Accordingly, it was felt that analysis of scans in a group of patients having severe hepatic parenchymal disease might provide information as to the incidence and characteristics of pseudo-mass lesions of the liver.

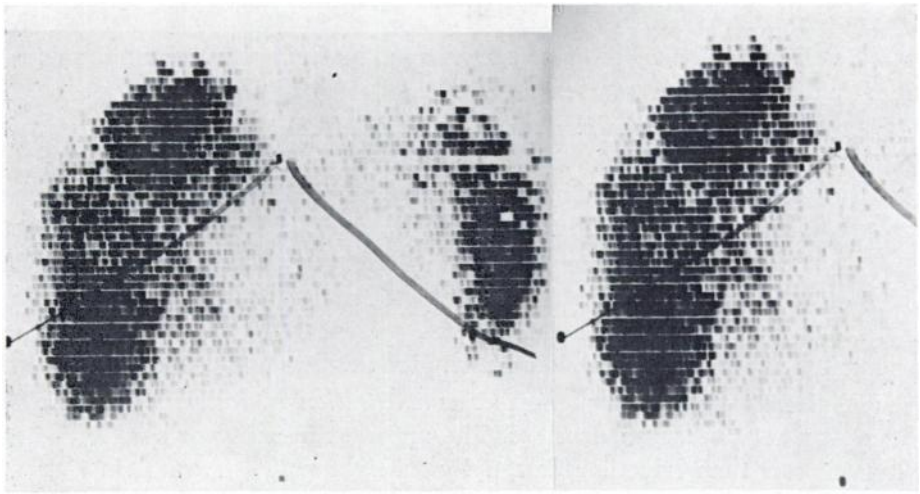

Fig. 4. Case 4: *Hepatic pseudo-mass in cirrhosis.* **(a) left. Scan (^{198}Au colloid) shows apparent space-occupying lesions in both lobes of the liver. However, the presence of splenomegaly with increased deposition of colloid raises the possibility of parenchymal disease (see Text). At laparotomy no hepatic mass was found. (b) right. Same scan with spleen excluded. A scan of this type is obtained with ^{131}I Rose Bengal and allied agents. The resultant lack of information as to extra-hepatic reticulo-endothelial radioactivity unnecessarily restricts interpretation of the scan.**

MATERIALS AND METHODS

The records of 24 patients undergoing porta-systemic anastomosis for portal hypertension were reviewed. The underlying disease, established by biopsy, was cirrhosiss (post-necrotic in six patients, Laennec's in 18.) Bleeding from esophageal varices had occurred in 23 patients. Routine tests of hepatic function, including serum bilirubin, sulfobromophthalien retention, and serum glutamic oxalacetic transaminase level, were elevated in all patients tested. The serum alkaline phosphatase level was elevated in only four patients. Ascitic fluid was present at operation in 14 patients; portal venous pressure was elevated at manometry in all patients. In each patient the liver had been explored at surgery and a satisfactory hepatic scan (^{198}Au colloid) was available.

The scans were evaluated with regard to hepatic size and configuration, distribution of radioactivity throughout the liver and the presence or absence of one or more focal areas of low or no radioactivity consistent with a space-occupying lesion. The presence of radioactivity in the spinal marrow and spleen, and the size of the spleen, were graded.

RESULTS (Table I)

(A) *Hepatic size.* The liver was considered to be enlarged in 21 patients, severely in six. It was contracted in two patients and normal in one. Surgical estimation of hepatic size concurred with these findings in 21 patients and differed in three (two patients exhibiting slight hepatomegaly, and one slight contraction, on scan.)

(B) *Hepatic configuration* was normal in eight patients. The left lobe was disproprotionately large in 11 and the right lobe in five patients.

(C) *Distribution of radioactivity* within the liver was non-uniform in all patient; this heterogeneity was marked in ten.

(D) *One or more localized areas of low or no radioactivity* were present in eight patients (Fig. 5) but a neoplasm (hepatoma) was found at surgery in only one. Thus seven patients exhibited hepatic pseudo-masses on scanning. There was no evidence of neoplasia in 16 patients.

(E) *The spleen* was demonstrable in 20 patients. It was not identified in three, perhaps because of confluence with the left hepatic lobe, which was enlarged in these patients. Splenomegaly was present in 18 patients; enlargement was marked in six. Splenectomy had been performed in one patient.

(F) *Relative splenic and hepatic concentration of radioactivity* was estimated from relative organ densities. The apparent intensity of splenic radioactivity was less than hepatic radioactivity in eight patients, equal in four and greater in eight patients.

(G) *Radioactivity in the marrow* was observed in 17 patients, including the three in whom the spleen was not visualized. There was no significant correlation between size of the spleen and its relative radioactivity, or between radioactivity levels in spleen and marrow.

DISCUSSION

The false-positive hepatic scan is one in which a discrete area of reduced or absent radioactivity erroneously suggests a space-occupying lesion. In the present series of 24 patients with advanced cirrhosis, false-positive scans were encountered in seven patients, an incidence of 29%. Others have noted that the false-positive scan is found most frequently in the presence of diffuse hepatic parenchymal disease, typically cirrhosis (2,5.)

In cirrhosis, several pathophysiological mechanisms affect the intrahepatic concentration of radiopharmaceuticals.

1. Both total and effective (sinusoidal) hepatic blood flow are diminished. Quantitative studies by Carter *et al* (9) have indicated an average volume reduction of 36% in the vascular bed of the cirrhotic liver. With portal hypertension there is a further, selective reduction of sinusoidal flow because of intrahepatic shunting. Under these conditions the polygonal cells and particularly the Kupffer cells, are poorly perfused; the rate of extraction of radiopharmaceuticals is correspondingly reduced. Superimposed regional decreases in sinusoidal flow occur when venous compression by focal scarring or regenerating nodules (10) locally augment intrahepatic shunting. These particularly affect the extraction of radiocolloids since Kupffer cells are confined to the sinusoids.

2. Regenerative processes and scarring in long-standing cirrhosis may cause deformity and irregularity of the liver. Regionally severe atrophy contraction can simulate the imprint of a space-occupying lesion, as illustrated (Fig. 3).

TABLE I

FINDINGS IN HEPATIC SCANS (^{198}Au COLLOID) IN 24 PATIENTS WITH ADVANCED CIRRHOSIS

I. *Liver*

A. Size: Normal (1), contracted (2), enlarged (21) (marked in 6)
B. Configuration: Normal (8), Rt/Lt lobe dominance 5/11
C. Distribution of Colloid: Normal (0), heterogeneous (24) (marked in 10)
D. Localized Area of Low or no Radioactivity:

Pseudo-mass	7
Neoplasm	1
None	16

II. *Extra-Hepatic Reticulo-endothelial Tissue*

A. Spleen: Identified (20), not identified (3), absent (1)
1. *Size:* normal (2), enlarged (18) (marked in 6)
2. *Relative Splenic Concentration of Radiocolloid*

Less than hepatic	8
Equal to hepatic	4
Greater than hepatic	8

B. Marrow

Normal (no concentration of colloid)	3
Abnormal concentration of colloid	17

3. Impairment of parenchymal transport mechanisms lowers extraction of ^{131}I-Rose Bengal and similar agents. The integrity of phagocytosis by Kupffer cells in cirrhosis is not well known because of the difficulty in separating reduced function as causes of inefficient extraction of colloids. Gabrieli *et al* (11) have postulated the condition of reversed phagocytosis to explain their observation of rising radioactivity in the left upper quadrant of some cirrhotic patients after administration of ^{131}I-colloidal albumin. They hypothesize that colloidal albumin particles are initially engulfed by Kupffer cells, but then are released without proteolysis, thus allowing their later removal by splenic reticulo-endothelial tissue. The experimental method employed, however, apparently did not permit differentiation between radioactivity in the spleen and that occurring in the stomach which, as shown by Taplin *et al* (12), follows intrahepatic proteolysis of colloidal albumin.

4. Whenever the level of radioactivity is low, variations in count rate due to the randomness of radioactive decay become relatively large, as Christie and MacIntyre have shown (13). These statistical fluctuations produce the "mottling" (heterogeneity) commonly observed in diffuse parenchymal disease. The "mottled" analogue liver scan may be incorrectly interpreted as positive, particularly by the inexperienced observer.

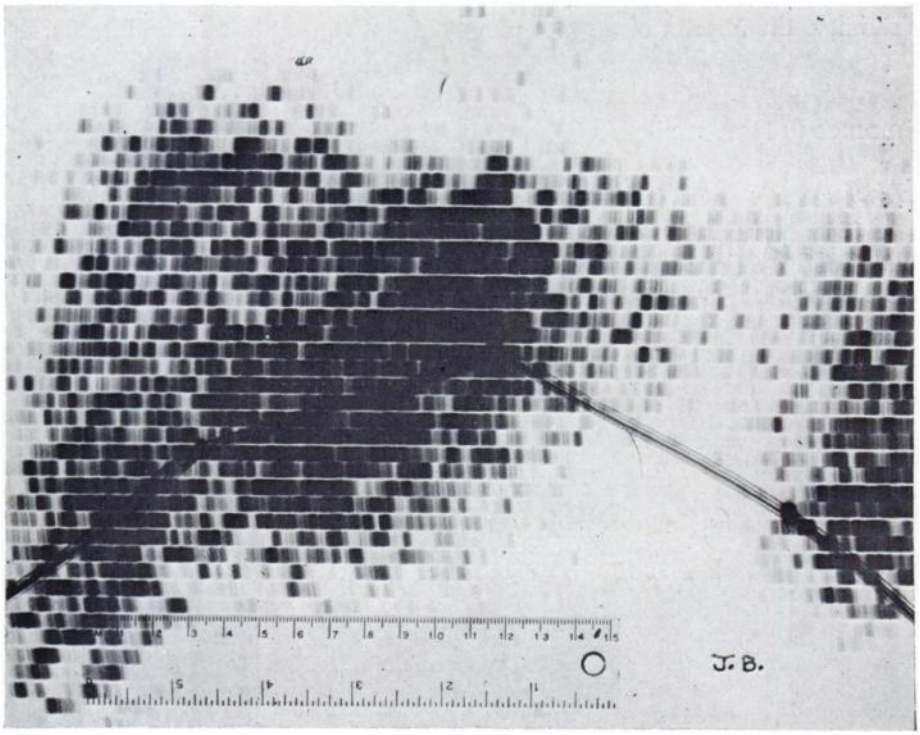

Fig. 5. (J.B. #166-01-13). An example of the pseudo-mass lesion encountered in seven of the 24 patients undergoing portasystemic shunting in this series. Post-mortem examination disclosed advanced Laennec's cirrhosis without intrahepatic neoplasm.

Other conditions resulting in locally reduced or absent radioactivity include dilatation of bile ducts in chronic obstructive jaundice (14) and regional suppression of polygonal & Kupffer cell function following external radiation therapy (15). These causes are immediately recognizable if, as good practice dictates, each patient is examined by a physician at the time of scan. Still other causes include uncommon developmental variations of the liver, such as hypersegmentation, and faulty scanning technique.

In the present series, a false-positive hepatic scan occurred in 29% of cirrhotic patients with severe portal hypertension. It is therefore evident that the hepatic scan must be interpreted with caution in the presence of cirrhosis. The differential diagnosis rests between primary carcinoma of the liver and a pseudomass on the basis of one of the mechanisms given above, since the incidence of hepatic metastases in cirrhosis is low.

Extrahepatic extraction of colloidal radiopharmaceuticals increases in cirrhosis (16). It is common to find increased radioactivity in the marrow and spleen, often with splenomegaly, when colloidal tracers are administered (17). Increased extrahepatic radioactivity due to intrahepatic metastases is uncommon, and usually requires fortuitous compression of the portal or hepatic veins by a strategically situated metastasis. Therefore, its presence should suggest the possibility that an intrahepatic "filling defect" may be a pseudo-mass. Such information is lost when tracers such as ^{131}I-Rose Bengal, extracted only by polygonal cells, are employed. For this reason primarily, we prefer colloidal radiopharmaceuticals for scintillation scanning of the liver.

It is unlikely that the false-positive hepatic scan can be eliminated. To disregard all apparent mass lesions in the scans of cirrhotic patients would inevitably result in failure to detect hepatoma. However, because hepatoma is a rare neo-

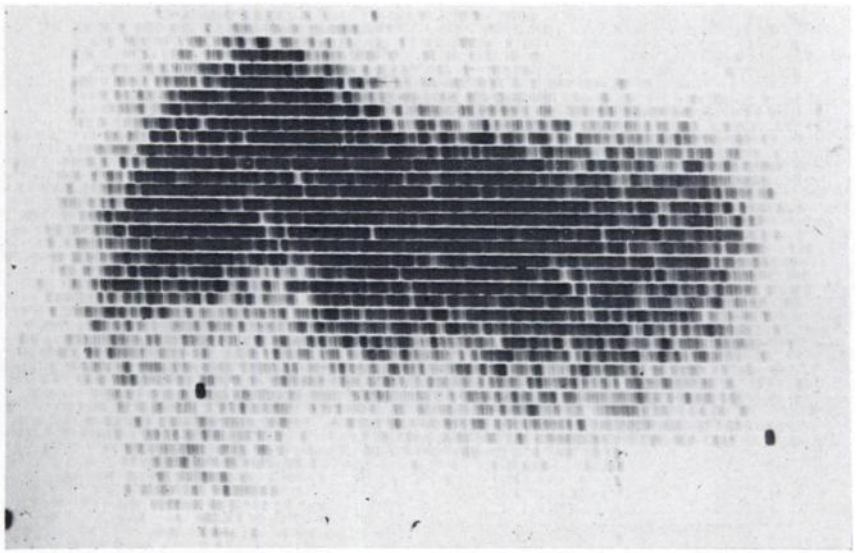

Fig. 6. (E.L. #142-54-64). In this patient, a large hepatoma was found at laparotomy. This represents the only case in this series in which an intra-hepatic space-occupying lesion was found at operation.

plasm, it would appear less objectionable occasionally to overlook its presence than to deny definitive surgery to a patient on the basis of presumed intrahepatic metastases.

SUMMARY AND ABSTRACT

Scintillation scans of the liver falsely suggestive for intrahepatic mass lesions were encountered in 7 of 24 cirrhotic patients undergoing porta-systemic anastomosis for portal hypertension. The false-positive hepatic scan results from regionally reduced or absent radioactivity. Several mechanisms that apparently contribute to the false-positive scan are discussed. Clues to its detection are found in the presence of significantly increased extrahepatic radioactivity. Colloidal radiopharmaceuticals are therefore recommended for hepatic scanning.

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