
Evolution of Nuclear Hepatology as a Clinical Subspecialty

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Nuclear hepatology has grown into a subspecialty during the last 25 years by offering solutions to clinical challenges. The field which had its beginning primarily as liver morphology imaging with radiocolloid has switched its role to imaging of physiology with ^{99m}Tc -HIDA agents. This single agent enables the study of the entire hepatobiliary tree by its unique ability to travel sequentially from the top to the bottom of the tree. The reciprocal relation between the gallbladder and the sphincter of Oddi function is studied with the use of morphine or cholecystokinin. Radiolabeled RBC and WBCs aid in the detection of the vascular abnormalities and infection, respectively. Gallium-67 and ^{111}In monoclonal antibodies or peptides provide differentiation of malignant from nonmalignant lesions. The use of cell- and function-specific agents that provide non-invasive and quantitative information for patient management will probably help nuclear hepatology grow even more.

Nuclear hepatology was just emerging as a new specialty when the Technologist Section of the Society of Nuclear Medicine was founded 25 years ago. When the *JNMT* was introduced in 1973, radiocolloid scanning of the liver and spleen with the rectilinear scanner was very popular and unchallenged by any of the other competing imaging modalities. Single-head rectilinear scanners and radiocolloid were the work horses. Dual-head rectilinear scanners were for large institutions, and very few cared for computers. Rose bengal ^{131}I testing was of great theoretical excitement but the clinical studies were rarely done. Technetium-99m-sulfur colloid was replacing ^{198}Au colloid. X-ray film or Polaroid (Santa Ana, CA) recording was the most common practice and color scanning belonged to the few elite institutions endowed with rich research projects. Nuclear medicine technologists had to know the focal length of the collimator, the scan speed and the dot intensity. Dual- and triple-head gamma cameras were nonexistent.

On the occasion of the 25th anniversary celebration of the Technologist Section, radiocolloid imaging of the liver and spleen is almost history. Cassen's first rectilinear scanner has found a noble place in the Smithsonian Institute. Yet, nuclear hepatology studies today are one of the most exciting imaging tests, combining the uniqueness of delineating the entire hepatobiliary morphology with the use of a single ^{99m}Tc -labeled agent, enabling testing of the physiological function with a high degree of precision and accuracy. Various pharmacological interventions have come to clinical use. Dual- and triple-head cameras are now the workhorses. For the silver anniversary, we would like to summarize our glorious past, and look forward to the future. We can prepare to meet the coming challenges with a thorough understanding of the physiological principals being tested during various pharmacological interventions.

Nuclear hepatology was conceived in the late 1940s with the introduction of radiolabeled agents whose clearance from blood was used as a measure of liver blood flow (1) and the birth coincided with the introduction of ^{198}Au radiocolloid imaging using an automated rectilinear scanner introduced by Cassen et al. (2). The field developed with the introduction by Taplin et al. (Fig. 1) of liver function test using ^{131}I rose bengal (3). Radiocolloid imaging enabled delineation of the liver morphology and the diseases were diagnosed using the parameters that changed the morphology. The annual number of radiocolloid liver images performed over the past 25 years at a large Veterans Affairs Medical Center, are shown in Figure 2A. The dramatic decline in radiocolloid liver imaging is a reflection of the effects of ultrasound and CT, both of which have now essentially replaced radiocolloid imaging of the liver. Today, radiocolloid imaging of the liver and spleen is performed occasionally to clarify an abnormality that has been seen with the other imaging procedures. So there is still some need to know the principle behind radiocolloid imaging.

PHAGOCYTOSIS BY KUPFFER CELLS

In 1884, Metchnikoff (4) observed the process of ingestion of microorganisms by polymorphonuclear leukocytes and by the cells lining the hepatic sinusoids. Kupffer described in detail the nature of these special cells (Fig. 3) in the hepatic sinusoids which today bear his name (5). After intravenous

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FIGURE 1. Gerbail T. Krishnamurthy (left) with the nuclear hepatology pioneers, George V. Tiplin (center) and Benedict Cassen (right), during the 1971 Society of Nuclear Medicine annual meeting in Los Angeles.

injection, ^{198}Au or $^{99\text{m}}\text{Tc}$ -sulfur colloid particles circulate in blood coated by opsonic proteins. When these opsonin-coated radiocolloids enter the liver, spleen and the bone marrow and come in contact with a Kupffer cell or a reticuloendothelial (RE) system cell, they initiate the process of phagocytosis. The cytoplasm of the stimulated Kupffer cell or the RE cell flows around the radiocolloid particle through an extension of the plasma membrane, or pseudopod. Pseudopods from both sides, surround, ingest and incorporate the particle into the cytosol, forming a phagosome, usually within 30 min (6,7).

LIVER FUNCTION IMAGING WITH TECHNETIUM-99M-HIDA

Several $^{99\text{m}}\text{Tc}$ -labeled hepatobiliary agents, including pyridoxylidene glutamate, were introduced as a replacement for ^{131}I rose bengal (8). None had as much of an impact as the $^{99\text{m}}\text{Tc}$ -HIDA agents. Introduction of $^{99\text{m}}\text{Tc}$ -labeled hepatic-iminodiacetic acid (HIDA) agents in 1976 gave a totally new direction to the development of nuclear hepatology (9). Because ultrasound and CT were already replacing liver radiocolloid imaging, the introduction of the first $^{99\text{m}}\text{Tc}$ -HIDA agent was not only timely, but it also met the clinical need for functional imaging to supplement the excellent morphology obtained with ultrasound and CT. The availability of the $^{99\text{m}}\text{Tc}$ -HIDA agent in a kit form at low cost made functional imaging a practical procedure even in a remote rural hospital. Technetium-99m-HIDA agents made it possible to image the entire hepatobiliary system with a single agent (10). The number of $^{99\text{m}}\text{Tc}$ -HIDA studies is increasing even in small community hospitals, and soon is likely to replace the number of radiocolloid studies of the 1970s and early 80s (Fig. 2B).

HEPATOBIILIARY TREE

The hepatobiliary system is very appropriately described as a hepatobiliary tree (Fig. 4). The leaves and the stalk of a tree

represent, respectively, the hepatocytes and bile canaliculi. The minor and major branches of the tree represent the small, segmental and large, lobar ducts, respectively. The common bile duct (CBD) and the gallbladder are akin to the trunk and a single large fruit of a tree. The root of the tree represents the sphincter of Oddi.

When a physician encounters a patient with a liver problem, he must know, for appropriate therapy, whether the problem relates to the leaves or the stalk (medical therapy) or to the branches, trunk or the fruit (surgical therapy), or to the root (medical or surgical therapy). Physical examination and biochemical tests provide some measure of the severity of the disease, but will not locate the exact site of the problem. Ultrasound and CT provide some indication of location of the disease when it involves the trunk and major branches, when the disease is relatively advanced. Both ultrasound and CT, which are excellent for detecting gallstones and space-occupying liver lesions, have a limited role in detecting diseases of the leaves (hepatitis) and stalk (cholangitis), unless they are very severe. Both CT and ultrasound fail to detect the early functional root (sphincter of Oddi) problems. Technetium-99m-HIDA agents are unique in their ability to detect, localize and quantitate the severity of the hepatobiliary disease, all the way from the leaves to the root level, with their ability to travel sequentially (Fig. 3) through the tree delineating the entire biliary system with one single agent (10).

KINETICS OF TECHNETIUM-99M-HIDA

The transit of $^{99\text{m}}\text{Tc}$ -HIDA after an intravenous injection can be divided into eight distinct phases (10,11):

1. Transport in blood, bound to serum albumin, forming an albumin- $^{99\text{m}}\text{Tc}$ -HIDA complex;
2. The albumin- $^{99\text{m}}\text{Tc}$ -HIDA complex dissociates in the space of Disse, very close to the organic anion receptor site;

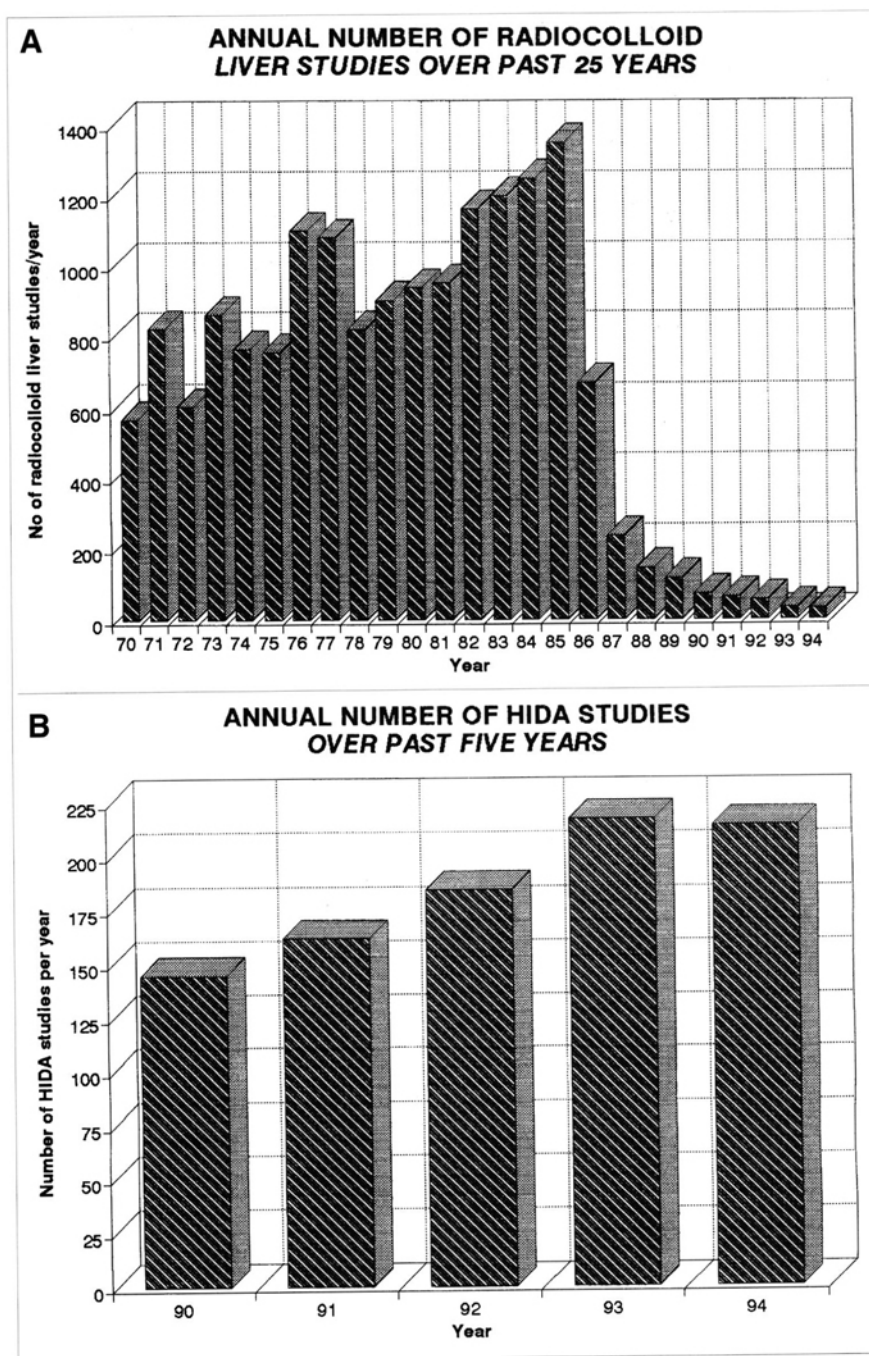


FIGURE 2. (A) The effect of ultrasound and CT on the annual number of radiocolloid liver studies at a large VA Medical Center. Note the rapid decline since 1985. In (B) the number of ^{99m}Tc -HIDA studies in a small community hospital (Tuality Community Hospital, Hillsboro, Oregon) has turned around and is gradually increasing in recent years. (Figure 2A courtesy of William H. Bland.)

3. Uptake of the released ^{99m}Tc -HIDA by the organic anion receptor, situated along the basolateral surface of the hepatocyte, by a process called receptor mediated endocytosis or RME (12,13);
4. Transport through the hepatocyte;
5. Secretion into bile canaliculi in the native form;
6. Flow through the bile ducts;
7. Entry into the gallbladder; and
8. Final discharge into the duodenum.

All of the above functions are carried out in an orderly and sequential fashion.

PATIENT PREPARATION

Proper patient preparation, which is not a major concern for a radiocolloid scan, is very critical for a ^{99m}Tc -HIDA study. Patients are prepared in a way that maximizes hepatic bile entry into the gallbladder under physiologic conditions (Fig. 5). Two factors that greatly influence bile entry into the gallbladder are concentration function of the gallbladder and the tone of the sphincter of Oddi.

Concentration Function

During fasting, the liver continuously secretes approximately 600–800 ml of bile per day (0.4–0.5 ml per min), of which 50%

TRANSPORT OF Tc - 99m HIDA THROUGH THE LIVER

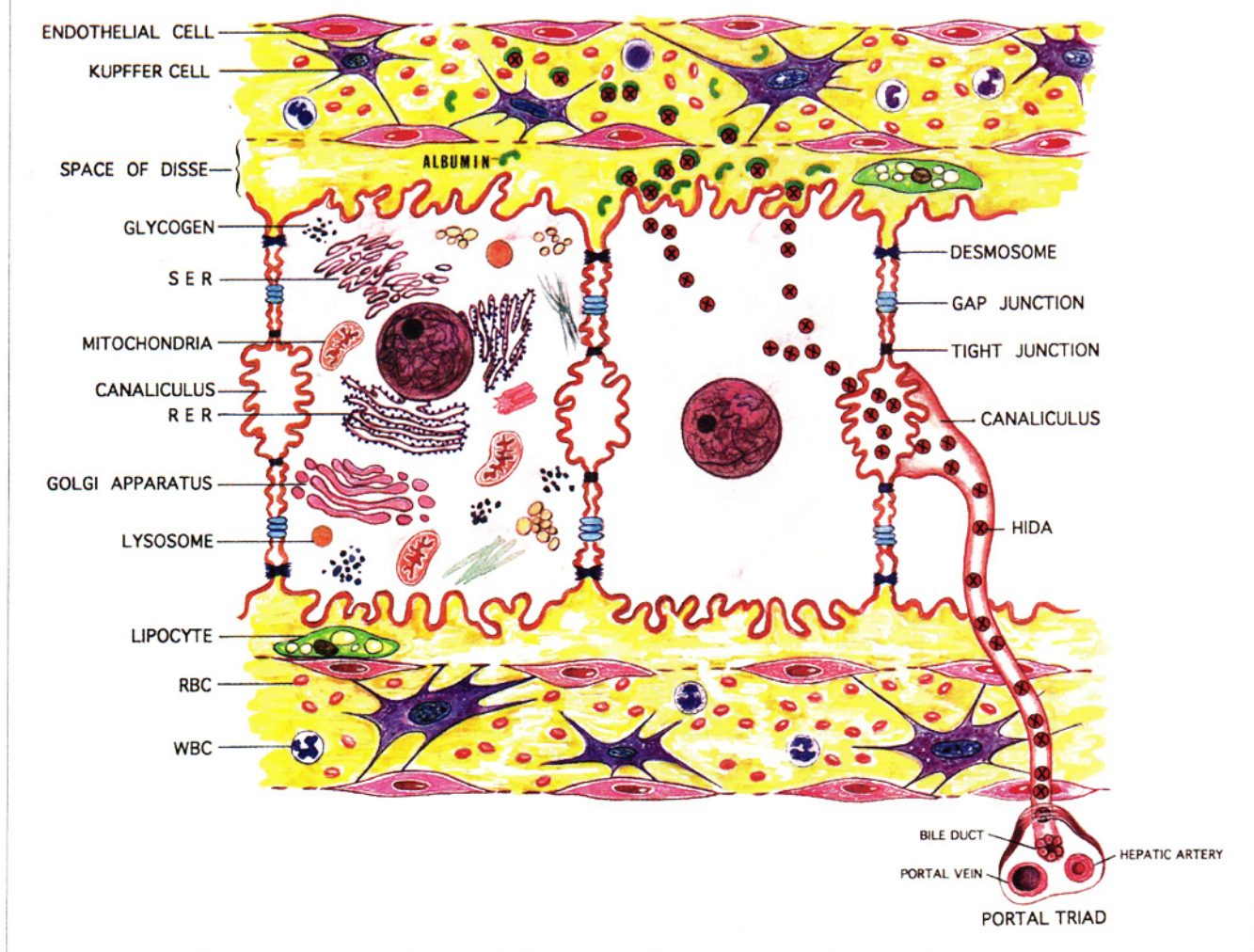


FIGURE 3. Transit of ^{99m}Tc -HIDA through the liver. Note albumin- ^{99m}Tc -HIDA dissociation in the space of Disse near the basolateral border of the hepatocyte. Only ^{99m}Tc -HIDA enters the hepatocyte by receptor mediated endocytosis. After intrahepatocyte transit, ^{99m}Tc -HIDA is secreted into bile canaliculi and later delineates the entire biliary tree. Kupffer cells in the endothelial space concentrate radiocolloid. Radiolabeled RBCs and WBCs circulate in the vascular space but do not enter the space of Disse.

enters the gallbladder (0.2–0.3 ml per min), and the remaining 50% enters the duodenum directly (14,15). After overnight fasting, the gallbladder is already filled with bile to its maximum capacity of 50 cc. The question can be asked; how can an already filled gallbladder accommodate an additional 0.2 to 0.3 ml hepatic bile per minute? This is possible because the gallbladder wall epithelium removes water from bile in the gallbladder lumen, making room for fresh hepatic bile (Fig. 5). A volume of 10 ml of hepatic bile placed inside the rabbit gallbladder decreases to less than 2 ml at the end of 6 hr, while at the same time, the bile salt concentration increases six- to seven-fold. This process of selective removal of water where there is higher bile salt concentration, is termed concentration function of the gallbladder (16). The water is absorbed through the distended lateral intercellular spaces between the columnar epithelial cells of the gallbladder wall. These spaces are widely

opened during fasting when the serum cholecystokinin (CCK) levels are at their lowest level.

Tone of the Sphincter of Oddi

The second factor that influences hepatic bile entry into the gallbladder is the increase in tone of the sphincter of Oddi (Fig. 5). After an overnight fast, the mean basal pressure is 15 cm of water pressure in the sphincter of Oddi, 12 cm in the CBD, and 10 cm in the gallbladder (17). An increase in the sphincter pressure forces half of the hepatic bile to enter the gallbladder. As explained above, the gallbladder makes room for this fresh bile by continuously absorbing water through its wall. The sphincter of Oddi pressure and the amount of water absorption through the gallbladder wall reach their peak level after 4–12 hr of fasting. Overnight fasting thus prepares the gallbladder to receive hepatic bile by maximizing both factors

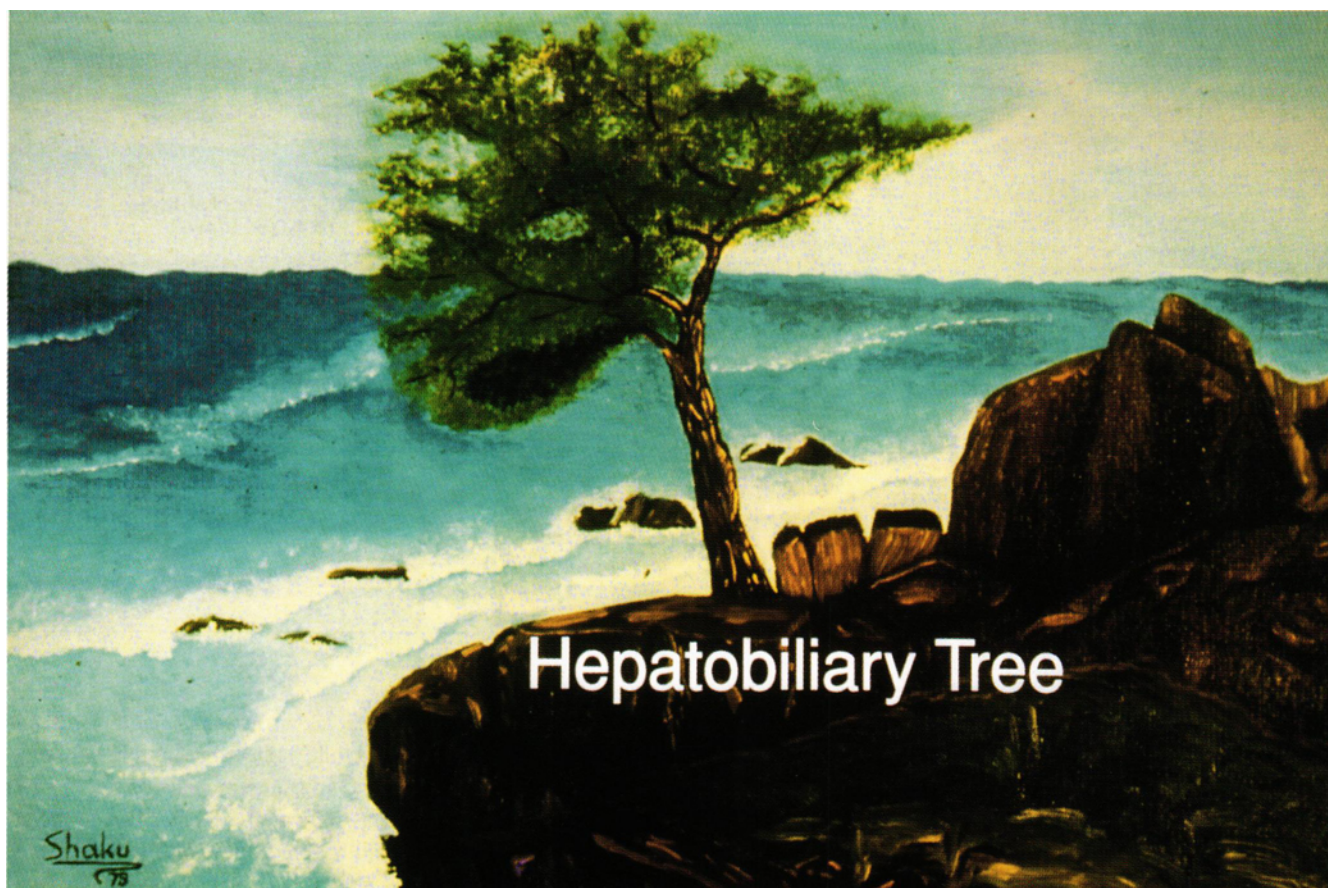


FIGURE 4. The hepatobiliary tree. The leaves and stalk represent the hepatocyte and the canaliculi, respectively. The minor and major branches of the tree represent the segmental and lobar ducts. The trunk and the fruit represent the common bile duct and the gallbladder, respectively. The root represents the sphincter of Oddi. (Original oil painting by Shakuntala Krishnamurthy.)

which promote bile entry into the gallbladder. Very low serum cholecystokinin levels during fasting also promotes an increase in sphincter tone, enabling bile entry into the gallbladder.

Gallbladder Pre-Emptying

In patients on parenteral nutrition or those who have fasted longer than 36–48 hr, gallbladder bile may reach hyperconcentration preventing any more absorption of water through the wall. This could result in nonentry of fresh hepatic bile and hence nonvisualization of gallbladder following ^{99m}Tc -HIDA injection (18). Under these circumstances, pre-emptying of the gallbladder is favored with the administration of cholecystokinin (Fig. 6). Following cholecystokinin, the gallbladder wall muscle contracts and the sphincter of Oddi relaxes, promoting gallbladder bile emptying. It may take as long as 60 min following CCK-8 injection for the sphincter of Oddi to regain its basal tone to force hepatic bile entry into the gallbladder. Therefore, one should ideally wait for at least 60 min after CCK injection before initiating a ^{99m}Tc -HIDA study to visualize the gallbladder (19). Even though the serum CCK level may fall below the basal level at the end of 12 min (20) after the cessation of CCK infusion, the sphincter seems to take a much longer time to regain its basal tone (19). This factor is important to consider whenever the CCK pre-emptying tech-

nique is employed prior to an HIDA study (Fig. 6). The need for CCK pre-emptying is not that critical these days because of the wide use of intravenous morphine in suspected acute cholecystitis.

DATA COLLECTION AND ANALYSIS

A large field-of-view gamma camera, fitted with a low-energy, parallel-hole, all-purpose collimator, is positioned over the right upper quadrant of the patient lying supine. The hepatobiliary study data collection should be ideally separated into the hepatic phase and the gallbladder phase. This is necessary because of the different natures of the physiologic parameters measured for the liver and the gallbladder functions.

Hepatic Phase Data Collection and Analysis

For patients with normal bilirubin, the usual dose of ^{99m}Tc -HIDA is 111–148 MBq (3–4 mCi). It does not matter if one chooses disofenin or mebrofenin when bilirubin is less than 5 mg%. However, in moderate to severe hepatocellular disease (bilirubin greater than 5 mg%) mebrofenin is much better because of high hepatic uptake in the presence of hyperbilirubinemia (14). The dose of ^{99m}Tc -HIDA should be adjusted

Mechanism of Bile Entry into the Gallbladder

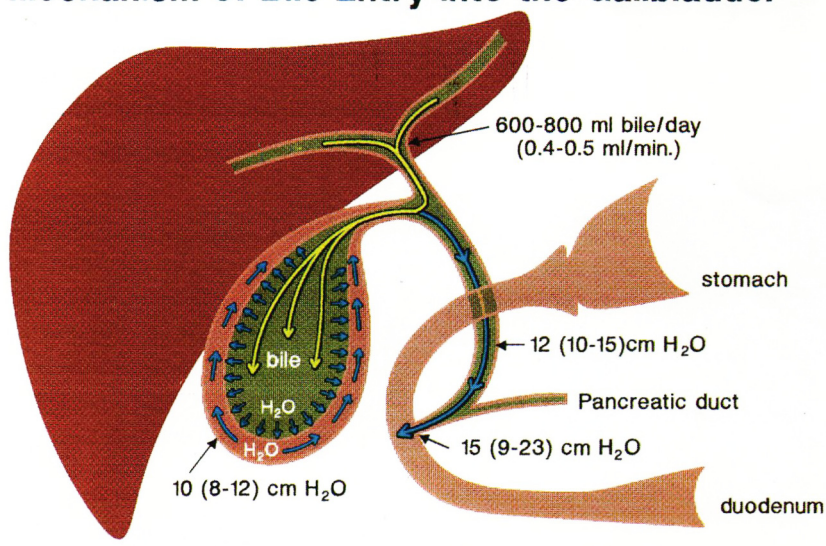


FIGURE 5. Mechanism of bile entry into the gallbladder. Increased pressure in the sphincter of Oddi (15 cm H₂O) and absorption of water through the gallbladder wall (arrows) facilitate hepatic bile entry into the gallbladder. Both of these mechanisms operate at their peak during fasting.

for the level of bilirubin; i.e., increase the dose as bilirubin level increases. A dose greater than 10 mCi is rarely needed. Hepatic phase data is collected at 1 frame/min for 60 min in $64 \times 64 \times 16$ -word mode matrix. The images can be reformatted later at 2–3 min per image. Two min per image is preferable for permanent film recording. Frames longer than 2–3 min per image result in loss of temporal resolution, as the identification of precise bile entry time into various structures would become inaccurate due to long image duration. Identification of first bile entry into duodenum versus CBD may be difficult if one uses longer than 2 min per image. Cine mode display of the original data on the computer screen will solve the temporal resolution problem.

For quantitative analysis, three regions of interest are chosen: the first over the upper right hepatic lobe; the second over the heart; and the third over the spleen. From these three regions of interest, the hepatic extraction fraction (HEF) and excretion half-time are calculated (21,22). The region of interest over the right hepatic lobe and the heart are used for calculation of hepatic extraction fraction using deconvolutional analysis. The liver and spleen ROIs are used for calculation of liver excretion half-time using the nonlinear least squares fit. The hepatic extraction fraction value facilitates separating primary hepatocyte disease from primary biliary disease in both adults and children (23,24).

Gallbladder Phase Data Collection

The gallbladder phase data collection begins at 61 min if the gallbladder is seen during the hepatic phase. The data are acquired on $64 \times 64 \times 16$ -word mode matrices at 1 frame per min for 30 min between 61 and 90 min postinjection. A magnification factor of 1.4 to 2 may be used after making sure that all of the gallbladder, common hepatic duct, right and left hepatic duct, the common bile duct and the duodenum are all in the field of view. The upper part of the liver may be

sacrificed to accommodate the clear details of the lower hepatobiliary tree. Occasionally, bile collection in the duodenal bulb may mimic a gallbladder in the latter part of the hepatic phase data collection. A glass of water will clear the duodenal bulb radioactivity and would have no effect on the gallbladder radioactivity.

CCK Infusion Versus Bolus Injection

Bolus injection of a large quantity of CCK-8 causes non-physiologic gallbladder emptying and should be avoided. Ideally, CCK-8 is infused through an infusion pump at a dose rate of 3.3 ng/kg/min for 3 min (10 ng/kg/3 min). CCK-8 infusion is begun at 5 min into the gallbladder phase, (at 65 min after the injection of ^{99m}Tc-HIDA). A longer duration of CCK-8 infusion may be used if desired. The normal gallbladder ejection fraction value of 35% or greater, however, was based on a 3-min infusion of 10 ng/kg CCK-8. This dose rate and duration should be maintained if one chooses to use a 35% or greater ejection fraction as the normal value. The variation in either duration or the dose, or both, of CCK-8 infusion is one of the most common technical errors made during the gallbladder phase study. This error is primarily attributed to information provided in the Kinevac package insert (Bristol Meyer Squibb, Princeton, NJ). The dose suggested in the package insert is for oral cholecystography and is too large for cholescintigraphy (25,26). The package insert suggests an initial dose of 0.02 ng/kg (20 ng/kg) or 0.04 μg/kg (40 ng/kg) infused over 30–60 sec. These doses are recommended for oral cholecystography, and for inducing bile and pancreatic enzyme secretions, are found to be nonphysiologic during cholescintigraphy, and cause abnormal gallbladder emptying and severe abdominal pain in many normal people (25,26). The package insert cautions that approximately 20% of patients may experience abdominal pain and discomfort which may not signify definite pathology.

Protocol for ^{99m}Tc -HIDA Study

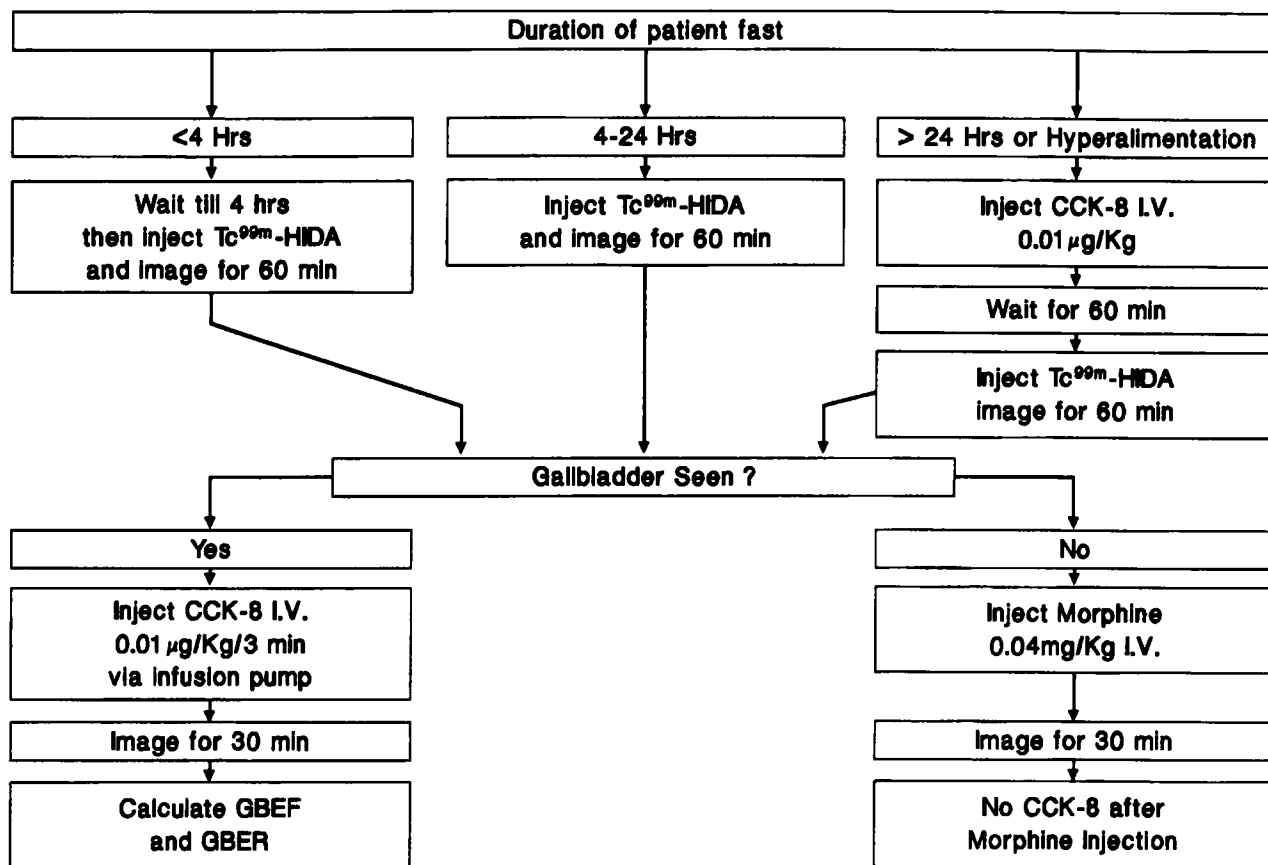


FIGURE 6. Patient protocol for a ^{99m}Tc -HIDA study. Ejection fraction is not measured when the gallbladder appears after the use of morphine, or the patient has taken opiates for the relief of pain.

A longer duration of CCK infusion may be used if desired. This problem of inappropriate dose and duration of infusion of CCK-8 is easily solved during cholescintigraphy simply by incorporating the correct dose and dose rate into the nuclear medicine procedure manual.

Use of Morphine

When the gallbladder is not seen during the 60-min hepatic phase and the clinical suspicion is one of acute cholecystitis, then morphine at a dose of 0.04 mg/kg is given intravenously (27). The gallbladder phase data collection for the 30 min remains the same (Fig. 6). Morphine causes immediate constriction of the sphincter of Oddi, and forces the hepatic bile to enter the gallbladder when the cystic duct is patent (28). The gallbladder is usually seen within 6–10 min after intravenous morphine, but on rare occasion, may be delayed beyond 15–20 min after morphine injection. When it is delayed, we have observed that it is usually due to prior CCK-8 administration given for gallbladder pre-emptying. CCK-8 stimulation and calculation of gallbladder ejection fraction becomes irrelevant once morphine is used because of its severe constrictive effect on the sphincter of Oddi (28).

Gallbladder Phase Data Analysis

The image that shows the gallbladder in its largest size is chosen to draw the ROI. Four ROIs are drawn using the images acquired between 60–90 min. An ROI is drawn over: (a) the gallbladder; (b) background, superior and lateral to the gallbladder; (c) the common hepatic duct (CHD) including the right and left hepatic duct; and (d) the CBD. Net gallbladder counts are obtained by subtracting the background. Because of only 30 min of data collection time, physical decay correction is not that critical. In the presence of distal CBD obstruction, part of the bile emptied from the gallbladder may reflux back into the common hepatic duct, right and left hepatic duct. In this circumstance bile may reenter in the gallbladder after cessation of CCK-8 infusion.

Calculation of Gallbladder Ejection Fraction

Introduction of the measurement of gallbladder ejection fraction EF by the count-based, nongeometric, nuclear technique in 1981, which replaced geometric methods, had a major impact on the clinical acceptance of quantitative nuclear hepatology (29). When CCK-8 is given at 5 min into the gallbladder phase data collection, the first five data points serve as the

Types of Post-CCK-8 Gallbladder Emptying Curves

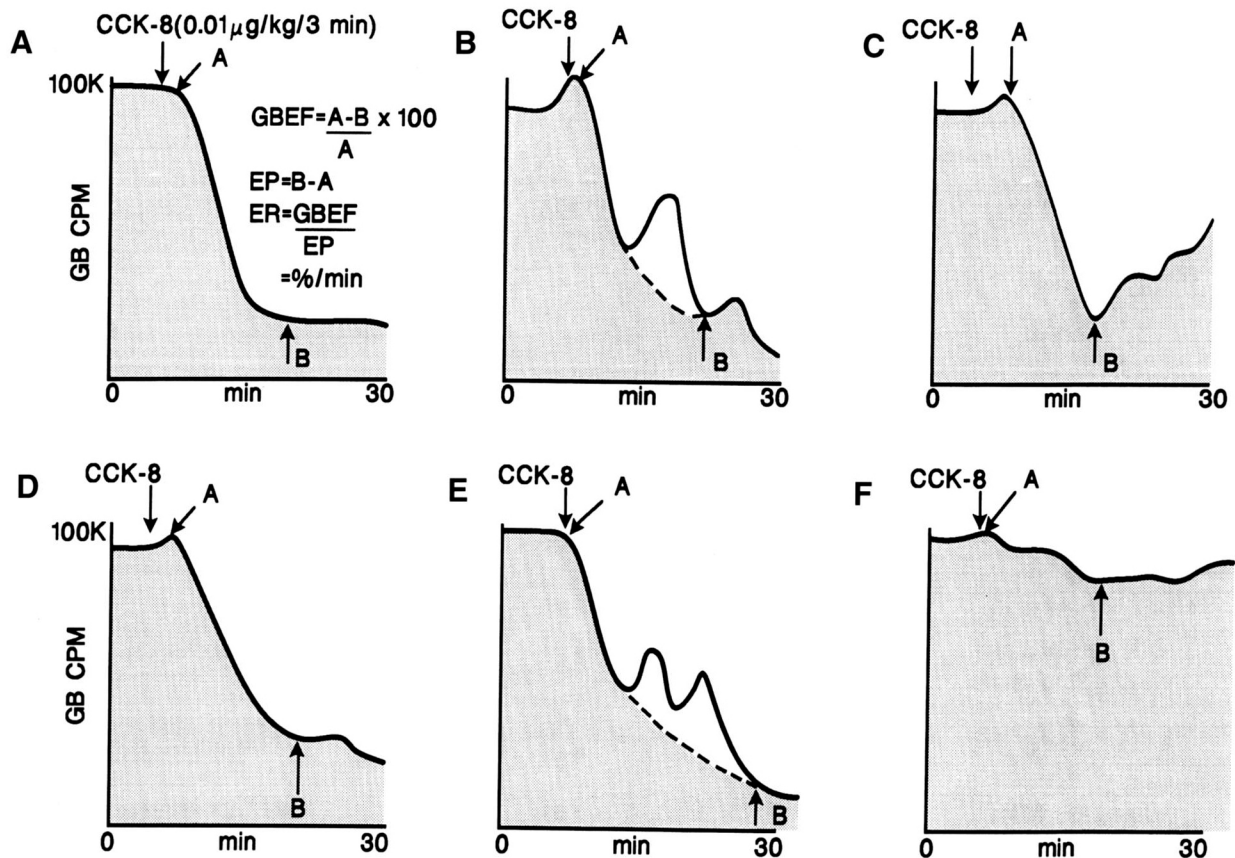


FIGURE 7. Calculation of post-CCK-8 ejection fraction and different types of gallbladder emptying curves. The counts at points A and B are used to calculate gallbladderEF and the time between A and B is the ejection period (EP). Ejection rate (ER) is obtained by dividing % gallbladderEF by EP.

baseline counts analogous to the end diastolic frame of a MUGA study (Fig. 7A). The gallbladder begins to empty within 2–3 min of CCK-8 infusion and empties for 8–12 min. Sometimes the gallbladder counts may actually rise after CCK-8 infusion before emptying begins (Fig. 7B). In such cases, the peak counts after CCK-8 are chosen to calculate the gallbladder ejection fraction. The first least count after emptying is used to represent the end of gallbladder emptying (Fig. 7A). The interval between the peak (beginning of emptying) and the first least count (end of emptying) represent the ejection period which normally ranges from 8 to 12 min for a 3-min CCK-8 infusion. Often, one may see a gradual slow downslope following rapid downslope when the least count may be seen at the end of 30 min (90 min after $^{99m}\text{Tc-HIDA}$). In such cases where the rapid emptying ends, this first nadir should be chosen to represent the end of gallbladder emptying (Fig. 7D). Occasionally, one may see immediate refilling of the gallbladder especially in the case of distal CBD obstruction (Fig. 7C). Various shapes and sizes of the area under the gallbladder curve that one may encounter are shown in Figure 6. When one (Fig. 7B) or two peaks (Fig. 7E) are found in the middle of the gallbladder curve, this usually is due to superimposition of the

duodenal bulb or the common bile duct radioactivity onto the gallbladder region of interest. These peaks usually disappear before the end of the gallbladder ejection and would not alter the calculation of gallbladder ejection fraction, but would have an effect on ejection period and the ejection rate.

CCK-8 STIMULATION AS A ROUTINE

When a clinician encounters a patient with biliary pain, the nuclear medicine physician is in a unique position to identify the origin of the biliary pain. In a clinical setting of acute cholecystitis, gallbladder nonvisualization with morphine confirms the diagnosis of acute cholecystitis (27). Once the diagnosis of acute cholecystitis is excluded by demonstrating the patency of the cystic duct (by visualization of the gallbladder) the nuclear physician should try to find the other causes of biliary pain. The changes in morphology of the biliary tree provide a clue as to the possible location of the biliary pain, if a ductal obstruction is confined to the CBD, CHD or right and left hepatic ducts (10). Low gallbladder ejection fraction provides a measure of the degree of biliary obstruction (30). For a 3-min infusion of 0.01 $\mu\text{g}/\text{kg}$ CCK-8 (10 $\text{ng}/\text{kg}/3$ min), the

normal ejection fraction is greater than 35% with an ejection rate of greater than 3.5% per minute.

How to Decide When to Use CCK-8 or Morphine

Near the end of the hepatic phase data collection at 60 min, the decision is made to administer CCK-8 or morphine. If the gallbladder is seen during the hepatic phase, then CCK-8 is chosen for the gallbladder phase. If the gallbladder is not seen at the end of the hepatic phase, and the clinical suspicion is one of acute cholecystitis, then morphine is chosen for the gallbladder phase. It is better to wait 60 min before giving morphine. Even though a majority of the normal gallbladders are seen within 30 min, about 5–10% of the normal gallbladders appear between 50 and 60 min after ^{99m}Tc -HIDA administration (15). If chronic cholecystitis is a clinical consideration, then it is better to wait 3–4 hr for the gallbladder to fill on its own accord because morphine, if used at 60 min, will reduce the gallbladder EF. Delayed appearance (beyond 60 min) is a diagnostic feature of chronic cholecystitis where the absorption of water through the gallbladder wall is reduced to make room for the fresh radioactive hepatic bile. Low gallbladder EF is a feature of chronic acalculous cholecystitis (31).

Is There a Contraindication for CCK-8 Administration?

Cholecystokinin is a natural hormone released endogenously in response to a meal. The peak serum CCK levels of 200 pg/ml are reached by 25 min post-meal (32). CCK-8 is a much smaller molecule and probably distributes in the extracellular water space of 20 liters reaching a peak level of 35 pg/ml following a 10 ng/kg/3 min infusion. These levels of CCK-8 in the serum are much lower than the peak endogenous CCK levels reached after a fatty meal. One clear contraindication for CCK-8 use is intestinal obstruction. Another relative contraindication is acute pancreatitis. Acute cholecystitis often coexists with acute pancreatitis resulting in gallbladder nonvisualization (33,34).

How Long to Infuse CCK-8?

The gallbladder ejection fraction can be controlled to any desired level simply by controlling the duration of infusion of cholecystokinin. A 3-min infusion is short and does not tie up the computer or the gamma camera in a busy nuclear medicine department. One recent report claims that a 30-min CCK-8 infusion is more advantageous than 3-min infusion (26). The short serum CCK half-life of 2.8 min and the reduction in the number of CCK receptors in the gallbladder smooth muscle in chronic cholecystitis (32) tempts one to speculate that the same reduced number of CCK-8 receptors are reused again and again following a meal, or a longer duration of CCK-8 infusion, or sequential (3–4) doses separated by 20 min between infusions (35). This should then suggest that the implication of gallbladder EF reduction would be the same whether one uses a 3-min infusion or a 30-min infusion. A 3-min infusion is short, simple and well-tolerated by the patient. At the Society of Nuclear Medicine's 42nd annual meeting in June 1995, in Minneapolis, more than 90% of about 800 nuclear

TABLE 1
Indications for Technetium-99m-HIDA Study

1. Acute cholecystitis
2. Biliary dyskinesia
3. Biliary obstruction
4. Intrahepatic cholestasis
5. CBD dilatation
6. Bile leak
7. Primary sclerotic cholecystitis
8. Primary biliary cirrhosis
9. Post-surgical sequelae
10. Hemangioma
11. Pre- and post-liver transplant sequelae
12. Pediatric application
13. Congenital biliary disorder
14. Miscellaneous related to bile flow abnormalities

medicine physicians and technologists in attendance at a hepatobiliary seminar indicated they preferred using a 3-min CCK-8 infusion.

ACUTE CHOLECYSTITIS

The greatest impact of the introduction of ^{99m}Tc -HIDA agents was felt immediately in the diagnosis of acute cholecystitis whose salient pathologic feature is shown to be obstruction of the cystic duct (36). The obstruction is usually due to hemorrhagic necrosis, infiltration with leucocytes, and edema of the wall of the gallbladder and the cystic duct (37). Early results with ^{99m}Tc -HIDA showed a sensitivity of 95% and specificity of 99% with an overall accuracy of 99% (38). A recent meta-analysis comprising 2,466 patients from 22 publications showed a sensitivity of 97% and a specificity of 90% for ^{99m}Tc -HIDA study and a sensitivity of 94% and a specificity of 78% for ultrasound in the detection of acute cholecystitis (39). Indium-111-labeled WBC imaging has similar sensitivity and specificity for the detection of acute cholecystitis (40) and may serve as an alternative test for detecting acute cholecystitis, especially in those patients on parenteral nutrition or those with inter-current infection, where a routine HIDA study without morphine has a high false positive rate. Prior to 1984, the diagnosis of acute cholecystitis took 3–4 hr and sometimes as long as 24 hr. Now with the use of morphine at 60 min, the diagnostic time interval has been reduced to 90 min (27). Intravenous morphine (0.04 mg/kg) constricts the sphincter of Oddi immediately, forcing the hepatic bile to enter the gallbladder when the cystic duct is patent. Nonvisualization of the gallbladder with morphine is a very reliable sign of acute cholecystitis. Postmorphine pressure rise is not high enough to force open an obstructed cystic duct of acute cholecystitis. Various types of hepatobiliary diseases that can be diagnosed with the use of ^{99m}Tc -HIDA, in addition to acute cholecystitis, are listed in Table 1.

OTHER RADIOLABELED AGENTS FOR DIFFERENTIAL DIAGNOSIS

Blood-pool imaging with ^{99m}Tc -RBCs is a highly reliable test for the detection of hepatic hemangioma (41). Indium-111 or

^{99m}Tc -HMPAO-labeled WBCs or ^{67}Ga -citrate are used for detection of hepatic abscess (42). Lymphoma and hepatoma are differentiated from other benign hepatic lesions by imaging with ^{67}Ga -citrate (43). Because of the capability to image the hepatocytes with ^{99m}Tc -HIDA, the Kupffer cells with ^{99m}Tc -sulfur colloid, the vascular compartment with radiolabeled RBCs, infection with radiolabeled WBCs and malignant tumors with ^{67}Ga , a wide choice of many ideal imaging agents now make nuclear hepatology able to determine specific diagnosis using cell-specific and function-specific agents. This message has to be carried to the primary care physicians, who are now in a position to diagnose liver diseases using noninvasive and quantitative tests and may be able to avoid often more expensive invasive diagnostic tests. This should enable nuclear medicine to recapture some of the liver studies lost to CT and ultrasound (Fig. 2). This will happen sooner if we make our tests not only noninvasive and quantitative, but also disease-specific.

THE ROLE OF THE NUCLEAR MEDICINE TECHNOLOGIST

The nuclear medicine technologist plays an important role in obtaining quantification of hepatobiliary function as an integral part of imaging (21). It has been well-documented that functional parameters of hepatic extraction fraction, excretion half-life and gallbladder EF are all highly reproducible within and between technologists, and within and between different hospitals (44). A high level of accuracy is possible because of the high count rate obtained during a hepatobiliary imaging study. The liver is the largest organ in the body and takes up to 98% of the injected dose of ^{99m}Tc -HIDA. None of the other organs in the body show this high level of radiotracer uptake following intravenous injection (10). It is relatively simple to make hepatobiliary quantification routine in all departments, both for the hepatic phase (by measuring the hepatic extraction and excretion half-life) and the gallbladder phase (by measuring gallbladder ejection fraction and ejection rate). Such an action will result in turning into reality the claim that most nuclear medicine tests are quantitative. In the fulfillment of this claim, and to harness the full potential of nuclear hepatology (45), technologists play an important role. The next 25 years of nuclear medicine accomplishments should be just as exciting, if not more so, as the past 25 years.

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