Clinical Evaluation of Tc-99m-Diethyl-IDA in Hepatobiliary Disorders

S. Pauwels, M. Steels, L. Piret, and C. Beckers

University of Louvain, Brussels, Belgium

N,α(2,6-diethylacetanilide)-iminodiacetic acid is a new Tc-99m-labeled radiopharmaceutical primarily excreted through the biliary tract. Its high concentration in the bile allows the imaging of the biliary tree and the gallbladder.

Scintigraphic studies were performed in 20 normal subjects and 42 patients suffering from various hepatobiliary disturbances. In normal subjects, the early liver uptake was followed by the accumulation of the tracer in the intrahepatic bile ducts and the gallbladder before its discharge into the duodenum. In cases of hepatocellular damage, the hepatic accumulation of the tracer was clearly depressed.

Any acute or subacute disorder of the gallbladder was clearly demonstrated by Tc-99m-diethyl-IDA. In cases of asymptomatic cholelithiasis, we observed delayed visualization of the gallbladder associated with its decreased accumulation of the tracer. The intrahepatic bile ducts were distended in cases of incomplete obstruction of the hepatobiliary ducts, whereas they were never visualized when there was severe hepatocellular damage or complete obstruction of the biliary tree.

J Nucl Med 19: 783–788, 1978

For many years, radioiodinated rose bengal has been used as the main hepatobiliary agent, taking advantage of its excellent concentration in the bile and its poor urinary excretion (*1*). The relatively long half-life of the radioiodine used to label the molecule, however, finally prevented its widespread use in clinical medicine. Later on, other hepatobiliary agents were investigated, such as dihydrothioctic acid (*2*), tetracycline (*3*), and pyridoxylideneglutamate (*4,5*). The main advantage of these compounds is their easy labeling with technetium. Further research in mice and dogs demonstrated the advantages of the N-substitutes of iminodiacetic acid (*6*). In baboons, Wistow et al. (*7*) found that Tc-99m-N-α-(2,6-diethylacetanilide)-iminodiacetic acid (Tc-99m-diethyl-IDA) was probably the most interesting in this family of compounds. As recently pointed out by Ronai in this journal, however, the question remained as to whether Tc-99m-diethyl-IDA will perform well in patients (*8*). Our aim in this work is to evaluate the performance of Tc-99m-diethyl-IDA in normal subjects and in patients suffering from various hepatobiliary disturbances. To achieve this goal, accurate scintigraphic criteria were established in normal subjects and a given scintigraphic diagnosis was compared with the final clinical diagnosis obtained from the classical criteria.

MATERIALS AND METHODS

In all, 62 adult subjects have been investigated, including 21 normal subjects and 41 patients with various hepatobiliary diseases: nine with gallstones, two with biliary colic of unknown origin, one with Odditis, one with a ligated main biliary duct, 14 with cholecystitis, two with angiocholitis, one with alcoholic pancreatitis, three with hepatitis, three with

Received Sept. 9, 1977; revision accepted Dec. 30, 1977.

For reprints contact: C. Beckers, Centre de Médecine Nucléaire, UCL 54.30, Avenue Hippocrate, 54, B-1200 Brussels, Belgium.

TABLE 1.

Scintigraphic diagnosis (HIDA)	Investigations performed to confirm the final clinical diagnosis						
	Intravenous cholangiogram	Echography	Retrograde cholangiogram	Hepatic biopsy	Surgery	Tc-99m colloid scan	Clinical chemistry
Cholecystitis (14)	12		2				
Cholelithiasis (3)	2				1		
Choledocholithiasis (6)	2		2		2		
Odditis (1)			1				
Ligation of the main biliary duct (1)					1		
Angiocholitis (2)				1			1
Alcoholic pancreatitis (1)			1				
Hepatitis (3)				1			2
Cirrhosis (3)				3			
Tumor of head of pancreas (3)			1		1		
Tumor of ampulla of Vater (1)					1		
Metastatic liver cancer (1)						1	

cirrhosis, three with tumors of the head of the pancreas, one with a tumor of the ampulla of Vater, and one with metastatic cancer of the liver. The final diagnosis of the hepatobiliary disease was obtained by one or several routine investigations, such as oral cholecystogram, intravenous cholangiogram, echography, retrograde cholangio-Wirsungography, laparoscopy and hepatic biopsy. In some cases, the diagnosis was confirmed by surgery (Table 1).

Labeling of the tracer was achieved by adding a pyrogen-free sterile [^{99m}Tc] pertechnetate solution (10–30 mCi; 1–4 ml) into a vial containing 40.2 mg of N,α-2,6-diethylacetanilide)-iminodiacetic acid obtained commercially. The colorless solution containing the end product had a final pH of 5.5. Paper electrophoresis (in barbital buffer, pH 8.6, 400 V for 2 hr at 4°C) demonstrated that 87.7% of the radioactivity corresponded to Tc-99m-diethyl-IDA, with less than 2% of free pertechnetate.

Except in seven subjects, all the investigations were performed after an overnight fast. The patients were injected intravenously with a standard dose of 5–8 mCi of Tc-99m-diethyl-IDA. No side effects were ever observed.

Scintigraphic studies. Using a scintillation camera equipped with a high-resolution collimator, anterior views of the abdomen were obtained every 5 min and then at other critical times—e.g., for duodenal or gallbladder transit times. If necessary, late pictures were obtained until the 24th hr.

The investigations were classified according to the following criteria: a) duration of kidney visualization; b) early and late hepatic pictures; c) characteristics of the main biliary ducts (diameter and relative concentration of the tracer); d) duodenal passage before and after administration of a standard fatty meal*; and e) time of beginning visualization of the gallbladder and intensity of the concentration of the tracer in this organ.

According to these criteria, the studies were classified into various groups of cases: a) normal studies, b) hypofunctional gallbladders, c) excluded gallbladders, d) incomplete biliary obstruction, e) complete biliary obstruction, and f) severe hepatocellular disease.

As shown in Fig. 1, a normal hepatobiliary study is characterized by the following phases: a) the early hepatic parenchyma phase with a clear-cut hepatic scintigram after the 4th min (the maximal activity having already been reached); b) the renal phase (until the 15th min after injection of the tracer); c) the phase corresponding to the visualization of the main biliary ducts (the tracer being concentrated there as early as 10 min after tracer injection, with the maximum obtained around the 20th min); d) the phase of duodenal visualization, starting after 27 min; and e) the gallbladder phase, the tracer appearing around the 13th min, to reach a maximum after 50 min. The administration of 100 ml of Bladex induces a significant discharge of the tracer from the gallbladder. There is also a late parenchymatous phase after 45 min, which demonstrates a good discharge of the tracer from the hepatocytes, and an intestinal phase, since, after longer intervals, most of the tracer is found in the gut.

Histograms. In five cases, magnetic-tape records in list mode were obtained from the beginning of the investigation (time zero until the 45th min). Four regions of interest of equal size were selected: the right hepatic lobe, the gallbladder area, the proximal common bile duct, and left kidney.

A typical histogram, obtained from a normal

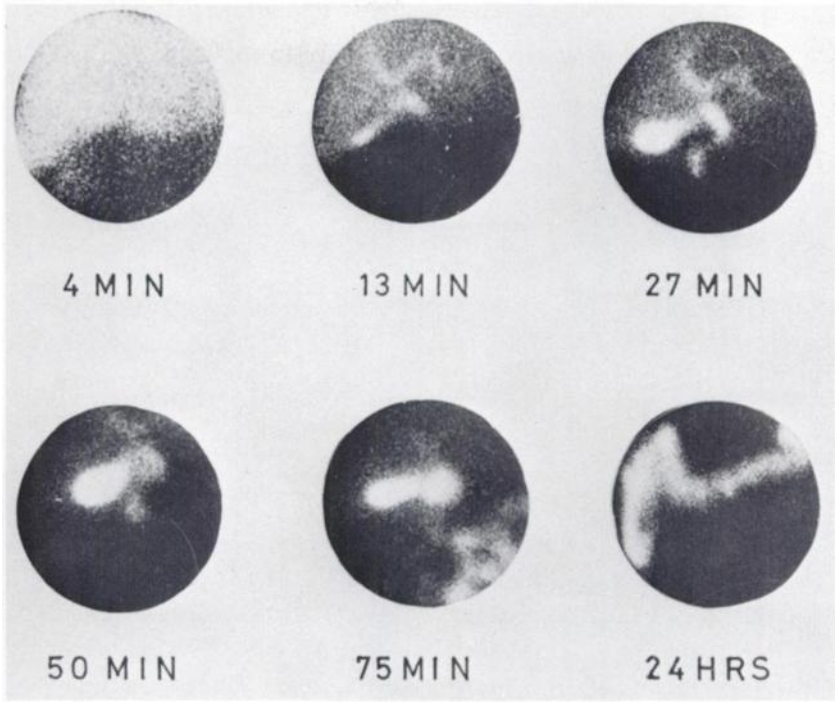

FIG. 1. Scintigraphic studies with Tc-99m-diethyl-IDA in a normal subject; 4th min: clear visualization of the liver, renal excretion of the tracer (under right lobe of liver); 13th min: appearance of gallbladder; 27th min: beginning of duodenal passage; 50th min: maximal accumulation in gallbladder; 75th min: gallbladder emptying 5 min. after administration of a standard fatty meal; 24th hr: picture of colon.

subject, is presented in Fig. 2. It shows: a) the renal curve, with a vascular peak followed by a phase of concentration that reaches its maximum at the 6th min and decreases until the 13th min; b) the hepatic-parenchyma curve, with maximal concentration at the 9th min, followed by a slow, regular decrease in radioactivity; c) the proximal common bile duct curve, characterized by relatively late appearance of the tracer due to the accumulation of most of the radioactivity in the gallbladder; and d) the gallbladder curve, characterized by a very rapid increase from the 6th min on, with a plateau after 40 min. Note that there is a tenfold concentration of the tracer in the gallbladder relative to the hepatocytes.

RESULTS

The main data obtained in all the groups under study are summarized in Table 2.

In 22 cases *a normal scintigraphic study* was found. This group included 19 clinically normal subjects and three patients with the following diseases: one with hepatitis at the end of its recovery period, and two other cases of biliary colic of undetermined origin, examined a long time after the acute phase. Five normal subjects were not fasting at the time of the study. The main data may be summarized as follows. The kidneys were no longer seen after 15 min. The hepatic parenchyma was seen clearly after 4 min. After 45 min, the liver radioactivity decreased significantly. The diameter of the biliary ducts was normal and the concentration of the tracer in the biliary ducts no longer increased after 30 min. In the fasting subjects, the gallbladder was always visualized between the 7th and the 25th min, and between the 15th and the 34th min in the five nonfasting normal subjects. In 18 cases, the duodenum was seen between the 5th and the 37th min. In the five other subjects, the duodenal visualization was observed within 10 min following the administration of Bladex, 45 min after the injection of the tracer.

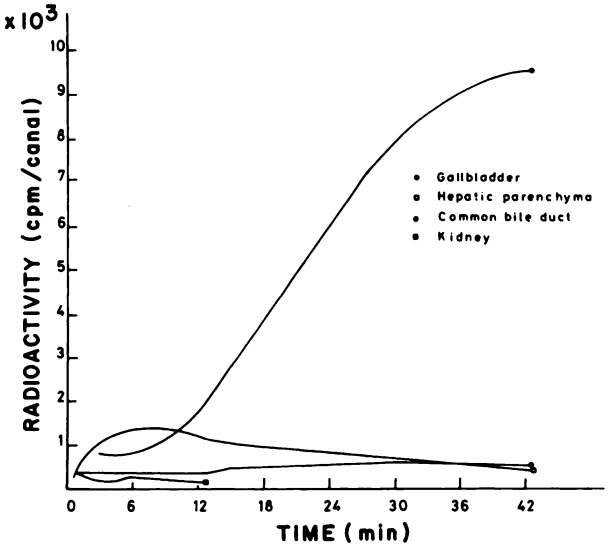

FIG. 2. Histogram obtained from a normal subject after injection of Tc-99m-diethyl-IDA, four zones of interest being selected: liver, kidney, gallbladder and common bile duct.

TABLE 2. SUMMARY OF PRINCIPAL DATA OBTAINED BY IMAGING WITH Tc-99m-DIETHYL-IDA IN VARIOUS HEPATOBILIARY DISORDERS

Groups of cases	Number	Kidney visualization mean time (min)	Early hepatic picture	Diameter of main biliary ducts	Time for maximal concentration in bile ducts	Duodenal passage mean time (min)	Gallbladder visualization mean time (min)
Fasting normal subjects	17	<15	N	N	N	19.4	13.3
Nonfasting normal subjects	5	<15	N	N	N	14.7	25.7
Hypofunctional gallbladder	5	<15	N	N	N	16.4	45.2
Excluded gallbladder	13	<15	N	I or N	I or N	26.8	0
Incomplete biliary obstruction	12	<15	N	I	I	31.9	0
Complete biliary obstruction	4	>360	N or D	0	0	0	0
Severe hepatocellular disease	6	150	±0	0	0	x	0

D = decreased
N = normal
I = increased
x = 4 cases: no passage; 1 case: passage after 16 min; 1 case: passage after 60 min.

Another group consisted of five cases presenting a *hypofunctional gallbladder* (three with asymptomatic biliary lithiasis, one with cholecystitis at the end of his illness, and one with alcoholic pancreatitis). In these five cases, the visualization of the gallbladder was delayed to the 30th–80th min, and in four of the five the concentration of the tracer in this organ was decreased. Moreover, in the case of almost-cured cholecystitis, an increase of the diameter of the main biliary ducts was noted, as well as concentration of the tracer in the intrahepatic bile ducts, still increasing after 30 min and therefore indicating an associated incomplete biliary obstruction.

An *excluded gallbladder* was observed in 13 cases (eight with acute cholecystitis, three with chole- and choledocholithiasis, and two nonfasting normal subjects). In none of these could the gallbladder be visualized within 120 min. In some patients, a superimposed incomplete biliary obstruction was present, as indicated by one or several of the following criteria: insufficient hepatic discharge of the tracer, dilatation of the main biliary ducts, or delay in the duodenal appearance of the tracer.

A group of 12 cases with *incomplete biliary obstruction* included five with cholecystitis, two with chole- and choledocholithiasis, two with angiocholitis, one with Odditis, one with tumor of the ampulla of Vater, and one with choledocholithiasis. In these cases, the total bilirubinemia ranged between 0.5 and 4.5 mg/100 ml. In seven out of 12 cases, the hepatic discharge of the tracer was delayed. In ten cases, the main biliary ducts were dilated, with the concentration of the tracer in the intrahepatic bile ducts still increasing after 30 min. The duodenum was always seen (between the 7th and 180th min). In none of these cases could the gallbladder be visualized (Fig. 3).

Four cases of *complete biliary obstruction* were investigated. This group included three tumors of the head of the pancreas and one case of ligation of the main biliary duct following cholecystectomy. In these cases, the bilirubinemia ranged between 7.2 and 19 mg/100 ml. The scintigraphic studies continued at least until the 6th hour following tracer injection. The kidneys were always seen after 6 hr. In three patients, a normal hepatic picture was seen early, in contrast with the fourth patient, in whom the picture was less evident, probably due to a superimposed hepatic cytolysis (as suggested by the results of the blood tests). As shown in Fig. 3, these cases were characterized by little if any hepatic discharge, and no visualization of the main biliary ducts, the duodenum or the gallbladder.

In six cases of severe hepatocellular disease (two alcoholic cirrhosis with hepatic insufficiency, one with postnecrotic cirrhosis, one with acute B-type hepatitis, one with toxic hepatitis with cholostasis, and one with metastatic cancer of the liver), the bilirubinemia ranged from 4.9 to 23 mg/100 ml. The kidneys remained visible for 29 min to 7½ hr. In three cases, the liver could hardly be distinguished from the surrounding background, whereas in the other three the kidney only was seen. It was not possible to see the main biliary ducts or the gallbladder in any of these cases. The duodenum was visualized in only two out of the six cases in this group (Fig. 3).

DISCUSSION

In 57 cases out of the 62, the scintigraphic findings

were in full agreement with the final diagnosis. Discrepancies were found in five cases. In two nonfasting subjects, an excluded gallbladder was observed while no vesicular disease was present. In two subjects who had presented acute biliary colic a long time before our study, a normal scan was obtained and all other tests remained normal. In one case of hepatitis, the scintiphoto was normal, without any evidence of hepatocellular damage. This was probably because the illness was at the end of its recovery period.

Summarizing these observations, we find that the gallbladder could be visualized in all the normal subjects provided they were in a fasting state, a condition that appears to be essential for any successful investigation. Indeed, the two false-positive results were both obtained in nonfasting subjects. Using T-99m pyridoxylideneglutamate, Matolo et al. have already stressed the importance of a fat-free diet to avoid false-positive results (*9,10*). The incidence of false-positive results appears to be higher with another tracer, Tc-99m dihydrothioctic acid (*11*).

Except in the two cases of nonfasting normal subjects, the 13 patients with no visualization of the gallbladder all suffered from some degree of acute or subacute disease of the gallbladder. In the fasting state, no single false-positive case was encountered, as recently reported in this journal (*12*). In cases of (sub)acute cholecystitis, an incomplete biliary obstruction associated to an excluded gallbladder was often observed.

We must stress that while Tc-99m-diethyl-IDA may significantly accumulate in the gallbladder, the visualization of the common bile duct may be greatly delayed without any pathologic significance. In these cases, the best studies of the discharge to the duodenum were obtained when Bladex was given after the tracer had filled the gallbladder.

In all the cases of asymptomatic cholelithiasis, the gallbladder was visualized but with some delay (later than 25 min after tracer administration). In two out of three cases, the accumulation of the tracer within the gallbladder was decreased.

The use of Tc-99m-diethyl-IDA appears to be very useful in the differential diagnosis of any state of jaundice. Indeed, the difference between incomplete and complete obstruction depends on whether or not the duodenum is visualized. The differential diagnosis between obstructive and hepatocellular damage can easily be done when the obstruction is incomplete. A dilatation of the main biliary ducts and a delayed duodenal visualization constitute pathognomonic signs of a partial mechanical obstruction.

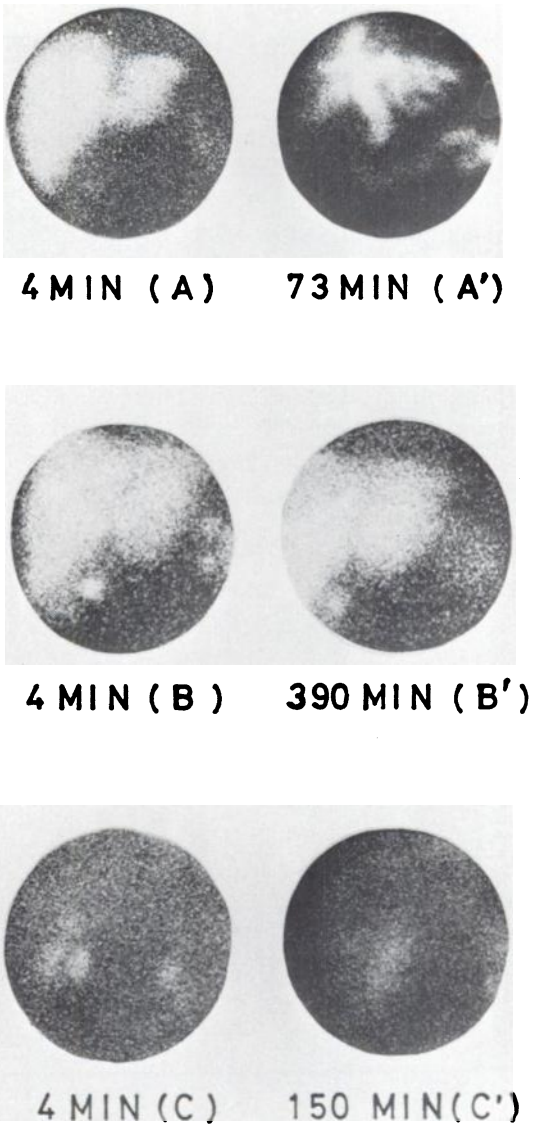

FIG. 3. Typical pictures obtained in different hepatobiliary diseases. 1. Incomplete common bile duct obstruction. (A) normal hepatic parenchyma and renal picture. (A′) absence of visualization of gallbladder, decreased and delayed passage of tracer into duodenum, distension of intrahepatic bile ducts. 2. Complete biliary obstruction. (B) normal liver picture and renal excretion. (B′) persistence of liver and kidney visualization contrasting with absence of gut visualization. 3. Complete obstruction due to a hepatocellular process. (C) kidney excretion, absence of hepatic visualization. (C′) persistence of kidney excretion, absence of hepatic and gut visualization.

The absence of any duodenal activity is typical of a complete obstruction (mechanical or hepatocellular in origin). In both situations, the kidneys remain visible during the test. The only criterion that may help to differentiate between an obstructive and a hepatocellular problem is the fact that in cases of a complete mechanical obstruction, the liver is clearly seen early, whereas in cases of complete hepatocellular obstruction, it is usually hard to rec-

ognize the liver. Accordingly, the differential diagnosis is almost impossible in cases of hepatocellular processes complicating a complete mechanical obstruction. This implies that when there is a complete biliary obstruction, the use of Tc-99m-diethyl-IDA never permits location of the site of the obstruction, since the main biliary ducts are not seen.

Technetium-99m-diethyl-IDA may also be used to assess the patency of a surgical biliary anastomosis. It allows the visualization of bile drainage along the Roux and y-anastomoses, and sometimes provides the demonstration of bile stasis in the anastomosed intestinal segment. This offers another type of clinical application of Tc-99m-diethyl-IDA that appears to be highly conducive to a better understanding of hepatobiliary disease.

FOOTNOTE

* Bladex, G.A. Laborat. Cochard, Brussels, Belgium.

ACKNOWLEDGMENTS

The cooperation of the Staff of the Department of Gastroenterology (Head: Prof. C. Dive), Cliniques Univ. St-Luc, B-1200 Brussels is gratefully acknowledged. The authors express their appreciation to N. De Bie, M. Godenir and F. Paquet for their excellent technical assistance.

REFERENCES

1. TAPLIN GV, MEREDITH OM, KADE H: The radioactive (I^{131}-tagged) rose bengal uptake-excretion test for liver function using external gamma-ray scintillation counting technique. *J Lab Clin Med* 45: 665–678, 1955

2. TONKIN AK, DELAND FH: Dihydrothioctic acid: A new polygonal cell imaging agent. *J Nucl Med* 15: 539, 1974 (Abst)

3. DEWANJEE MK, FLIEGEL C, TREVES S, et al: ^{99m}Tc-tetracyclines: Preparation and biological evaluation. *J Nucl Med* 15: 176–182, 1974

4. BAKER RJ, BELLEN JC, RONAI PM: Technetium-99m-pyridoxylideneglutamate: A new hepatobiliary radiopharmaceutical. I. Experimental aspects. *J Nucl Med* 16: 720–727, 1975

5. RONAI PM, BAKER RJ, BELLEN JC, et al: Technetium-99m-pyridoxylideneglutamate: A new hepatobiliary radiopharmaceutical. II. Clinical aspects. *J Nucl Med* 16: 728–737, 1975

6. LOBERG MD, COOPER M, HARVEY E, et al: Development of new radiopharmaceuticals based on N-substitution of iminodiacetic acid. *J Nucl Med* 17: 633–638, 1976

7. WISTOW BW, SUBRAMANIAN G, VAN HEERTUM RL, et al: An evaluation of ^{99m}Tc-labeled hepatobiliary agents. *J Nucl Med* 18: 455–461, 1977

8. RONAI PM: Hepatobiliary radiopharmaceuticals: Defining their clinical role will be a galling experience. *J Nucl Med* 18: 488–490, 1977

9. MATOLO NM, STADALNIK RC, WOLFMAN EF: Clinical evaluation of ^{99m}Tc-pyridoxylideneglutamate for heptobiliary scanning. *Am J Surg* 132: 716–719, 1976

10. STADALNIK RC, MATOLO NM, JANSHOLT AL, et al: Technetium-99m-pyridoxylideneglutamate (P.G.) cholescintigraphy. *Radiology* 121: 657–661, 1976

11. EIKMAN EA, CAMERON JL, COLMAN M, et al: Radioactive tracer techniques in the diagnosis of acute cholecystitis. *J Nucl Med* 14: 393, 1973 (Abst)

12. PAUWELS S, STEELS M, PIRET L, et al: Diethyl-IDA: A promising hepatobiliary radiopharmaceutical. *J Nucl Med* 18: 1141, 1977

SNM GREATER NEW YORK CHAPTER
FOURTH ANNUAL SCIENTIFIC MEETING

Nov. 10–12, 1978 **The Hilton Hotel of Philadelphia** **Philadelphia, Pa**

The 4th Annual Scientific Meeting of the Greater New York Chapter of the Society of Nuclear Medicine will be held Friday through Sunday, November 10–12, 1978 at the Hilton Hotel of Philadelphia in Philadelphia, Pennsylvania.

In addition to selected scientific papers and commercial exhibits, the meeting will feature survey papers, teaching sessions, and workshops conducted by invited faculty. There will be a business meeting on November 11 at 3:30 p.m.

Submitted papers should be sent no later than Sept. 11, 1978 to:

HARRY J. LESSIG, M.D., Program Chairman
Director, Department of Nuclear Medicine
Episcopal Hospital
Front and Lehigh Avenues
Philadelphia, PA 19125