COMPARISON OF ^{131}I-MACROAGGREGATED LIVER SCANNING AND SELECTIVE HEPATIC ARTERIOGRAPHY

Bruce C. Kirkham, Ian B. Tyson and George W. Wirtanen

University of Wisconsin, Madison, Wisconsin

The possibility of using ^{131}I-macroaggregated albumin (^{131}I-MAA) intra-arterially in identifying hepatic neoplasms was raised by King, Wood, Morlen and Colapinto in a report of a case of clinical-pathologic correlation (*1*). Blank and Tyson in 1969 injected ^{131}I-MAA through percutaneously placed intra-arterial hepatic catheters in 12 patients, and scans showed positive images of abnormal areas of increased uptake which correlated with negative images of ^{198}Au scans (*2*). Improved visual detection of hepatic neoplasm could be obtained compared with colloidal ^{131}I-labeled albumin injected intravenously (*3*) and colloidal gold (^{198}Au) (*4*); the latter technique produced liver scans with areas of reduced uptake indicating abnormality.

This study using clinical data and an animal experiment was carried out to compare selective hepatic arteriograms and ^{131}I-MAA and ^{198}Au scans.

METHOD

Clinical data. Twenty-one patients with percutaneous transbrachially placed catheters receiving continuous hepatic artery chemotherapeutic infusions were studied with ^{198}Au liver scans, selective hepatic arteriograms and ^{131}I-MAA liver scans, usually in this sequence. A dose of 6 μCi/kg body weight of ^{131}I-MAA was diluted to a volume of 20 cc with normal saline and injected through the infusion catheter, followed by 20 cc of normal saline. The liver was scanned immediately after the injection with a dual-headed scanner with two 2 $\times$ 5-in. NaI(Tl) crystals with information density of 300 counts/in. Scans required about 15 min for simultaneous AP-PA view. The ^{198}Au scans were done with a baseline of 391 keV and the ^{131}I-MAA scans with a baseline of 344 keV, both with windows of 40 keV. In addition, seven of the 21 patients had ^{131}I-MAA scans carried out using a scintillation camera. Selective hepatic arteriography was performed with the injection of 40 cc of 60% meglumine diatrizoate delivered at a rate of 5 cc/sec, and serial films were obtained at 2-sec intervals for 20 sec, followed by films at 5-sec intervals for 10 sec.

One patient had a second arteriogram 30 min after injection with ^{131}I-MAA.

Animal data. An "irritant granuloma" in the liver was produced in a 15-kg dog injecting Sephadex G-25* suspension into a single anterior lobe at laparotomy. Six days later a ^{131}I-rose bengal liver scan was obtained using a scintillation camera (photoscintogram). Following the scan, transfemoral catheterization of the common hepatic artery and serial arteriography were performed using a technique analogous to that used in patients. Six microcuries per kilogram of body weight of ^{131}I-MAA diluted to a volume of 10 cc with normal saline was injected through the intra-arterial catheter, followed by 10 cc of normal saline. A photoscintogram and arteriogram were obtained. Repeat catheterization and intra-arterial injection of ^{131}I-MAA were carried out and scans were obtained hourly up to 5 hr and at 22 hr after injection. Repeat arteriography was performed following the 5-hr scan. On the subsequent day open biopsy of the hepatic granuloma was obtained.

RESULTS

Clinical data. Metastatic replacement of liver tissue was indicated by decreased uptake on the ^{198}Au scans while ^{131}I-MAA scans showed increased uptake in these same areas. These areas of increased uptake on the ^{131}I-MAA scans corresponded in 19 of 21 patients to the arteriographically neovascular areas which were more hypervascular than the normal areas of the liver (Figs. 1 and 2). The ^{131}I-MAA

Received Aug. 15, 1969; original accepted Dec. 17, 1969.

For reprints contact: Ian B. Tyson, Div. of Nuclear Medicine, University of Wisconsin, Medical Center, Madison, Wis. 53706.

* Pharmacia Fine Chemical, Inc. Sephadex—G-25 Coarse.

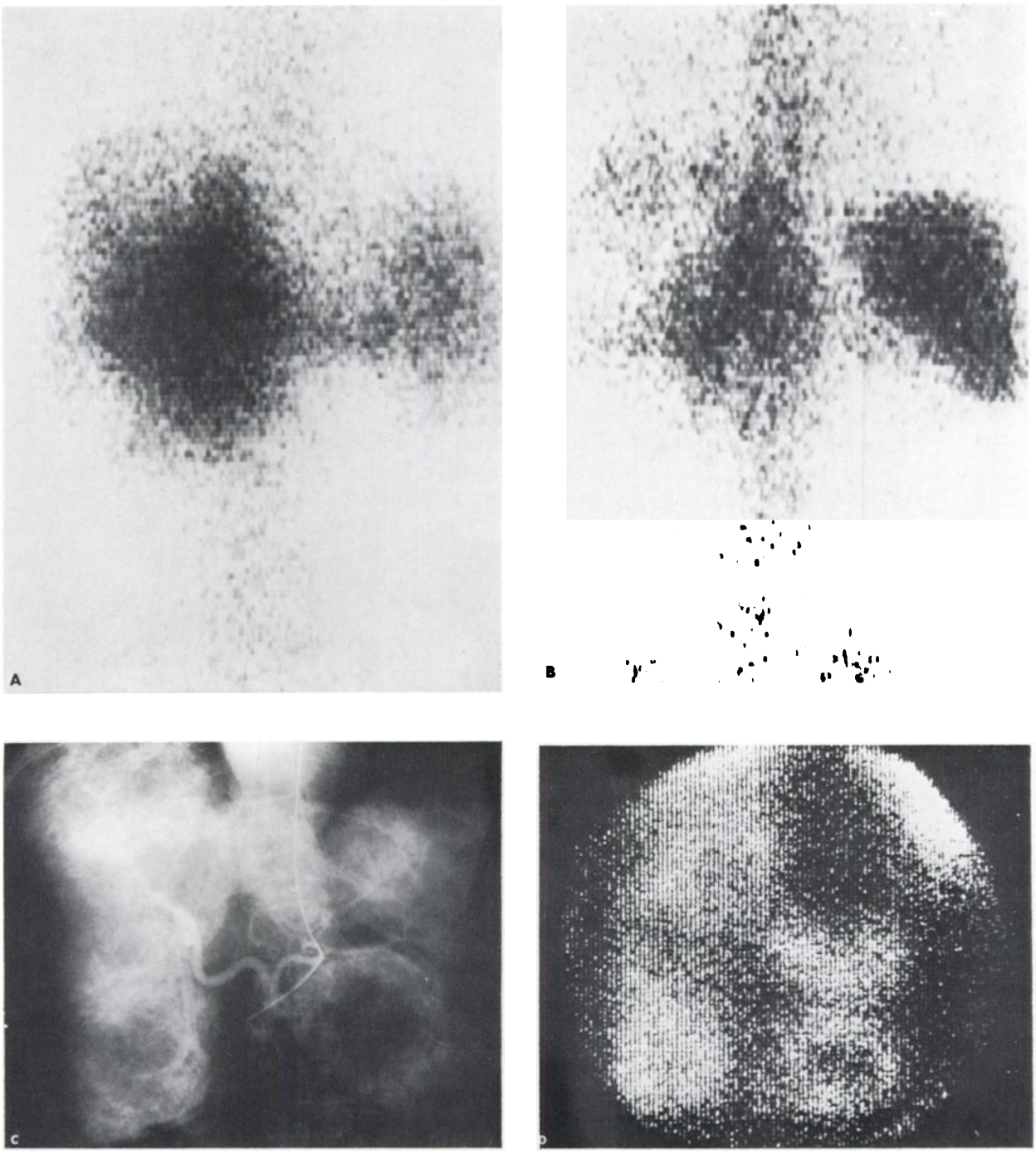

FIG. 1. Anterior (A) and posterior (B) ^{198}Au scans show multiple areas of decreased uptake predominantly involving lateral superior and inferior aspects of right lobe and medial superior and inferior aspects of left lobe. There is increased uptake in bone marrow and spleen indicative of portal hypertension (B). Selective common hepatic arteriogram (C) reveals right and left lobe almost completely replaced by multiple areas of neovascularity. There are two large nodules in left lobe with inferior nodule demonstrating poorly vascularized center. Photoscintogram with intra-arterial ^{131}I-MAA (D) shows increased uptake corresponding to areas of hypervascularity on arteriogram and abnormal areas of decreased uptake on ^{198}Au scans.

was selectively injected into the splenic artery in the other two patients, and therefore the ^{131}I-MAA was delivered selectively to the spleen.

In a patient with adenocarcinoma of the gallbladder the arteriogram demonstrated neovascularity originating from both the superior posterior and superior anterior pancreatico-duodenal arteries. There were also diffuse, poorly defined hypervascular nodules distributed throughout the liver parenchyma (Fig. 3A).

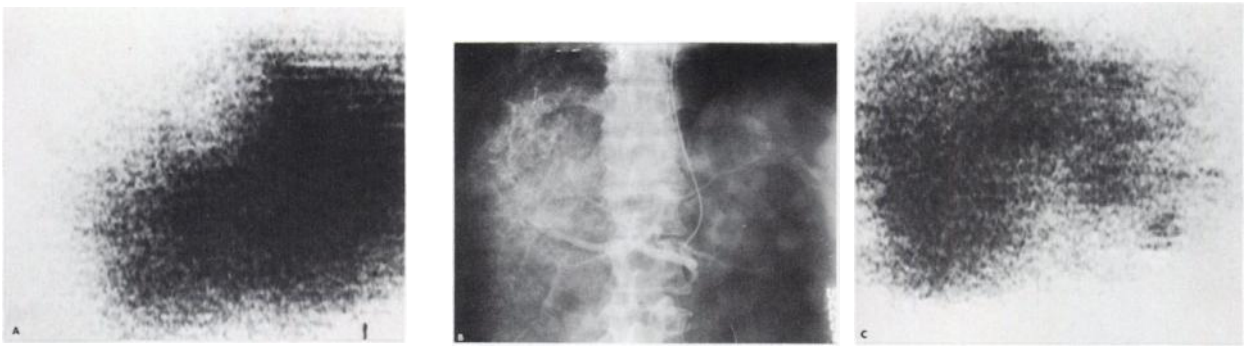

FIG. 2. ^{198}Au scan (A) shows significant areas of decreased uptake predominantly in superior aspect of right upper lobe. Selective common hepatic arteriogram (B) conglomerate hypervascular nodularity nearly replacing right lobe and small distinct neovascular nodules scattered throughout parenchyma of left lobe. Intra-arterially injected ^{131}I-MAA (C) reveals areas of increased uptake on scan corresponding to hypervascular nodules on arteriogram of same area.

A second arteriogram following the injection of ^{131}I-MAA showed decreased vascularity in the region of the gallbladder bed, as shown in Fig. 3B and the intrahepatic nodules were less well demonstrated.

There was increased uptake of ^{131}I-MAA in the left lobe of the liver in three patients although definite neovascularity in this area could not be demonstrated arteriographically.

Four patients had normal ^{198}Au liver scans but the ^{131}I-MAA scans and arteriograms as shown in Fig. 4 were abnormal, with the predominant area of abnormality in the region of the liver hilus.

Six patients had increased activity of ^{131}I-MAA in the lungs as shown in Fig. 1D. Five of these had extensive venous collateralization on selective splenic artery splenoportography, compatible with portal hypertension, and one had a small AV malformation in the left lobe of the liver (Fig. 5).

Animal experiment. The ^{131}I-rose bengal liver scan in the dog showed an area of decreased uptake in the central inferior aspect of the liver (Fig. 6A). Arteriography showed a 5-cm area of neovascularity and hypervascularity (Fig. 6B), and ^{131}I-MAA injected intra-arterially produced an area of increased uptake corresponding to this area (Fig. 6C). Repeat arteriography 30 min after the injection of ^{131}I-MAA demonstrated distention of the common hepatic artery and its major branches with reflux of contrast proximally. There was delayed appearance of the

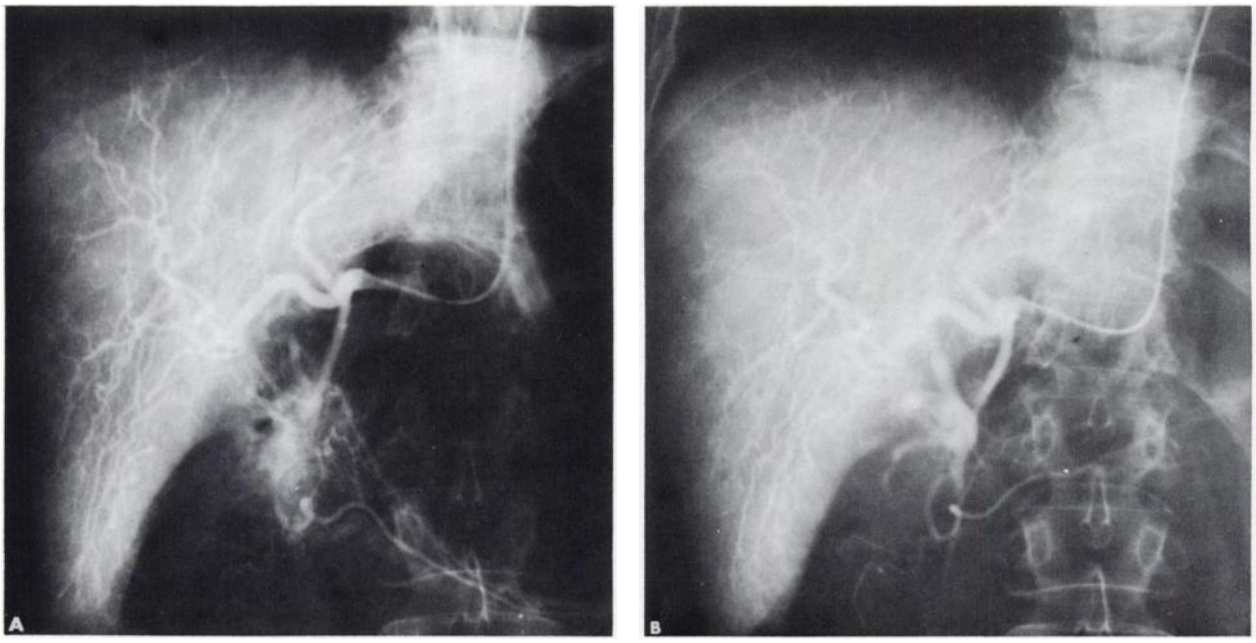

FIG. 3. Selective common hepatic arteriogram (A) reveals tumor neovascularity in gallbladder bed supplied by posterior superior and anterior superior pancreatico-duodenal arteries. Diffuse hypervascular nodules are present throughout liver parenchyma. Following intra-arterial ^{131}I-MAA injection arteriogram (B) demonstrates decreased vascularity in region of liver hilus, less tumor neovascularity and poor delineation of intra-hepatic tumor.

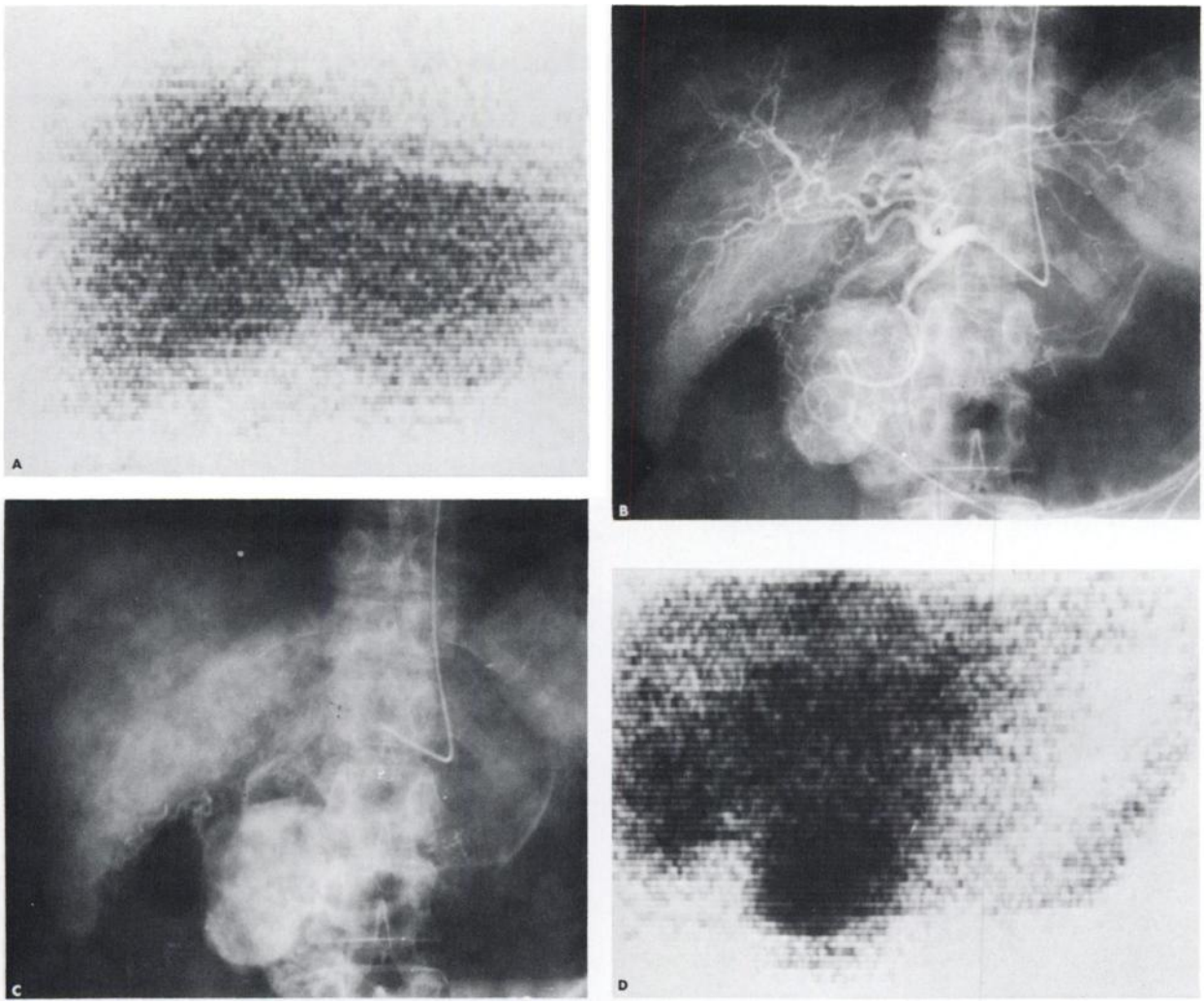

FIG. 4. ^{198}Au liver scan interpreted as within normal limits (A). Selective hepatic arteriogram (B) reveals areas of neovascularity in region of liver hilus during arterial phase. Small diffuse hypervascular nodules throughout both lobes (C) were demonstrated during venous phase. ^{131}I-MAA intra-arterial liver scan (D) shows mottled increased activity throughout liver most marked in region of liver hilus corresponding to hypervascularity on arteriogram.

hypervascular area and better delineation of the proximal intrahepatic vessels (Fig. 6D). The multiple photoscintograms carried out 6 days later showed that the region of increased activity persisted throughout the 5-hr postinjection period but became less definite during the interval; by 22 hr no lesion could be identified (Fig. 7). Repeat arteriography 5 hr after the injection of ^{131}I-MAA showed that the hypervascular hepatic lesion was comparable to the pre-^{131}I-MAA arteriogram done 6 days earlier and did not demonstrate vessel distention and contrast reflux (Fig. 8).

Open liver biopsy of the lesion revealed thickening and mottling on gross examination of the liver capsule. Microscopically (Fig. 9) the liver capsule was thickened and edematous with inflammatory cells, a few giant cells and considerable amounts of fibrin. There were irregular globular foci of foreign material surrounded by foreign body giant cells. There was a suggestion of necrosis of parenchymal cells in the periphery. There was a fine neovascularity throughout with some fibrosis as indicated by increased numbers of fibroblasts. A moderate degree of inflammatory cell infiltration was present with some lymphocytes and histiocytes but neutrophil was the predominant cell type. Portal triads seemed enlarged in general due to vascular dilatation, and in some instances there was extravasation of red cells into loose connective tissue. In the more severely congested foci, red cells were found between cell cords.

DISCUSSION

In our material, tumor replacement of hepatic tissue is angiographically demonstrated by neovascularity which is hypervascular when compared with areas of normal liver tissue. Areas of increased uptake on ^{131}I-MAA intra-arterial liver scans corre-

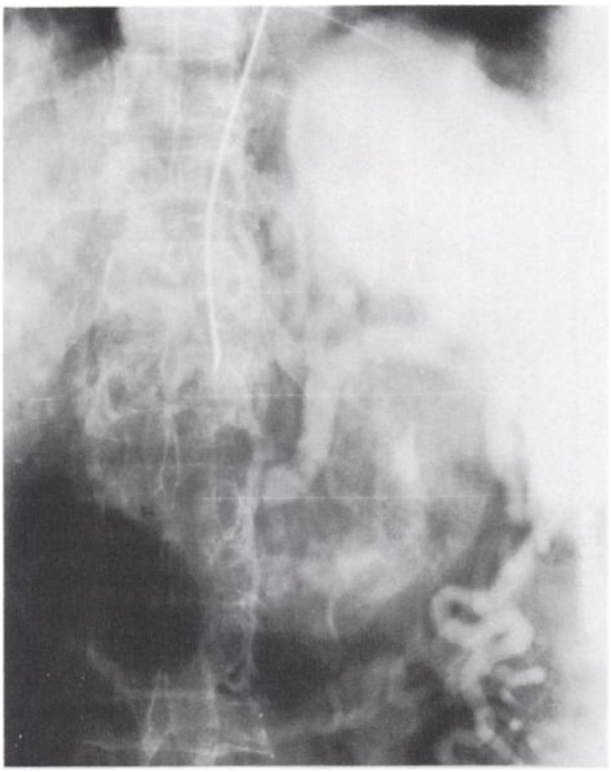

FIG. 5. Selective splenic artery injection of 50 cc of 60% Meglumine diatrizoate demonstrates extensive venous collateralization.

lated with the hypervascular tumor areas on the arteriograms in 19 of 21 patients. Capillary blockade is produced by ^{131}I-MAA particles as shown by Taplin, Johnson, Dore and Kaplan (*5*), and there is destruction of the particles by normal reticuloendothelial cells as demonstrated by Taplin *et al* (*6*). Therefore a positive liver scan could be produced by a combination of both the relatively greater concentration of isotope in areas of neovascularity due to tumor and the absence of reticuloendothelial cells resulting in reduced disposal rate in tumor compared to disposal rates in normal liver tissue. The ability to detect tumor is enhanced when compared with the negative images of the colloidal gold scans, especially in the region of the liver hilus. The disadvantage of this procedure is the necessity for arterial catheterization. The ^{131}I-MAA scan showed areas of tumor replacement in the left lobe of the liver not readily seen on routine arteriography. This difference may be due to less contrast reaching the left lobe through a smaller hepatic artery, and the relatively small amount of radioactivity may be more readily detected in a large vascular organ which requires larger amounts of contrast to be visualized arteriographically. This demonstration of tumor in the left lobe has significance in evaluating patients for partial hepatectomy.

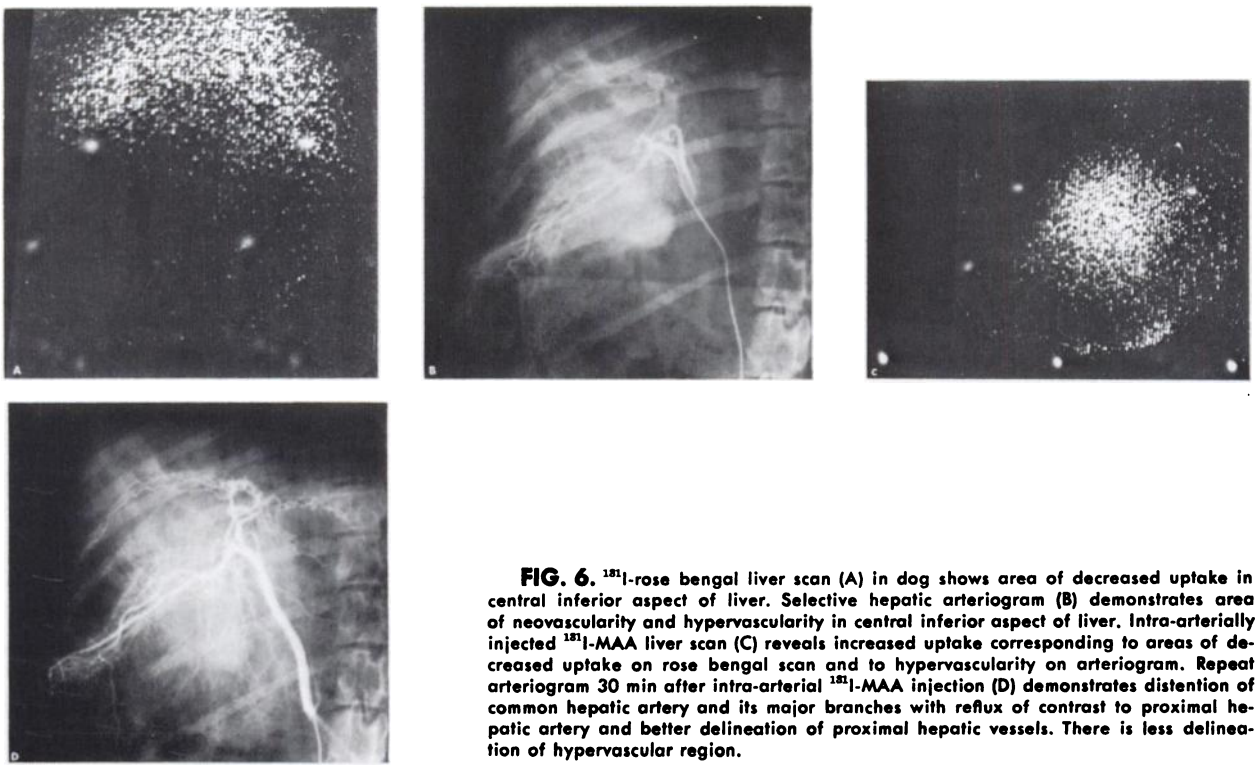

FIG. 6. ^{131}I-rose bengal liver scan (A) in dog shows area of decreased uptake in central inferior aspect of liver. Selective hepatic arteriogram (B) demonstrates area of neovascularity and hypervascularity in central inferior aspect of liver. Intra-arterially injected ^{131}I-MAA liver scan (C) reveals increased uptake corresponding to areas of decreased uptake on rose bengal scan and to hypervascularity on arteriogram. Repeat arteriogram 30 min after intra-arterial ^{131}I-MAA injection (D) demonstrates distention of common hepatic artery and its major branches with reflux of contrast to proximal hepatic artery and better delineation of proximal hepatic vessels. There is less delineation of hypervascular region.

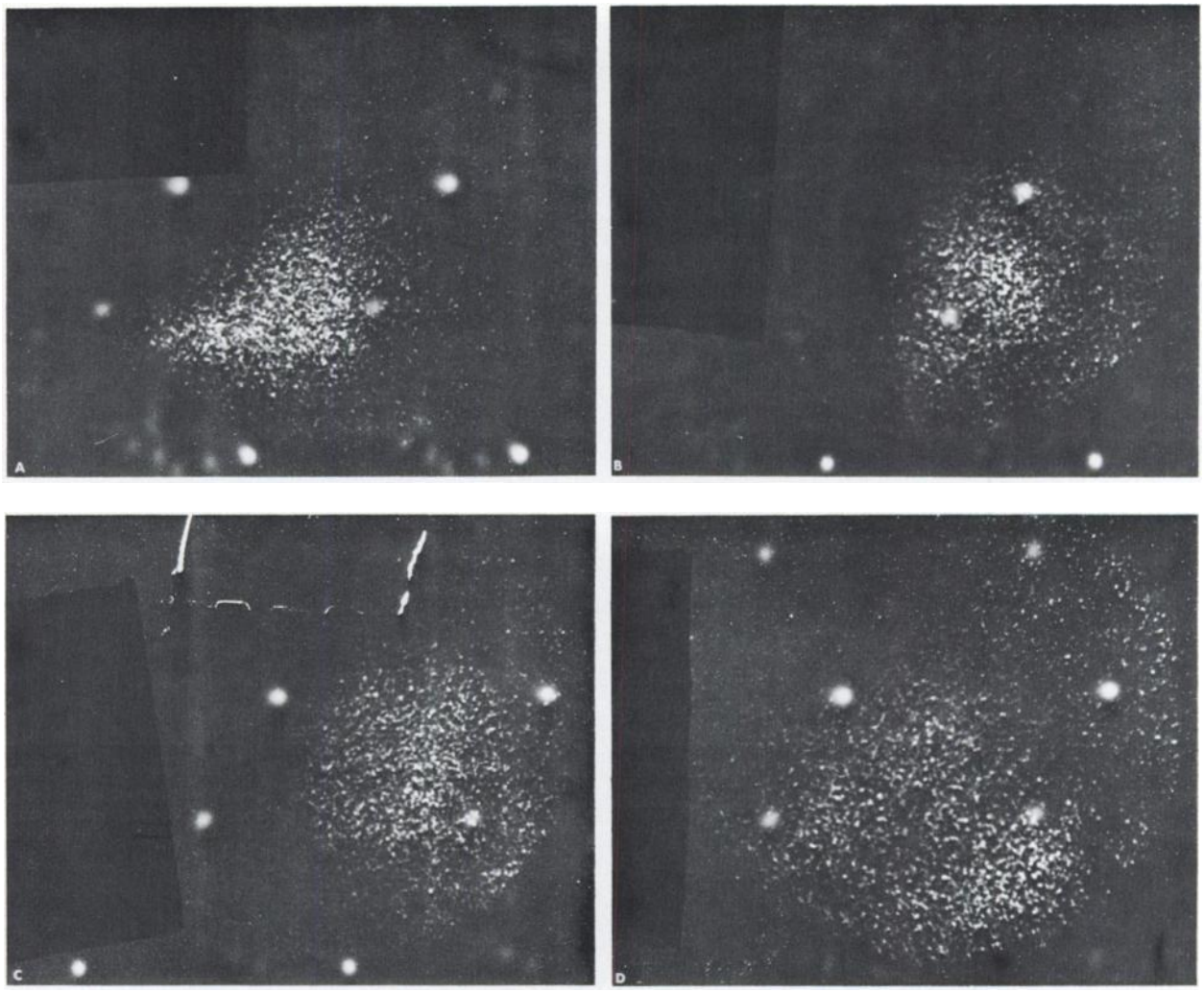

FIG. 7. Intra-arterially injected ^{131}I-MAA liver photoscintograms performed 6 days later than initial ^{131}I-MAA scan (Fig. 6C) over a 5-hr period reveals the area of increased uptake to become progressively less delineated and at 22 hr postinjection no definite lesion can be identified. A was taken 3–5 min postinjection; B taken 3 hr postinjection; C was taken 5 hr postinjection; and D was taken 22 hr postinjection.

The single animal experiment producing an "irritant granuloma" correlates with clinical findings.

This study also suggests that positive liver scans could be used as an objective measure of tumor response in patients undergoing intrahepatic artery chemotherapeutic infusion in conjunction with angiographic studies.

SUMMARY

Twenty-one patients receiving infusion of chemotherapeutic agents by intra-arterial hepatic catheters were studied with ^{198}Au liver scans, selective hepatic arteriograms and intra-arterial ^{131}I-macroaggregated albumin (^{131}I-MAA) liver scans. The ^{131}I-MAA scans correlated with the hypervascular tumor areas on the arteriograms in 19 of 21 cases. The suggested mechanism is secondary to neovascular capillary blockage with delay in reticuloendothelial disposal of the aggregated particles producing positive images of abnormalities on the scans. The following patients are discussed: Three patients with increased uptake on the ^{131}I-MAA scans in the left lobe of the liver difficult to identify on arteriograms; four patients with normal ^{198}Au liver scans and abnormal ^{131}I-MAA scans; and six patients with shunting of ^{131}I-MAA to the lungs. A single dog experiment producing an "irritant granuloma" showed decreased uptake on the ^{198}Au liver scan, increased uptake on the ^{131}I-MAA liver scan and hypervascularity on selective hepatic arteriogram. The pathologic specimen revealed foreign body reaction with neovascularity.

ACKNOWLEDGMENT

The authors wish to express their gratitude to Walter H. Jaeschke, Professor of Surgical Pathology, University of

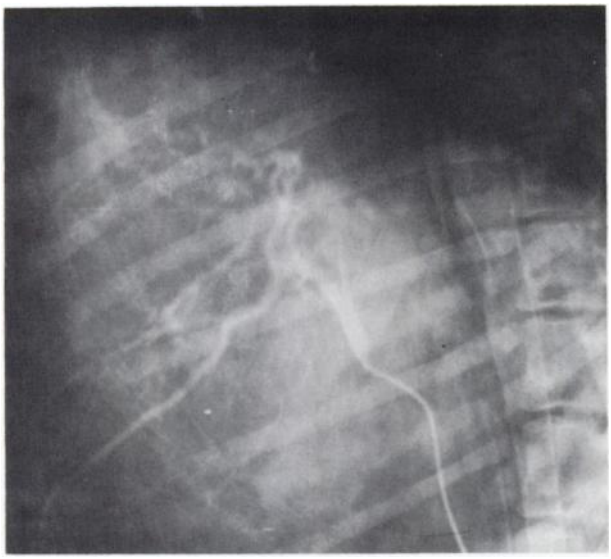

FIG. 8. Repeat hepatic arteriogram 5 hr post-^{131}I-MAA demonstrates hypervascular lesion somewhat less distinctly than pre-^{131}I-MAA liver scan done 6 days earlier (Fig. 6C), but there is no vascular distention or reflux of contrast material.

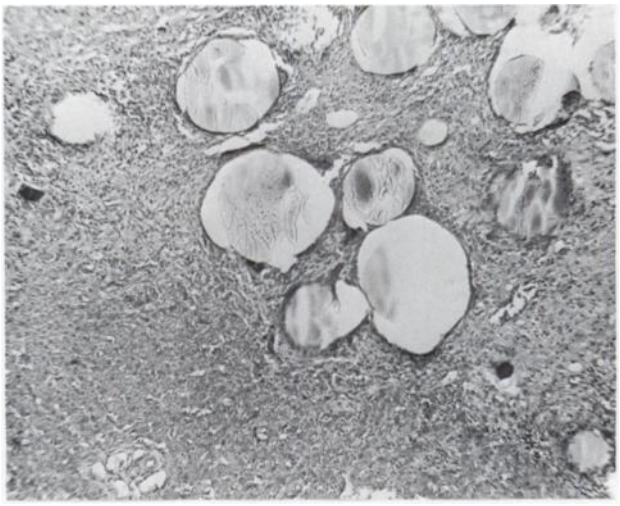

FIG. 9. Microscopic slide of open liver biopsy in dog revealed irregular globular foci of foreign material surrounded by foreign body giant cells. In periphery there was suggestion of necrosis of parenchymal cells. There was fine neovascularity throughout with some fibrosis as indicated by increased numbers of fibroblasts. Moderate degree of inflammatory cell infiltration was present, with portal triads being somewhat enlarged secondary to vascular dilatation.

Wisconsin Medical School, for his review and interpretation of the microscopic slides.

This work was supported in part by American Cancer Society Grant No. 133-6312 and National Institutes of Health Grant No. 5P02CA06295 RAD.

REFERENCES

1. KING, E. G., WOOD, D. E., MORLEY, T. P. AND COLAPINTO, R.: Scanning with macroaggregates of radioiodinated human serum albumin as an adjunct to celiac arteriography. *J. Can. Med. Assoc.* **95**:1,225, 1966.

2. BLANK, R. AND TYSON, I.: ^{131}I macroaggregated albumin in intra-hepatic tumors. *J. Nucl. Med.* **10**:514, 1969.

3. STIRRETT, L. A., YUHL, E. T. AND LIBBEY, R. L.: New techniques for diagnosis of carcinoma metastatic to the liver. *Surg. Gynecol. Obstet.* **96**:210, 1953.

4. STIRRETT, L. A., YUHL, E. T. AND CASSEN, B.: Clinical applications of hepatic radioactive surveys. *Am. J. Gastroenterol.* **21**:310, 1954.

5. TAPLIN, G. V., JOHNSON, D. E., DORE, E. K. AND KAPLAN, H. S.: Lung photoscans with macroaggregates of human serum radioalbumin. Experimental and initial clinical trials. *Health Phys.* **10**:1,219, 1964.

6. TAPLIN, G. V., JOHNSON, D. E., DORE, E. K. AND KAPLAN, H. S.: Suspension of radioalbumin aggregates for photoscanning the liver, spleen, lung, and other organs. *J. Nucl. Med.* **5**:259, 1964.