LIVER SCINTIPHOTOGRAPHY AS AN INDEX OF LIVER ABNORMALITY

Jack F. Mangum and Malcolm R. Powell

Martinez Veterans Administration Hospital, Martinez, California, and University of California, San Francisco, San Francisco, California

A year's experience with liver scintiphotographic interpretation was reviewed and correlated with available liver histologic and anatomic findings. Further correlation was made with available liver function tests and clinical estimation of liver size. Liver histology or information from laparotomy without biopsy was available for comparison in 173 patients. In 143 patients (83%) there was complete agreement in the comparison while in 30 patients (17%) there was some area of disagreement. In 137 agreement cases with proven liver abnormality the scintiphotography was more sensitive in demonstrating the abnormality than combined liver function tests and clinical estimation of liver size in 20% of patients with malignant liver disease, 35% of patients with benign space occupying lesions of the liver, and 14% of patients with parenchymal liver disease. Liver scintiphotography appears to be highly sensitive in detecting all types of liver abnormality and is recommended as a primary method of investigating suspected liver abnormality.

Liver imaging by rectilinear scanning or scintiphotography shows the size, shape, position, and structure of the liver by the phagocytic action of hepatic reticuloendothelial cells on intravenously injected particles of radioactive colloid. This diagnostic information is not easily obtained by any other study technique. Normally, reticuloendothelial cells are uniformly distributed throughout the liver. Absence, displacement, or decreased function of these cells causes a decrease of radiocolloid in the affected area.

Some controversy exists as to the sensitivity of this study technique, particularly when compared to routine liver function tests as a means of detecting liver abnormality. Gollin (*1*) suggested in 1964 that scanning was slightly more sensitive than serum alkaline phosphatase tests in detecting focal liver disease. Smith and Williams (*2*) reported in 1968 little evidence that scanning was more accurate than the more simple BSP and alkaline phosphatase tests in detecting focal liver disease and resulted in a high percentage of false-positive and false-negative reports. Ferrante and Maxfield (*3*) reported in 1968 that scans were helpful in diagnosing large hepatic lesions but were less accurate than needle biopsy and tests of function in diffuse hepatic disease. Jhingren, et al (*4*) reported in 1971 that radioisotope imaging gave fewer false positives than liver function tests and was as accurate as a combination of BSP and alkaline phosphatase tests in detecting metastatic hepatic disease. In the first three reports, imaging had been performed using ^{198}Au-colloid and the rectilinear scanner, and the fourth report included studies using this method and ^{99m}Tc-sulfur colloid and the scintillation camera. Since 1967, the University of California, San Francisco, has used the scintillation camera and ^{99m}Tc-sulfur colloid exclusively for all liver imaging (*5–8*). It is the purpose of this report to evaluate the sensitivity of liver scintiphotography in detection of proven liver abnormality and correlate it with liver function tests and clinical estimation of liver size as an index of abnormality.

METHODS

All liver scintiphotographic examinations performed at this hospital from May 1967 to May 1968 were reviewed and compared with available anatomic liver findings from necropsy, open surgical biopsy, laparotomy without biopsy, and needle biopsy. All scintiphotographic studies had been made using ^{99m}Tc-sulfur colloid (3.5 mCi i.v. with adjustment by body weight for children). An anterior view of the liver with a lead costal margin marker was made recording 500,000 counts. The marker was then removed and anterior, lateral, and posterior views of the liver and spleen using the same time exposure were performed (Fig. 1). The liver scintiphotographs were evaluated in the following respects: (A) the size, shape, position, and general outline of the liver and spleen; (B) the relative amounts of colloid uptake

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For reprints contact: Malcolm Powell, Nuclear Medicine Section, Dept. of Radiology, Univ. of California Medical Center, San Francisco, Calif. 94122.

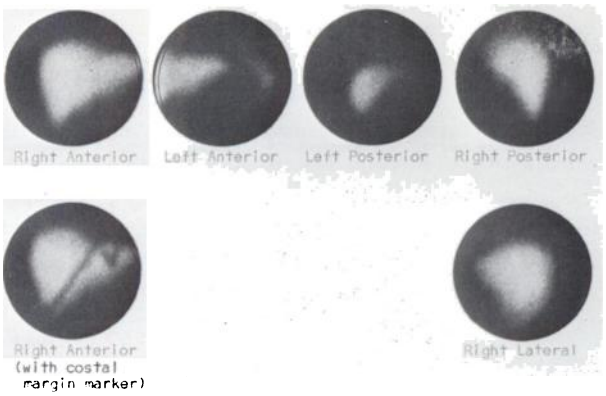

FIG. 1. Results of normal liver examination that were confirmed by extensive histologic evaluation one week after scintiphotographic study. Conventional views of liver and spleen are shown in addition to anterior view of liver. Radiopaque markers are superimposed over liver image at costal margin on right and xyphoid process in one view to show liver position with patient supine. Liver labeling is uniform and normal in amount with reference to spleen labeling.

by the liver, spleen, and bone marrow in comparison to the relative volumes of each organ; and (c) the internal distribution of colloid within each organ. Localized areas of decreased colloid uptake having well-defined margins and definite shapes were called "focal" abnormalities and were described according to size, shape, and location (Fig. 2). Large focal abnormalities were usually visible in more than one standard view. Decreased colloid uptake with no well-defined margins were described as "irregular labeling" (Fig. 3).

The original written interpretations were classified as normal or minimally, moderately, or markedly abnormal. Mixed abnormalities with focal lesions clearly more prominent than irregularity of labeling were classified as focal. Analysis was restricted to the liver although the size of the spleen and uptake of colloid by the spleen and bone marrow are always important considerations in interpreting the study.

In comparing the study interpretations with available anatomic information, the data were considered in "agreement" if both the scintiphotographic study and the anatomic findings were both normal or similarly abnormal in character (well-defined focal lesions or generalized or localized abnormality), degree (minimal, moderate, or marked), and location. For the purpose of this review, any variance of character, degree or location of abnormality between the scintiphotographic study and liver examination constituted "disagreement."

Space-occupying or other localized liver lesions such as metastatic nodules, abscesses, or cysts were expected to appear as focal abnormalities if the size of the individual lesions exceeded the minimal spacial resolution of the scintillation camera (*9*). Because of the resolution limits of the camera (Pho/Gamma III Model 6404, manufactured by Nuclear-Chicago Corporation, Des Plaines, Ill.), space-occupying lesions 2 cm or smaller were expected to appear as an irregularity of labeling rather than as focal defects. Less well-localized liver diseases such as fatty change, fibrosis, congestion, and hepatitis should have appeared as a more generalized abnormality with irregular decrease of labeling unless accompanied by areas of necrosis or nodular fibrosis large enough to cause focal abnormalities. Anatomic correlations were quite clearcut in the necropsy series where the entire liver was available for examination. The correlations were also well-defined in the surgical biopsy cases and, for the most part, in patients who had laparotomy without biopsy and in whom abscesses, cysts, or metastatic nodules were seen. In the needle biopsy cases with limited tissue available, a more general correlation was necessary. Thus, if focal or localized abnormalities were reported on the liver scintiphotographic study and metastatic disease was reported by needle biopsy, the findings were considered in agreement. Over 90% of the liver scintiphotographic studies had been interpreted by one observer (MRP) and reported immediately after they were performed. All cases in disagreement due to original misinterpretation of the study were recorded as such.

These cases were then compared with available liver function tests performed at the approximate time of the liver study. The three liver function tests most frequently available were the BSP retention at 45 min, the serum alkaline phosphatase, and the serum bilirubin. Usually, when other tests were abnormal, there were equivalent abnormality in one or more of the evaluated tests. The tests were recorded as normal or minimally, moderately, or markedly abnormal as determined from Table 1. A single rating was used to express the results of all tests—the rating reflecting the most abnormal test not known to be related to extrahepatic disease. For example, if the alkaline phosphatase were markedly abnormal but the BSP and serum bilirubin were normal, the tests were recorded as markedly abnormal.

In those cases where the degree of abnormality as seen in the liver scintiphotographic study was more marked than that expressed by the liver function tests, a further comparison was made with the clinical examination of the liver size at the time of the study.

RESULTS

The study included 613 examinations on 512 consecutive patients. Of these, 173 (34%) had available liver findings from necropsy, surgical biopsy, laparotomy without biopsy, and percutaneous needle

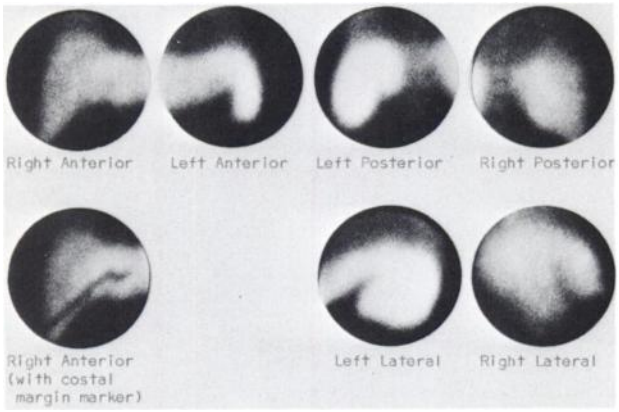

FIG. 2. Moderately severe cirrhosis has caused decreased liver labeling relative to spleen labeling, irregularity of liver labeling, and increased prominence of interlobar and intersegmental fissures of liver (best shown by right lateral scintiphotograph). Increased prominence of fissures suggests increase of liver consistency, as would be expected in cirrhosis. Estimated volume of liver appears to be in upper normal ranges. Decreased liver labeling by colloid implies reduced hepatic portal blood flow. Reduction of portal return provides increased opportunity for spleen and marrow labeling, which is seen in this set of photographs. Spleen is brightly labeled and is also somewhat enlarged, consistent with portal hypertension. Central marrow labeling is somewhat increased, which is best seen as visible labeling within vertebral bodies in right posterior view. No evidence is seen of any well-defined focal defect within liver or spleen such as would be caused by masses that displace liver or spleen parenchyma.

biopsy. Mean time intervals were 7.8 weeks for the necropsy cases, 28 days for the open surgical biopsy cases, 29 days for the laparotomy without biopsy cases, and 10 days for the punch-needle biopsy cases. The time interval between the camera study and liver examination was considered insufficient to invalidate the comparison in each case. Of these 173 cases, 143 (83%) met the criteria for liver scintiphotographic study agreement with histologic or laparotomy findings and 30 (17%) showed some area of disagreement. The percentage of agreement was higher in the necropsy (93%) and open surgical biopsy (96%) cases than in the laparotomy (84%) and percutaneous-needle biopsy (67%) cases where the anatomic liver examination was more limited. These data are summarized in Table 2.

One hundred and forty-three cases with scintiphotographic and histologic or laparotomy findings in agreement. The 143 patients with agreement of scintiphotographic and histologic or laparotomy findings were classified by anatomic liver diagnosis into those with normal livers, those with malignant disease of the liver, those with benign space-occupying lesions or extrinsic pressure defects of the liver, and those with parenchymal diseases of the liver. Of the 143 cases, 6 had anatomically normal livers and 137 had liver abnormalities. All 6 cases with normal livers had both normal liver scintiphotographic studies and normal liver function tests. Of the 137 patients with liver abnormalities, 56 had malignant diseases of the liver, 17 had benign space-occupying lesions or extrinsic pressure defects, and 64 had parenchymal liver diseases.

Fifty-six cases of malignant liver diseases with scintiphotographic and histologic or laparotomy findings in agreement. The 56 patients with malignant diseases of the liver included one case of primary hepatoma and 55 cases of metastatic tumor. The liver scintiphotographic evaluation of these 56 patients showed focal abnormalities in 44 (79%) and irregularity of labeling in 12 (21%). The 12 cases of metastatic malignancy with irregularity of labeling consisted of 3 patients with leukemia or lymphoma causing diffuse malignant infiltration rather than malignant nodules and 9 patients with small metastatic nodules measuring 2 cm or less in size. In 5 of these 9 cases, the observed irregularity of labeling was localized in one or more areas of the liver by liver scintiphotographic study rather than being more generally distributed as might be expected with parenchymal diseases.

In the malignant disease cases, the abnormality shown by liver scintiphotographic study was compared with the degree of abnormality shown by the liver function tests: 27 (48%) showed the same degree of abnormality; 24 (43%) showed greater abnormality by the liver scintiphotographic study than by liver function tests; and 5 (9%) showed liver scintiphotographic abnormalities less abnormal in degree than liver function tests. Of the 24 cases with more marked scintiphotographic abnormality, 18 showed moderate to marked abnormalities at a time when the liver function tests were normal (12 cases) or minimally abnormal (6 cases); 6 of the 18 cases had both normal liver function tests and normal sized livers by clinical examination; one had a minimal liver function test abnormality and normal sized liver by clinical examination; four had normal liver function tests and minimal liver enlargement by clinical examination; five had minimal liver function test abnormalities and minimal liver enlargement by clinical examination; and two had normal liver function tests and livers that were moderately to markedly enlarged by clinical examination. The liver scintiphotographic abnormalities were focal in 16 and irregular in 2 of these 18 cases. Thus, in 11% of the cases with malignant liver disease, the liver scintiphotography showed highly significant abnormalities at a time when the liver function tests and liver size by clinical examination were both normal, and another 18% showed major liver scintiphotographic abnormalities at a time when the liver function tests and liver size by palpation considered together suggested no more than minimal liver abnormality.

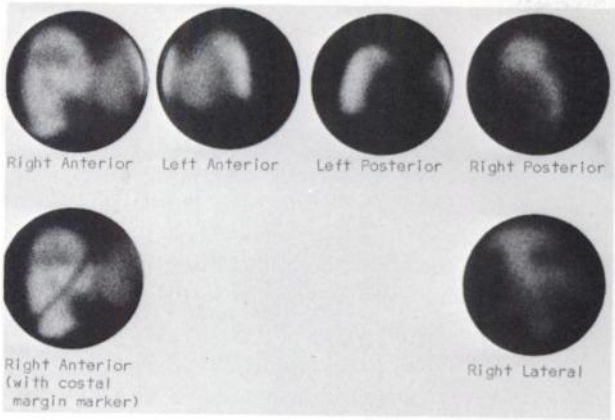

FIG. 3. Enlarged liver with sharply defined focal defects of labeling in all segments of major lobes. Uptake of colloid by liver, compared with that of spleen, is decreased. Spleen is slightly enlarged. Finding of well-defined focal defects scattered throughout liver image in association with mild liver enlargement is consistent with space-occupying lesions in liver. Generalized decrease of liver uptake of colloid shown here is often seen with extensive involvement by malignant disease. It suggests generalized abnormality of reticuloendothelial function in liver parenchyma or of distribution of hepatic blood flow. This abnormality appears not to be severe portal hypertension, since spleen is only slightly increased in size and bright labeling that would be expected with moderate to marked portal hypertension is absent. Characteristics of defects of liver labeling that identify them as focal defects are their well-defined margins around complete circumference of each intrahepatic defect. They are readily distinguished from surrounding liver tissue. Individual defects may be identified in more than one view, indicating exact position of lesions within liver and confirming intrahepatic location.

Seventeen cases of benign space-occupying lesions or extrinsic pressure defects with scintiphotographic and histologic or laparotomy findings in agreement. Of the 137 patients with agreement between liver scintiphotographic findings and histologic or laparotomy findings, 15 had benign space-occupying lesions within the liver and two had extrinsic pressure defects in the liver. All of these 17 patients showed focal abnormalities in the liver scintiphotographs. Comparison of degree of abnormality found in the liver function tests in these 17 patients showed that seven (41%) had the same degree of abnormality, ten (59%) showed greater abnormality by liver scintiphotography than by liver function tests, and none showed less abnormality by liver scintiphotography than by liver function tests. In seven of the ten patients with more marked scintiphotographic abnormality, the liver study showed a moderate to marked abnormality whereas the liver function tests were normal in six and minimally abnormal in one. The livers in these seven patients were clinically normal sized in three, minimally enlarged in three, and moderately enlarged in one. These seven cases included four hepatic abscesses and one each of polycystic liver disease, benign adenoma of the liver, and pancreatic pseudocyst exerting extrinsic pressure. The remaining three of these ten cases had moderate liver function test abnormalities and included an hepatic abscess, hematoma of the liver, and a cavernous transformation of the hepatic vein (with extrinsic pressure defect)—all showing marked focal abnormalities by liver scintiphotography. Thus, in 6 (35%) of these 17 patients the liver scintiphotographic study showed highly significant abnormalities at a time when the liver function tests and clinical estimation of liver size were both normal or when considered together suggested only minimal abnormality.

Sixty-four cases of parenchymal liver disease with scintiphotographic and histologic or laparotomy findings in agreement. Of the 137 patients with agreement between the liver scintiphotographic and histologic or laparotomy findings, 64 had various forms of parenchymal liver diseases. The liver scintiphotographic study showed a generalized irregularity of labeling in 61 (95%) of these patients and both focal abnormalities and irregularity of labeling in three (5%), one case of biliary cirrhosis, and two cases of postnecrotic cirrhosis. Comparison of the liver scintiphotographic study with liver function tests showed that 20 (31%) had the same degree of abnormality; 12 (19%) showed greater liver scintiphotographic abnormality than liver function test abnormality; and 32 (50%) showed liver scintiphotographic findings less abnormal in degree than

TABLE 1. CLASSIFICATION OF FINDINGS BY LIVER FUNCTION TESTS

	BSP (% retention at 45 min)	Alkaline phosphatase (S.J.R. units)	Total bilirubin (mg%)
Normal	Less than 6	2–6.8	Less than 1
Minimally abnormal	7–10	6.9–8	1–3
Moderately abnormal	10–20	8–12	3–6
Markedly abnormal	Over 20	Over 12	Over 6

TABLE 2. LIVER SCINTIPHOTOGRAPHY—LIVER ANATOMY CORRELATION

	No. of cases	Agreement group	% of group	Disagreement group	% of group
Necropsy	54	50	93	4	7
Open surgical biopsy (wedge or needle)	24	23	96	1	4
Laparotomy without biopsy	37	31	84	6	16
Percutaneous needle biopsy	58	39	67	19	33
TOTALS	173	143		30	
Percent of total		83		17	

liver function studies. Of the 12 cases showing more marked scintiphotographic abnormality, ten showed moderate to marked scintiphotographic abnormalities at a time when liver function tests were normal (two cases) or minimally abnormal (eight cases). These ten cases included six with fatty change, two with diffuse fibrosis, and one each of cholangitis and hemochromatosis. The clinical estimation of liver size was normal in six, minimally enlarged in two, and moderately to markedly enlarged in two of these patients. Thus, in eight (14%) of the cases with parenchymal liver diseases, the liver scintiphotographic studies showed highly significant abnormalities at a time when the liver function tests and clinical estimation of liver size were both normal or, when considered together, suggested minimal liver abnormality.

Patients with scintiphotographic abnormality less than liver function test abnormality. The patients with malignant liver disease and hepatocellular disease included 37 with scintiphotographic abnormality less marked in degree than liver function test abnormality. These 37 patients included 21 with either obstructive jaundice (7 cases) or far advanced hepatocellular disease (14 cases) to account for the markedly abnormal liver tests. The scintiphotographic study showed minimal abnormality in 13 of these cases, moderate abnormality in 24, and in none was it interpreted as normal.

Disagreement of scintiphotographic and histologic or laparotomy findings. Of the 173 cases, 30 (17%) failed to meet the criteria for agreement between liver scintiphotographic study and histologic or laparotomy findings. In one of these cases the disagreement was actual, in five the disagreement was due to misinterpretation of the liver scintiphotographic study, and in 24 the disagreement was considered unresolved. The one case of actual disagreement occurred in a patient who died of acute heart failure following surgery 11 days after the scintiphotography, which was interpreted as normal. In all probability the markedly enlarged liver with congestive changes found at necropsy developed after the liver scintiphotographic study was performed. The five cases of disagreement due to liver scintiphotographic study misinterpretation included three cases of minimal to moderate liver parenchymal diseases with the liver scintiphotographs interpreted as normal when there was actually minimal to moderate irregularity of labeling; a fourth case had extensive liver involvement with 2 cm or smaller metastatic nodules with the liver scintiphotograph interpretation reported as showing minimal irregularity of labeling when moderate irregularity was present; the fifth case was that of a normal anatomic variant (an unusual costal margin impression) that was erroneously interpreted as an intrahepatic focal abnormality.

Of the 24 cases considered unresolved, one had open surgical biopsy of the liver, six had description of the liver visually and by palpation at the time of laparotomy without biopsy and 17 had liver tissue descriptions from percutaneous-needle biopsies. Primary carcinoma was known to be present at sites other than the liver in 8 of these 24 cases. The liver scintiphotographic studies showed focal abnormalities in six of these and irregular labeling in two. The liver as described at surgery (three cases) or by percutaneous-needle biopsy (three cases) was normal except for a single case that showed minimal lymphocytic infiltration. The liver function tests in the eight carcinoma cases were normal in one, minimally abnormal in three and moderately to markedly abnormal in four. Another 10 of the 24 unresolved cases had primary diseases frequently associated with liver abnormalities. Of these ten, five had irregularity of labeling and five had focal abnormalities by liver scintiphotographic study. The liver was described at surgery (one case) or by percutaneous-needle biopsy (nine cases) or normal (eight cases) or minimally abnormal (two cases) but less abnormal in degree than indicated by the scintiphotographs. Liver function tests in these ten cases were normal in two, and moderately to markedly abnormal in eight.

The remaining 6 of the 24 unresolved cases had diseases infrequently associated with liver abnormality (two with G.I. bleeding, two with fever of unknown origin, one with pneumonia, and one with pulmonary tuberculosis). The liver tissue as described by percutaneous-needle biopsy was normal in five of these cases; the other case showed minimal fatty change that was less in degree than the reported scintiphotograph abnormality. The liver function tests were minimally abnormal in two, and moderately to markedly abnormal in four of these six cases.

Thus, of the 24 unresolved disagreement cases, all had liver scintiphotograph study abnormalities and liver function tests were abnormal in 19 but 21 had normal liver description reported by punch-needle biopsy or liver observation and palpation at surgery. The remaining three unresolved cases showed minor liver abnormalities inconsistent with the more marked abnormality seen by liver scintiphotographs at a time when liver function tests were moderately to markedly abnormal. The abnormal liver function tests in the great majority of the unresolved cases strongly indicate that significant hepatic abnormality existed and would have been apparent with more extensive histologic examination of the liver.

DISCUSSION

Of the 512 patients reviewed, 173 (34%) had information available from histologic examination of the liver or from examination during laparotomy without biopsy. In 84% of the cases, there was anatomic agreement between the interpretation of the scintiphotographic study and the available histologic or laparotomy information. Disagreement was found in 30 cases. The agreement cases included six normal livers, 56 abnormal livers due to malignant liver disease, 17 abnormal livers due to benign space-occupying lesions, and 64 cases with parenchymal liver disease.

Of the 30 disagreement cases, one showed actual disagreement and five disagreed because of misinterpretation of the scintiphotographs. The single case of actual disagreement is probably due to liver change occurring after the scintiphotographic study was performed. The five cases of disagreement due to scintiphotographic misinterpretation were largely a matter of underinterpretation in that minimally irregular uptake of colloid in three patients was interpreted as a normal, small structure of the liver, and in a fourth patient a moderately abnormal scintiphotographic study was interpreted as minimally abnormal. The fifth study was misinterpreted because of failure to recognize an unusual costal margin impression upon the liver and interpretation of the area as a focal abnormality in the liver.

The 24 unresolved cases are instances of definite scintiphotographic abnormalities in patients who generally also had abnormal liver function tests but where the available tissue was reported as normal or showed less abnormality than shown by the liver scintiphotographs. (A late followup study 9 months after the original study and 18 months after the liver scintiphotograph examinations showed that 3 of the 24 unresolved cases had either surgical or postmortem examination of the liver with findings in agreement with the scintiphotographic examination.)

The types of intrahepatic abnormalities seen in the images correlated well with the types of disease present in the liver. Focal abnormalities were identified in 79% of patients with malignant diseases of the liver and in 100% of patients with benign space-occupying lesions. Irregular uptake of colloid, usually generalized, was seen in 95% of patients with hepatic parenchymal diseases. Small metastatic nodules of a size below the spatial resolution of the scintillation camera and infiltrative malignant diseases of the liver appeared as irregularity of liver labeling.

A comparison of the degree of abnormality in the liver scintiphotographs and the liver function studies for the agreement cases showed moderate or marked liver scintiphotographic abnormality when simultaneous liver function tests and clinical estimation of liver size were either normal or no more than minimally abnormal in 29% of patients with malignant diseases, 35% of cases with benign space-occupying lesions, and 14% of cases with parenchymal liver diseases.

CONCLUSIONS

Liver scintiphotography with the Anger scintillation camera and ^{99m}Tc-sulfur colloid is a highly sensitive method for detecting liver abnormality. The method appeared to be accurate for identifying the normal liver in a small number of cases. Liver scintiphotography is frequently more sensitive in detection of hepatic abnormality than the usual liver function tests and clinical estimation of liver size. In addition, the liver scintiphotographic examination provides unique anatomic information about the extent and distribution of liver lesions. This information can be used to select a site for percutaneous-needle biopsy, for serial evaluation of abnormalities, or for detecting new lesions in a liver that is already known to be abnormal by prior examinations. The liver scintiphotographs provide useful information about the anatomy of liver abnormalities, but a biopsy is required for exact diagnosis. Thus, liver scintiphotography is a highly useful adjunct to the more conventional tests for all types of liver abnormality and appears to have an accuracy and sensitivity, if not specificity, that recommend it as a primary test for liver evaluation in any patient who might have significant hepatic disease.

REFERENCES

1. GOLLIN FF, SIMS LR, CAMERON JR: Liver scanning and liver function tests. *JAMA* 187: 111–116, 1964
2. SMITH LB, WILLIAMS RD: The relative diagnostic accuracy of liver radioactive isotope photoscanning. *Arch Surg* 96: 693–697, 1968
3. FERRANTE WA, MAXFIELD WS: Comparison of the diagnostic accuracy of liver scans, liver function tests and liver biopsies. *Southern Med J* 61: 1255–1263, 1968
4. JHINGRAN SG, JORDAN L, JOHNS MF, et al: Liver scintigrams compared with alkaline phosphatase and BSP determinations in the detection of metastatic carcinoma. *J Nucl Med* 12: 227–230, 1971
5. HARPER PV, LATHROP KA, RICHARDS P: Tc^{99m} as a radiocolloid. *J Nucl Med* 5: 382, 1964
6. HARPER PV, LATHROP KA, JIMINEZ F, et al: Technetium-99m as a scanning agent. *Radiology* 85: 101–109, 1965
7. ANGER HO: Scintillation camera with multichannel collimators. *J Nucl Med* 5: 515–531, 1964
8. ANGER HO: Gamma-ray and positron scintillation camera. *Nucleonics* 21: 56–59, 1963
9. VIDRIH VE, HIGGINS HP: Accuracy of liver scintiphotography using a plastic and water phantom. *Canad J Surg* 14: 273–279, 1971