MASTER

A NEW CHOLESCINTIGRAPHIC AGENT: *RUTHENIUM-97-DISIDA*

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INTRODUCTION

Although Tc-99m-IDA derivatives are the agents of choice for most hepatobiliary imaging, there are clinical conditions where the use of a longer-lived tracer is advantageous (i.e. differential diagnosis of neonatal hepatitis). Previous animal studies have suggested the usefulness of Ru-97-IDA derivatives as an alternative to I-131 Rose Bengal which has been used for this application (1). Ruthenium-97 has excellent imaging properties (Table 1) and is produced by proton spallation of rhodium foil at the BLIP (Brookhaven Linac Isotope Producer) facility using the Rh-103 (p,2p5n) Ru-97 reaction (2). The labeling procedure is similar to the technique used to label DISIDA (2,6-diisopropylphenyl-carbamoylmethyliminodiacetic acid) with Tc-99m (2,3). This is the first presentation of Ru-97-DISIDA imaging in humans. We have explored the utilization of this radiopharmaceutical in patients with a variety of hepatobiliary clinical problems and also in conjunction with a solid test meal labeled with Tc-99m-Sulfur Colloid for the simultaneous observation and quantification of duodenogastric reflux and gastric emptying. This technique is an alternative to the simultaneous administration of Tc-99m-DISIDA and a liquid meal labeled with In-111-DTPA or to the delayed administration of a solid meal labeled with Tc-99m-Sulfur Colloid. A solid meal has the advantage of stimulating gallbladder emptying.

METHODS

We utilized the previously reported method for labeling Ru-97-DISIDA (3). On occasion, the product, due to contamination of Ru-97 by small amounts of carrier, was not completely soluble in saline. Use of 10% ethanol/saline eliminated this problem. Biodistribution studies were performed in normal BNL mice following injection of Ru-97-DISIDA (0.2 ml) I.V. via the tail vein, with and without 10% ethanol. The animals were sacrificed 5, 30, and 120 min post-injection and activity determined in tissue samples (Table 2).

For all patients, the commercially available DISIDA kit was utilized, with 10% ethanol in the final preparation. Patients fasted for at least 12 h prior to tracer administration. A LFOV camera fitted with a medium energy collimator was used with the photopeak window set at 216 keV $\pm$ 10%. Sequential images of the superior abdomen were obtained during one hour following tracer injection. Delayed images were obtained as required. In some patients, gastric images were also obtained following the administration of Tc-99m-Sulfur Colloid in a standard meal (cooked egg whites, Lipomul, and water) (4) with the energy window set at 140 keV $\pm$ 10%. There was no appreciable overlap between the Tc-99m and Ru-97 photopeaks. Enterogastric reflux and the gastric emptying were measured according to previously reported techniques (4,5). Demographic data, diagnoses, and administered doses for all patients are presented in Table 3.

RESULTS

1. Biodistribution studies. Table 2 is a summary of typical data. Tissue distribution of Ru-DISIDA was very similar in the two groups of animals. Comparison with previous data (1,3) reveals similarity to the distribution of corresponding Tc-99m labeled agents. High hepatic uptake and negligible renal excretion were noted.

2. Patient studies. The hepatobiliary images obtained in patients were of excellent quality. Prompt blood clearance of the radiopharmaceutical was evident. Representative images are shown in Figures 1A - 3. Image quality was excellent during the first hour and in delayed views. The Ru-97 scintiscans correlated well with other imaging procedures and clinical findings (Table 2). For example, we were able to correctly rule out biliary atresia in an infant in whom the gallbladder was not visualized. Surgical exploration revealed the presence of chronic and subacute cholecystitis and a patent common bile duct.

Simultaneous quantification of duodenogastric reflux (DGR) and gastric emptying (GE) were easily performed (Figures 2,3). As previously stated, the energy peaks of Tc-99m and Ru-97 are sufficiently separated so that there was no spill-down of counts from the higher to the lower energy window (in the standard methodology, compensation for spill-down of In-111 counts into the Tc-99m window is essential before the quantification of DGR may be carried out) (4).

CONCLUSIONS

These studies demonstrate the first application of Ru-97-DISIDA in human subjects. High quality images were obtained. Scintigraphic findings in patients with hepatobiliary disorders were consistent with the biodistribution data obtained in experimental animals and with other imaging procedures and clinical findings.

Administration of Ru-97-DISIDA I.V. and of a solid test meal labeled with Tc-99m-Sulfur Colloid allowed simultaneous detection and quantification of duodenogastric reflux and determination of the gastric emptying rate. This represents an advantage as compared to the currently used techniques which necessitate two separate studies if a solid meal is used, or would mandate a liquid meal for a simultaneous study.

The excellent nuclear decay characteristics of Ru-97 (t1/2 69.6 h, gamma 216 keV, 86%, no betas) permit delayed study of the hepatobiliary system with considerably less radiation exposure than I-131 Rose Bengal and with a marked improvement in image quality. Further patient studies are in order to confirm the clinical utility of this agent.

REFERENCES

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TABLE 1

Decay Data of ^{97}Ru

Half-Life	- 69.6 hours
Decay Mode	- electron capture, no betas
Gamma Rays	- 216 keV (86.0%) 324 keV (10.2%)

Production		Parameters
Nuclear Reaction	-	$^{103}Rh(p,2p5n)^{97}Ru$
Target Material	-	rhodium foil, 0.25 mm thick
Proton Energy	-	200 MeV
Production Rate	-	0.25 mCi/μAh
Total Yield	-	0.5-1 Ci per run at 80 μA with 0.25 mm thick target
Specific Activity	-	carrier free
Radioimpurity	-	none detectable

TABLE 2

Tissue Distribution (Percent Dose Per Organ) of Ruthenium-103 Labeled Acetate and Diisopropyl-IDA (DISIDA) in Mice[1]

Tissue	Time (min)	Compound: Acetate	DISIDA (Saline)	DISIDA (10% Ethanol/saline)
Blood	5	13.20 ± 1.11	3.13 ± 0.32	2.95 ± 0.16
	30	8.46 ± 0.46	0.50 ± 0.17	0.53 ± 0.04
	120	5.94 ± 0.31	0.24 ± 0.03	0.24 ± 0.08
Stomach	5	0.77 ± 0.04	0.73 ± 0.48	1.98 ± 1.87
	30	0.59 ± 0.09	0.42 ± 0.40	5.43 ± 4.81
	120	0.97 ± 0.32	0.86 ± 0.68	0.82 ± 0.35
Liver	5	10.20 ± 0.58	18.20 ± 3.42	20.80 ± 2.73
	30	8.91 ± 0.14	3.65 ± 1.60	5.56 ± 1.37
	120	7.96 ± 0.28	1.53 ± 1.13	1.61 ± 0.66
Gut	5	7.32 ± 0.50	49.80 ± 7.99	40.90 ± 7.15
	30	7.76 ± 0.40	77.00 ± 9.81	70.50 ± 4.80
	120	11.60 ± 1.41	81.40 ± 3.01	79.60 ± 9.20
Kidneys	5	3.77 ± 1.31	1.54 ± 0.30	2.07 ± 0.39
	30	2.13 ± 0.09	0.53 ± 0.11	0.51 ± 0.18
	120	1.81 ± 0.12	0.53 ± 0.09	0.43 ± 0.25
Whole Body	5	79.5 ± 12.5	95.8 ± 5.9	92.6 ± 3.9
	30	59.4 ± 1.3	99.3 ± 6.9	94.5 ± 1.3
	120	53.8 ± 2.4	94.2 ± 1.2	92.8 ±11.8

[1]Results are the average of 3 mice ± 1 std. deviation. Blood volume was assumed to be 7% of total body weight. All data were normalized for 25 g mice.

TABLE 3

Results of Ru-97-DISIDA Study in Patients

Patient	Sex/Age	Dose (mCi)	Scintigraphic Diagnoses	Confirmation
1	F/84	0.70	Acute cholecystitis	(+) Clinically
2	F/34	1.09	Normal	(+) Id. to repeat ^{99m}Tc-DISIDA (-) Surg: Subacute cholecystitis
3	F/14	0.50	Delayed GE. DG reflux (*)	(+) Clinically
4	M/51	0.66	Acute cholecystitis	(+) Surg: Subacute cholecystitis
5	M/6W	0.09	Biliary atresia R/O. Non-visualization GB	(+) Surg: Chronic and subacute cholecystitis
6	F/23	0.80	Delayed GE. No DG reflux (*)	(+) Clinically
7	M/13	0.96	Delayed GE. No DG reflux (*)	(?) Suspected DGR by pH study
8	M/81	1.32	Chronic cholecystitis	(+) Clinically, US
9	M/55	1.40	Acute cholecystitis R/O. Low grade obstruction of CBD.	(+) Surg: Chronic cholecystitis. Cholelithiasis
10	M/16	0.75	Delayed GE. No DG reflux (*)	(?) Suspected DGR by pH study
11	M/16	0.86	Normal GE. No DG reflux (*)	(+) Clinically
12	F/78	0.83	High-grade obstruction of CBD R/O. DG reflux?	(+) Borderline US, CT
13	F/70	1.00	Acute cholecystitis	(+) Surg: Chronic active cholecystitis
14	M/22	0.79	Hepatic dysfunction. Acute cholecystitis R/O.	(+) Surg: Hodgkin's disease of liver, cholestasis, chronic cholecystitis

DG = Duodenogastric reflux. GE = Gastric emptying. R/O = Ruled out. CBD = Common bile duct. US = Sonogram. GB = Gallbladder. (*) = Concomitant measurement of DG and GE using Tc-99m-Sulfur Colloid p.o.

Figure 1. A. Sequential composite scintiphotos, 0-60 min p.i. Ru-97-DISIDA (1.1 mCi) in patient No. 2. Prompt filling of the gallbladder and passage of tracer into the intestine are evident.

B. Scintiphotos, 10-60 min p.i. Tc-99m-DISIDA (3.0 mCi) in same patient performed 17 d prior to previous test. Similar findings are noted in both examinations.

Figure 2. A. Composite scintiphotos 0-40 min p.i. Ru-97-DISIDA in patient No. 3. Images of the gallbladder, common bile duct, and duodenum. Suspicion of duodenogastric reflux at 30-40 min.

B and C. Composite scintiphotos 0-60 min, patient No. 3, with (C) and without (B) superimposition of regions of interest corresponding to the liver and stomach. The gastric region was obtained following the administration of a solid meal labeled with Tc-99m-Sulfur Colloid, 100 μCi. The biliary reflux reaches the region of the stomach.

Figure 3. Sequential scintiphotos 0-90 min post Tc-99m-Sulfur-Colloid in a solid test meal in patient No. 11. The first and third vertical columns from the left are Ru-97 images and the second and fourth columns are Tc-99m views. Normal filling of GB, passage of tracer to the intestine, and gastric emptying are noted. Duodenogastric reflux is not present.

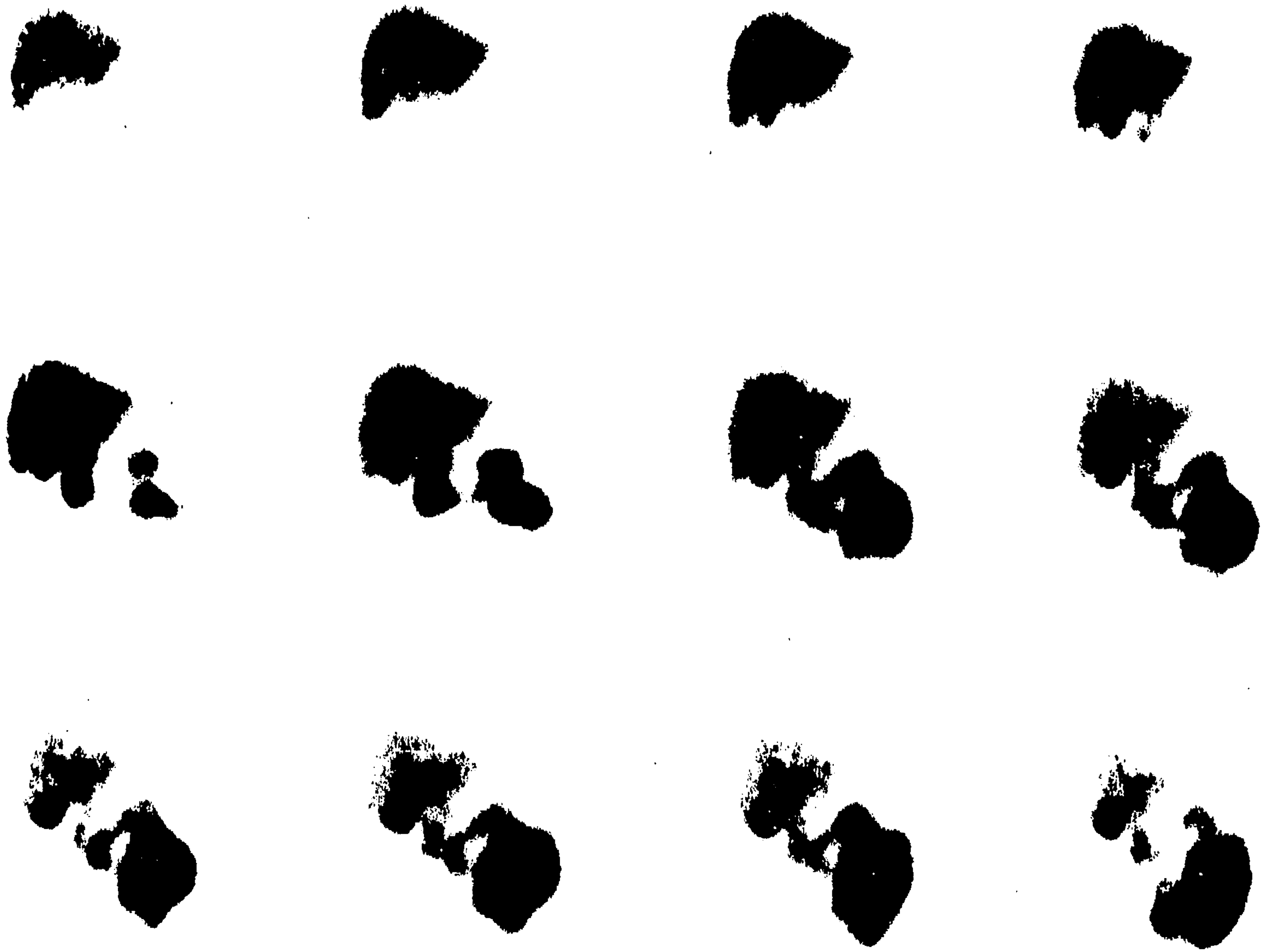


Figure 1A

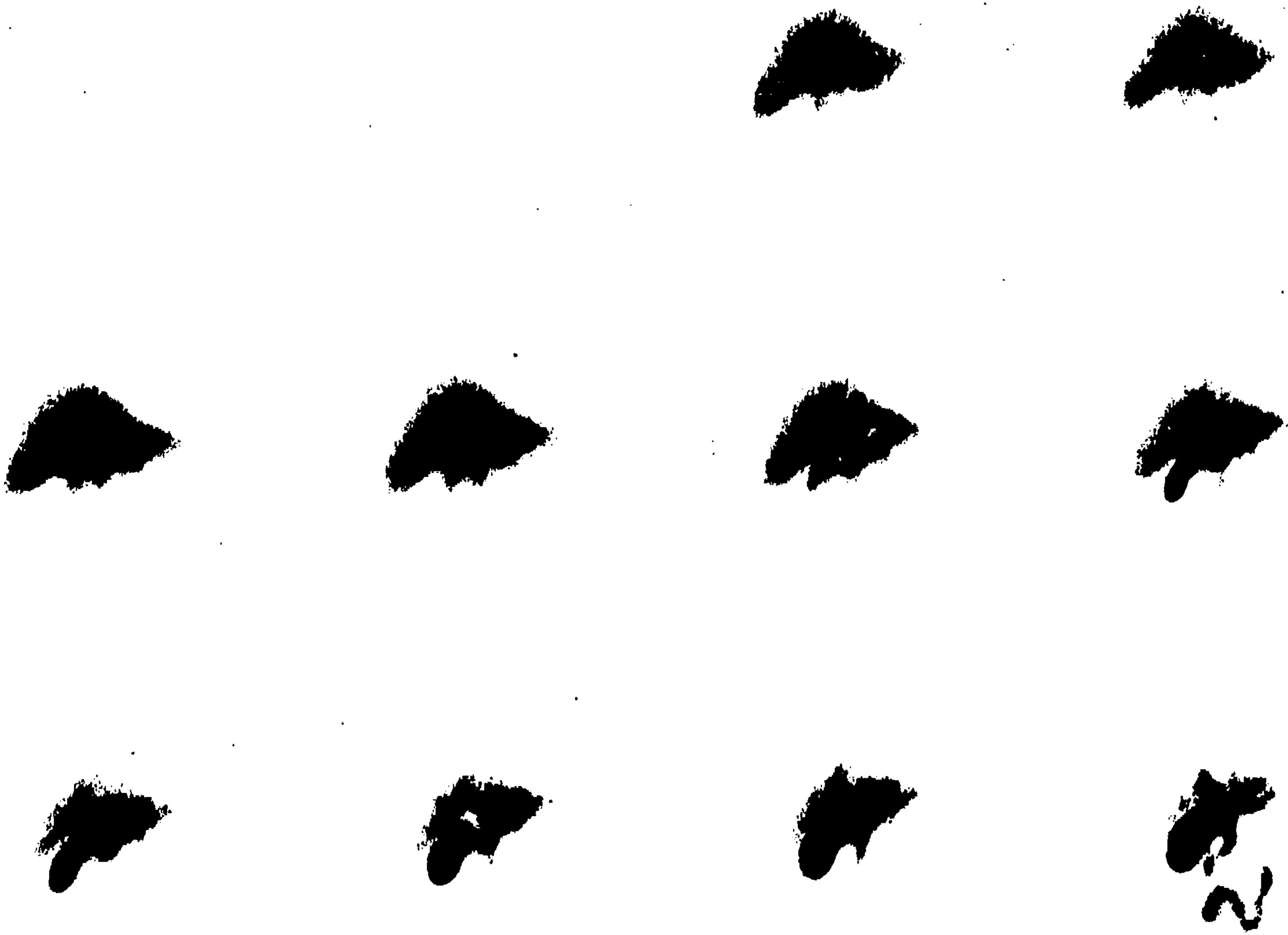


Figure 1B

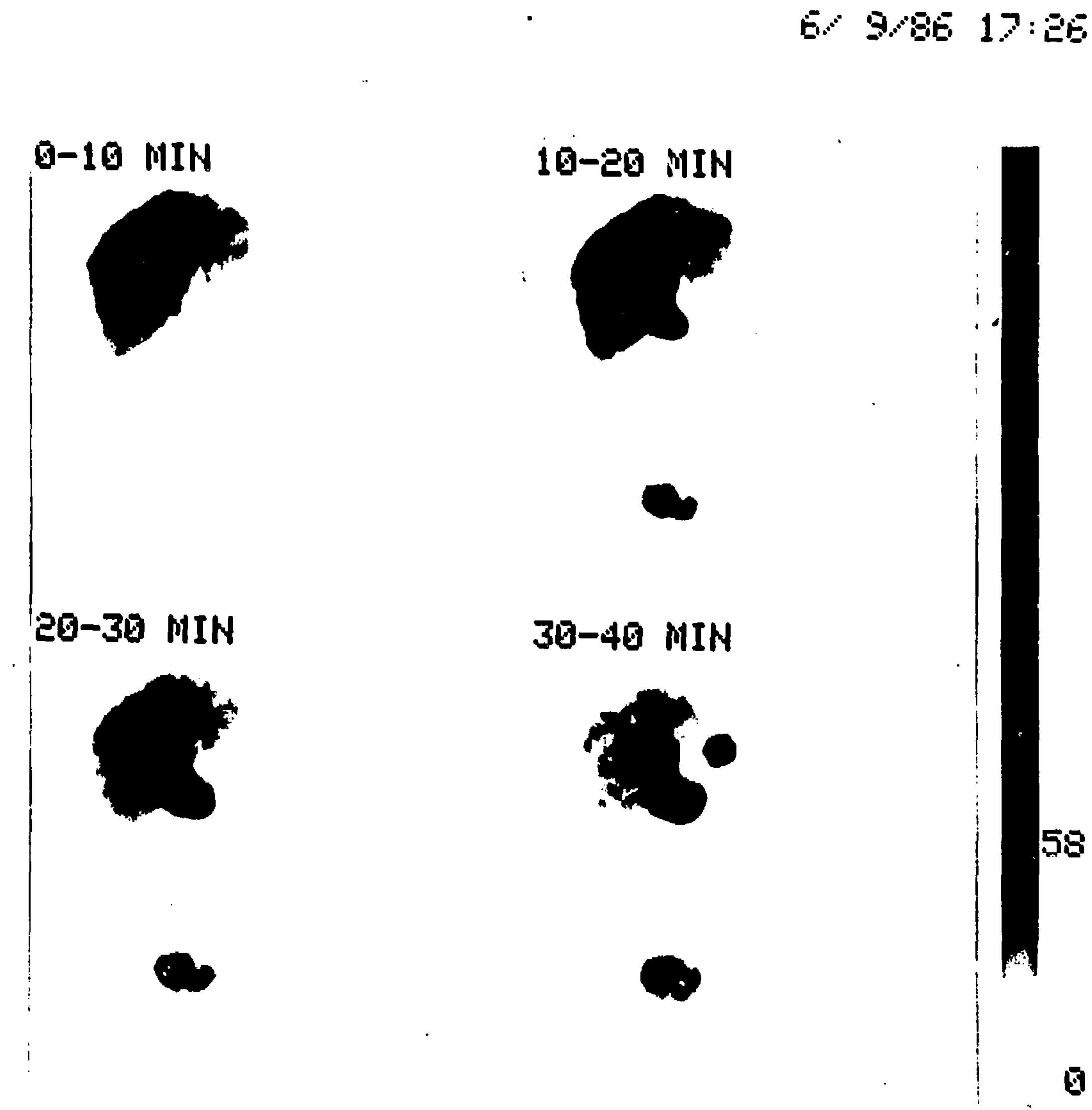
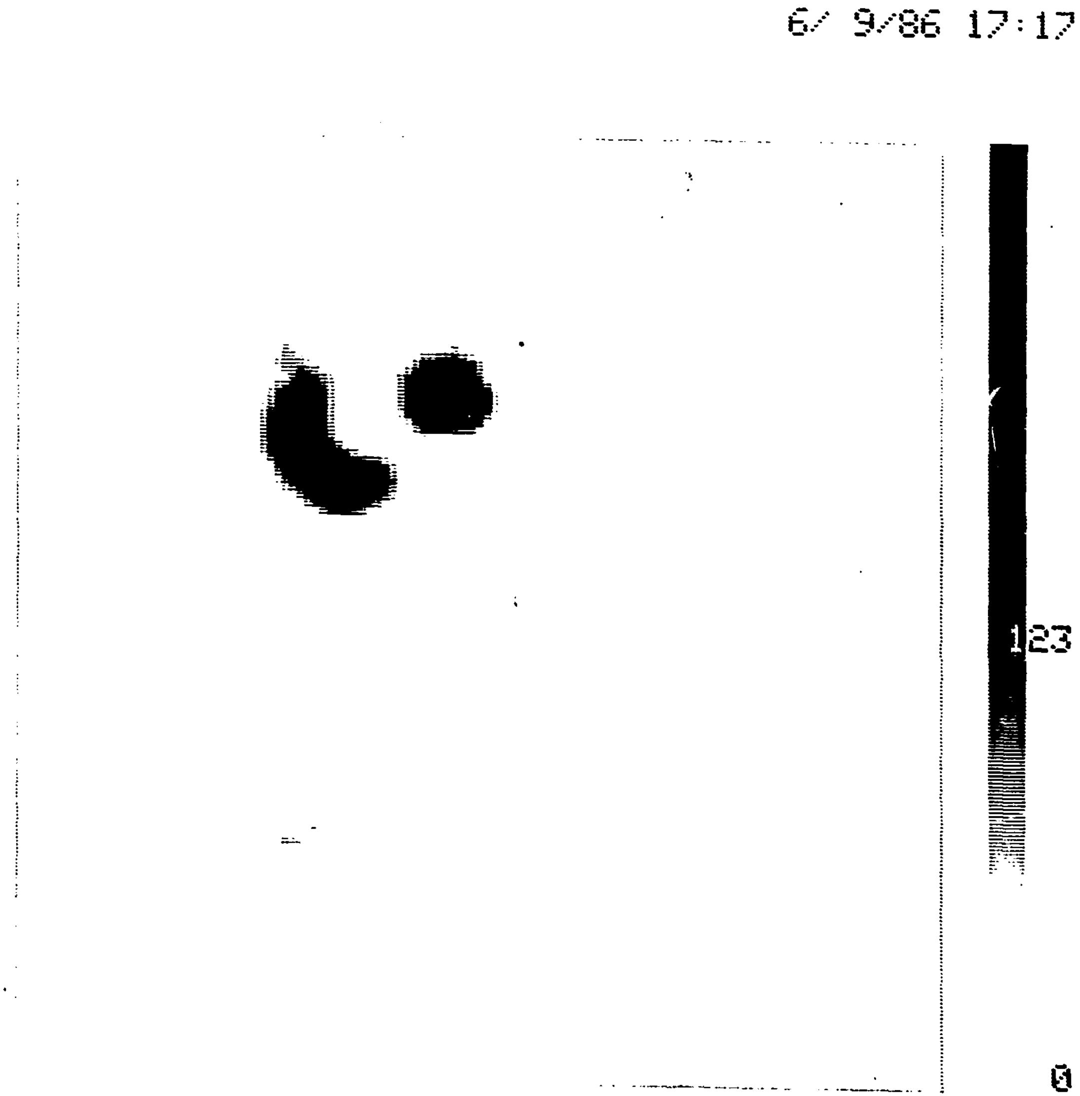


Figure 2A



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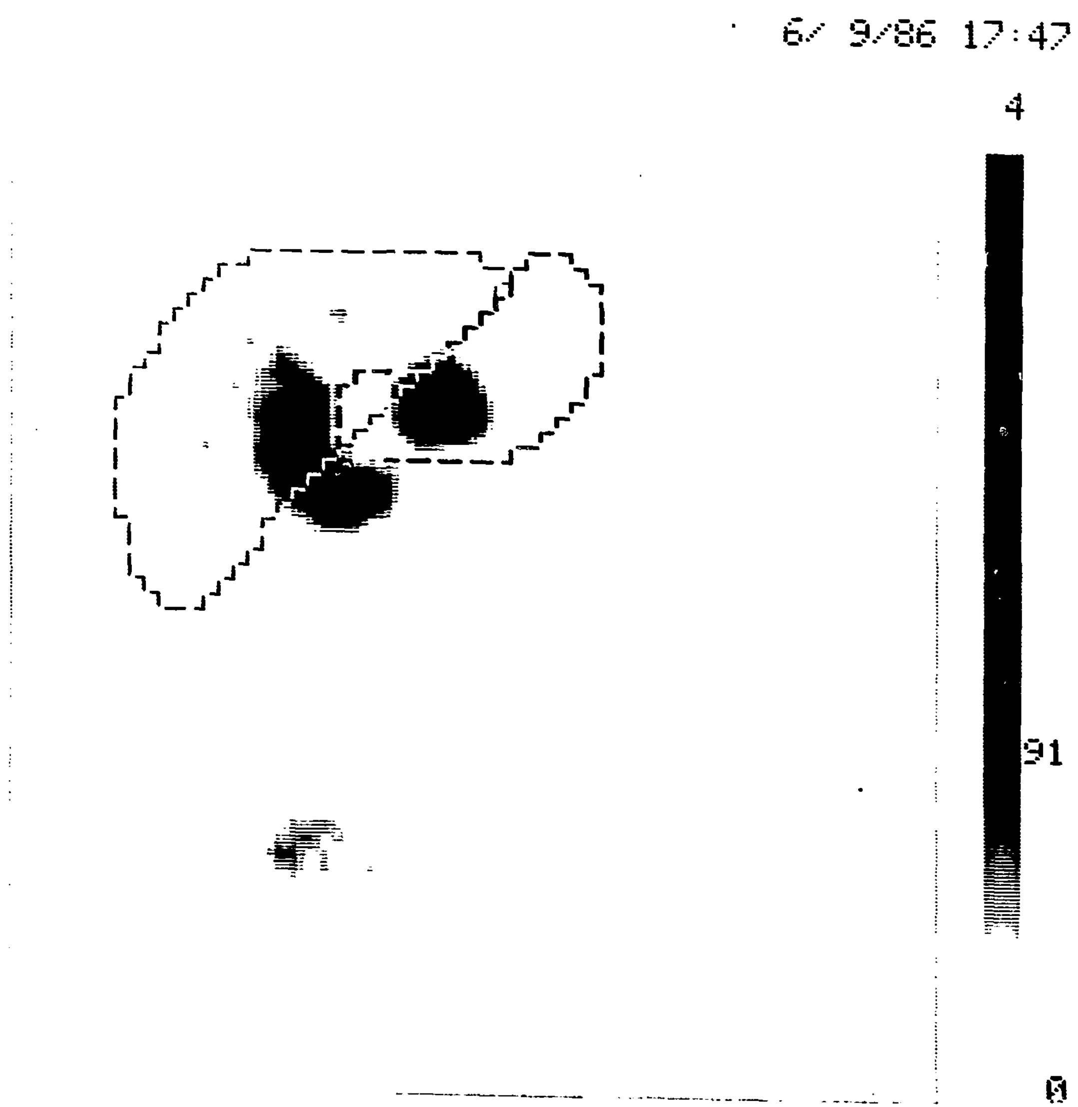

Figure 2C

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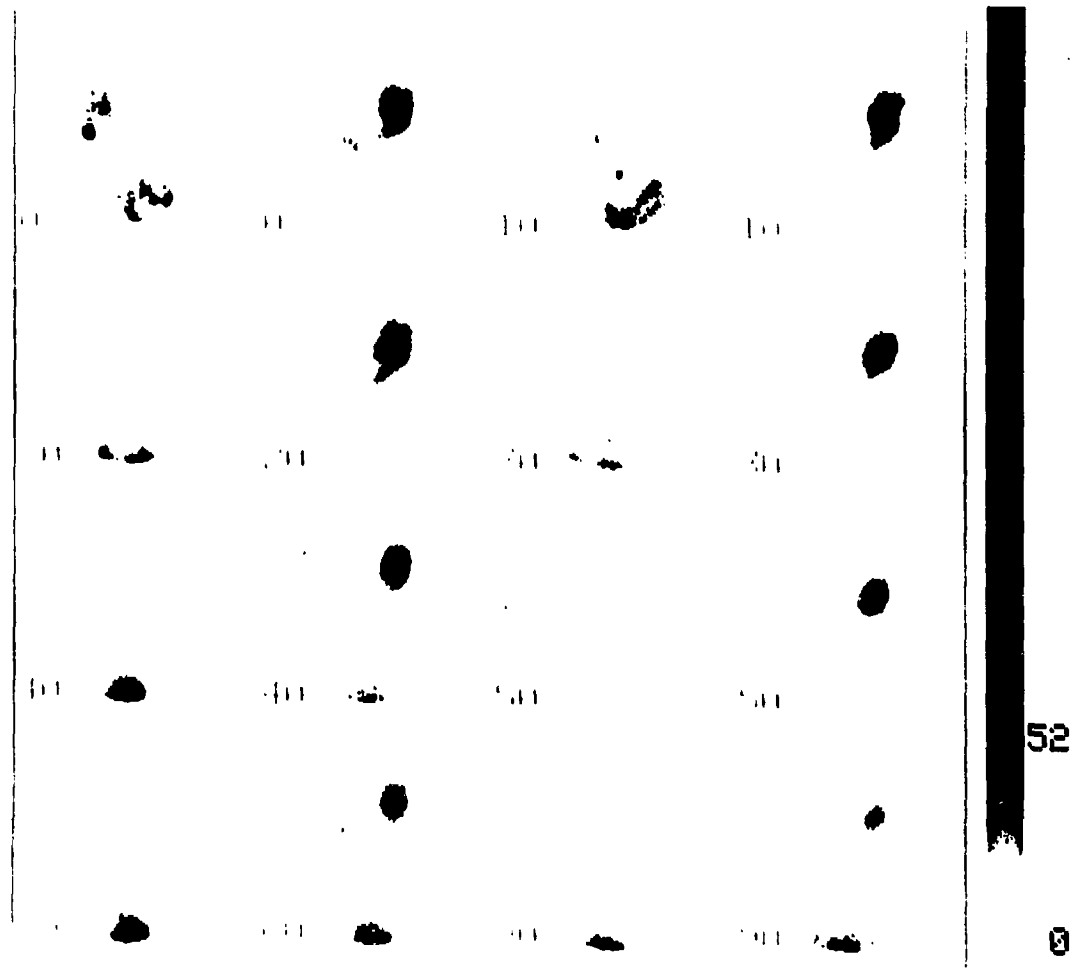

Figure 3