# Quantification of Hepatobiliary Function as an Integral Part of Imaging with Technetium-99m-Mebrofenin in Health and Disease

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A study was undertaken to check the feasibility of measuring the hepatic extraction fraction (HEF) and excretion T-1/2 values as an integral part of hepatobiliary imaging with technetium-99m-mebrofenin in health and disease. In 18 controls subjects, the HEF was 100% and the T-1/2 excretion mean ± s.e. value was 15.23 ± 1.4 min. The mean appearance times of the common bile duct (CBD), gallbladder (GB), and small intestine were 15.8 ± 1.52, 20.2 ± 2.7, and 23.8 ± 3.08 min, respectively. Rising serum bilirubin in patients decreased HEF and increased T-1/2 excretion value resulting in delayed appearance of CBD, GB, and small intestine. In control subjects and patients with bilirubin <5 mg%, T-1/2 excretion values at 30, 40, and 50 min were similar to those values calculated using the entire 60 min of data, suggesting that the hepatic phase study time could be reduced to 30–40 min and still use the normal reference values established for 60 min. In patients with bilirubin >5 mg%, the data collection duration should be continued for 60 min.

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After a thorough clinical and biochemical profile analysis, imaging procedures are often used as part of the complete work-up for the diagnosis of various hepatobiliary diseases. Over the years, radiocolloid scintigraphy, ultrasound, computed tomography, and/or magnetic resonance imaging have been used as primary imaging modalities. Because computed tomography and magnetic resonance imaging provide far superior morphologic details of the liver, the role of scintigraphy has now shifted more towards the study of hepatobiliary function using technetium-99m- ($^{99m}$Tc) IDA (iminodiacetic acid) agents. The general trend in nuclear medicine has been towards more quantification of function as an integral part of organ imaging (*1*).

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The introduction of $^{99m}$Tc-labeled IDA analogs in 1976 has had a major impact on the diagnostic work-up of hepatobiliary diseases because of their dual capacity to provide morphologic and physiologic information simultaneously (*2*). Specific diagnosis of various hepatobiliary diseases are made by combining morphologic alterations seen on scintigraphy with the physiologic parameters measured quantitatively (*3*). Two physiologic parameters that have shown the greatest value in discriminating hepatocyte from biliary diseases are: (a) hepatic extraction fraction (HEF) measured by deconvolution analysis and (b) excretion T-1/2 values measured by non-linear least-square's techniques (*4*).

The blockade of hepatocyte uptake by bilirubin is well known, but it is not known what effect high bilirubin has on the secretion of $^{99m}$Tc-IDA by the hepatocyte into hepatic bile, a function that has a critical role in the delineation of biliary morphology during scintigraphy. Of all the $^{99m}$Tc-IDA agents, mebrofenin has shown the most ideal biochemical characteristics in both in vivo and in vitro studies (*5,6*).

The primary objectives of this project were to:

1. Establish normal HEF and T-1/2 excretion values for $^{99m}$Tc-mebrofenin.
2. Test what affect rising serum bilirubin has on HEF and T-1/2 excretion value in patients and how much effect the altered liver function will have on the delineation of biliary morphology.
3. Test whether $^{99m}$Tc-mebrofenin clears from the liver rapidly enough to permit reduction in the duration of imaging to less than 60 min without affecting reference normal values based on 60-min data.

## MATERIALS AND METHODS

Eighteen adult healthy volunteers (controls) and 24 patients were studied. The control subjects (12 males and 6 females) ranged in age from 23 to 71 yr with a mean age of 57 yr (Table 1). They had no previous history of gastrointestinal or liver disease and presently were not on any medication that would influence hepatobiliary function. They had normal

**TABLE 1**
Hepatic Extraction Fraction and Excretion T-½ Values at Various Time Intervals and the Time of First Appearance of the CBD, Gallbladder, and Small Intestine in 18 Normal Subjects (Controls)

| | Appearance (min) | | | | 60 min | 50 min | 40 min | 30 min |
|---|---|---|---|---|---|---|---|---|
| Patient | CBD | GB | INT | HEF | T-½ | T-½ | T-½ | T-½ |
| 1 | 8 | 12 | 14 | 100 | 10.94 | 10.94 | 10.94 | 12.36 |
| 2 | 10 | 20 | 12 | 100 | 12.16 | 12.16 | 11.56 | 10.32 |
| 3 | 14 | 12 | 16 | 100 | 12.42 | 10.94 | 12.08 | 13.75 |
| 4 | 12 | 14 | 20 | 100 | 11.33 | 11.41 | 11.90 | 13.31 |
| 5 | 10 | 12 | 18 | 100 | 9.81 | 9.81 | 10.29 | 10.54 |
| 6 | 12 | 10 | 52 | 100 | 31.81 | 29.75 | 26.81 | 20.90 |
| 7 | 20 | 14 | NS | 100 | 17.05 | 16.62 | 16.80 | 19.22 |
| 8 | 18 | 44 | 22 | 100 | 17.94 | 17.94 | 20.24 | 21.60 |
| 9 | 12 | 24 | 12 | 100 | 9.80 | 9.80 | 9.74 | 11.23 |
| 10 | 14 | 12 | 26 | 100 | 9.92 | 9.92 | 10.28 | 9.24 |
| 11 | 10 | 16 | 12 | 100 | 8.50 | 8.50 | 8.60 | 10.90 |
| 12 | 12 | 34 | 16 | 100 | 15.10 | 14.70 | 13.50 | 13.00 |
| 13 | 16 | 12 | 34 | 100 | 12.80 | 10.40 | 13.50 | 15.50 |
| 14 | 24 | 16 | NS | 100 | 25.10 | 25.80 | 26.20 | 23.40 |
| 15 | 20 | 18 | 42 | 100 | 15.30 | 15.10 | 12.10 | 12.20 |
| 16 | 34 | 14 | 42 | 100 | 15.60 | 15.70 | 16.60 | 18.30 |
| 17 | 16 | 34 | 20 | 100 | 20.00 | 19.10 | 18.00 | 15.40 |
| 18 | 22 | 46 | 22 | 100 | 18.60 | 18.40 | 19.20 | 22.20 |
| n | 18 | 18 | 16 | 18 | 18 | 18 | 18 | 18 |
| mean | 15.8 | 20.2 | 23.8 | — | 15.23 | 14.83 | 14.91 | 15.19 |
| s.d. | 6.43 | 11.4 | 12.3 | — | 5.97 | 5.80 | 5.41 | 4.59 |
| s.e. | 1.52 | 2.70 | 3.08 | — | 1.41 | 1.37 | 1.27 | 1.08 |
| p | | | | | | 0.051 | 0.431 | 0.959 |
| Correlation coefficient r | | | | | | 0.991 | 0.960 | 0.796 |

NS = not seen; CBD = common bile duct; GB = gallbladder, INT = intestine; and HEF = hepatic extraction fraction.

values for serum bilirubin, alkaline phosphatase, gamma glutamyl transferase, lactic dehydrogenase, albumin, and total protein. On ultrasound examination, they had normal architecture of the hepatobiliary system and normal caliber of the intra- and extrahepatic ducts. There were no gallstones inside the gallbladder. The subjects gave informed consent on a form approved by the hospital's human use committee.

Twenty-four patients were selected from the list of patients referred to nuclear medicine for hepatobiliary imaging between October 1987 and November 1989. Patients whose computer data were not available for analysis were excluded from the study. The patients were divided into two groups based on their serum bilirubin level. Serum bilirubin level (as explained later) had a major impact on the rapidity of excretion of mebrofenin into bile and a 5 mg% cut off value clearly separated the patients into two groups. Group I consisted of 14 patients (13 males, 1 female) with serum bilirubin value <5 mg% (Table 2). They ranged in age from 37 to 74 yr with a mean age of 57 yr. Group II consisted of 10 patients (9 males, 1 female) with serum bilirubin levels >5 mg% (Table 3). They ranged in age from 34 to 74 yr with a mean age of 60 yr.

## Scintigraphy

After 4–6 hr of fasting, the subjects were studied while lying supine under a large field of view gamma camera fitted with a low-energy high-resolution parallel-hole collimator. The detector was positioned over the upper abdomen to include all of the liver, spleen, heart, and upper small intestine. The dose of $^{99m}$Tc-mebrofenin (Choletec, Squibb & Sons, Princeton, NJ) was adjusted based on serum bilirubin level. All normal subjects and patients with a normal bilirubin level were given 2–3 mCi; patients with a bilirubin between 1 and 5 mg% received 3–5 mCi, and patients with a bilirubin >5 mg% received 5–10 mCi of $^{99m}$Tc-mebrofenin. Computer data acquisition was started simultaneously at the time of injection. Digital images were obtained at 1 frame/minute for 60 min and recorded in a 64 × 64 × 16 matrix and 2-min images were recorded on 8 × 10 X-ray film (Fig. 1). At the end of 60 min, right lateral and posterior images (2-min each) of the liver were obtained for better separation of biliary structures from overlying or underlying small intestine or kidney, respectively. The patients whose gallbladder did not visualize by 60 min had additional images at 2–5 or 22–24 hr.

## Data Analysis

*Visual Interpretation of Hepatobiliary Images.* The images were assessed from both 8 × 10 X-ray films and computer cine projection for the pattern of hepatic uptake, the time of first appearance of the common bile duct (CBD), gallbladder, and the intestine. The flow of bile from the peripheral liver through the bile ducts was analyzed for any evidence of bile pooling in an intra- or extrahepatic duct. Images obtained between 0–10 min were used to note the position, size, shape

**TABLE 2**
Hepatic Extraction Fraction and Excretion T-½ Values at Various Time Intervals and the Time of First Appearance of the CBD, Gallbladder, and Intestine in 14 Group I Patients (Bilirubin ≤ 5.0 mg%)

| | Appearance (min) | | | | | 60 min | 50 min | 40 min | 30 min |
|---|---|---|---|---|---|---|---|---|---|
| Patient | BILI | GB | CBD | INT | HEF | T-½ | T-½ | T-½ | T-½ |
| 1 | 1.9 | 42 | 20 | 42 | 88.3 | 51.0 | 53.4 | 46.1 | 33.5 |
| 2 | 1.5 | SA | 22 | 24 | 78.6 | 27.9 | 29.3 | 30.9 | 35.7 |
| 3 | 2.0 | 39 | 20 | 18 | 78.3 | 54.4 | 56.8 | 63.3 | 102.9 |
| 4 | 1.4 | SA | 14 | 22 | 100.0 | 13.1 | 13.1 | 12.9 | 11.5 |
| 5 | 4.9 | 14 | 14 | 20 | 100.0 | 19.6 | 18.7 | 16.7 | 14.3 |
| 6 | 4.4 | 180 | 16 | 20 | 100.0 | 25.2 | 24.8 | 21.9 | 15.7 |
| 7 | 4.0 | 28 | 38 | 58 | 92.2 | 28.9 | 25.6 | 20.6 | 27.0 |
| 8 | 3.8 | 210 | 210 | 210 | 87.9 | 180.5 | 167.7 | 211.7 | 337.1 |
| 9 | 3.4 | 64 | 22 | 18 | 89.9 | 73.6 | 72.0 | 65.5 | 70.9 |
| 10 | 4.0 | SA | 16 | 26 | 85.6 | 50.0 | 57.0 | 43.8 | 43.4 |
| 11 | 2.3 | 14 | 72 | 76 | 65.2 | 49.1 | 39.4 | 40.2 | 45.0 |
| 12 | 2.4 | 46 | 14 | 16 | 100.0 | 11.7 | 11.9 | 11.6 | 15.1 |
| 13 | 2.2 | NV | 12 | 20 | 100.0 | 13.9 | 15.3 | 13.4 | 16.4 |
| 14 | 1.4 | 20 | 18 | 20 | 100.0 | 20.0 | 19.8 | 23.8 | 27.8 |
| n = 14 | 14 | 10 | 14 | 14 | 14 | 14 | 14 | 14 | 14 |
| mean | 2.3 | 65.70 | 36.28 | 42.14 | 90.43 | 44.21 | 43.20 | 44.46 | 56.82 |
| s.d. | 1.6 | 70.24 | 52.35 | 51.43 | 10.78 | 43.54 | 40.65 | 51.37 | 85.53 |
| s.e. | 0.4 | 22.21 | 13.99 | 13.75 | 2.88 | 11.64 | 10.86 | 13.73 | 22.86 |
| p | — | — | — | — | — | — | 0.463 | 0.943 | 0.302 |

NV = nonvisualization; SA = surgical absence; CBD = common bile duct; INT = intestine; Bili = bilirubin; GB = gallbladder; and HEF = hepatic extraction fraction.

of the liver, and for any evidence of defects within the liver. The later images were used to assess the pattern of bile flow from the liver into the gallbladder and intestine. The course of the right and left hepatic duct, CBD, and the pattern of bile flow through the first and second part of the duodenum were scrutinized from the cine projection. Specific diagnosis of each disease entity was based on the combination of morphologic and quantitative physiologic changes as described in our previous articles (*3,4,6,7*).

*Quantification of Hepatobiliary Function.* Three regions of interest (ROIs) over the heart, the upper right hepatic lobe, and the spleen were drawn. Two functional parameters are

**TABLE 3**
Hepatic Extraction Fraction and Excretion T-½ Values at Various Time Intervals and the First Time of Appearance of the CBD, Gallbladder, and Intestine in 10 Group II Patients (Bilirubin > 5.0 mg%)

| | Appearance (min) | | | | | 60 min | 50 min | 40 min | 30 min |
|---|---|---|---|---|---|---|---|---|---|
| Patient | BILI | GB | CBD | INT | HEF | T-½ | T-½ | T-½ | T-½ |
| 1 | 8.2 | 180 | 20 | 24 | 100.0 | 22.4 | 27.4 | 19.3 | 18.2 |
| 2 | 5.3 | NV | 18 | 20 | 88.3 | 57.2 | 60.3 | 49.3 | 43.7 |
| 3 | 6.2 | NV | NV | NV | 11.6 | neg | neg | neg | neg |
| 4 | 9.9 | NV | NV | NV | 40.8 | neg | 509.1 | 382.9 | 106.2 |
| 5 | 14.4 | NV | NV | NV | 29.5 | 126.1 | 92.6 | 140.0 | neg |
| 6 | 12.2 | NV | NV | NV | 6.9 | 186.2 | 191.0 | 237.8 | 294.0 |
| 7 | 26.0 | NV | NV | NV | 2.9 | 72.5 | 62.5 | 51.4 | 39.7 |
| 8 | 14.4 | 240 | 28 | 28 | 28.4 | 25.3 | 40.8 | 79.6 | neg |
| 9 | 18.0 | 28 | NV | 52 | 26.5 | neg | neg | 144.9 | 130.4 |
| 10 | 19.8 | 144.0 | NV | NV | 2.3 | 86.0 | 88.6 | 86.4 | 76.0 |
| n | 10 | 4 | 3 | 4 | 10 | 7 | 8 | 9 | 7 |
| mean | 13.4 | 148.0 | 22.0 | 31.0 | 33.72 | 82.24 | 134.04 | 121.29 | 101.17 |
| s.d. | 6.5 | 89.3 | 5.29 | 14.38 | 34.42 | 58.15 | 159.61 | 118.64 | 93.69 |
| s.e. | 2.1 | 44.6 | 3.06 | 7.19 | 10.88 | 21.98 | 56.43 | 39.55 | 35.41 |
| p | — | — | — | — | — | — | 0.775 | 0.302 | 0.740 |

NV = nonvisualization; CBD = common bile duct; INT = intestine; Bili = bilirubin; GB = gallbladder; and HEF = hepatic extraction fraction.

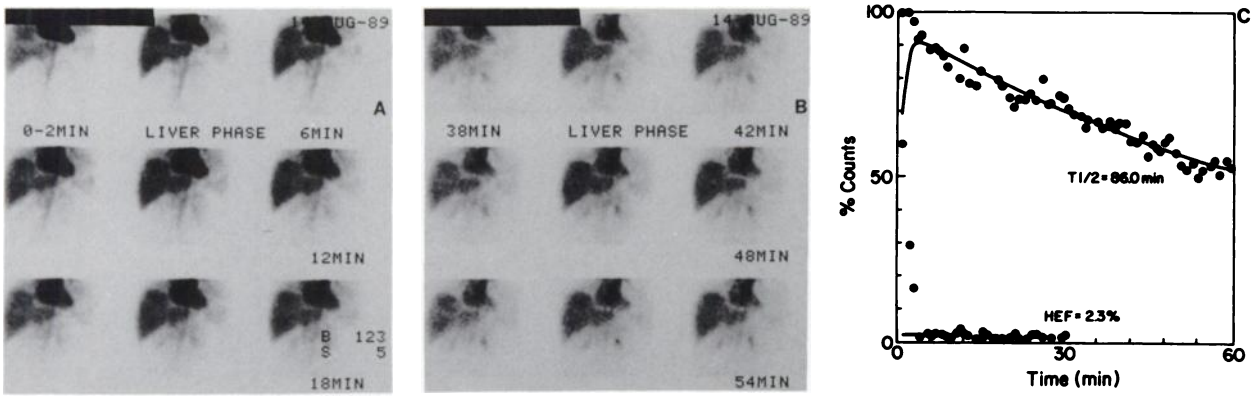


**FIGURE 1**
Hepatocyte disease. Hepatobiliary images between 0–18 min (A) and between 38–54 min (B) in an AIDS patient show persistence of marked cardiac blood pool throughout the study. The HEF of only 2.3% indicates that activity seen on images represents mostly hepatic blood pool. Excretion T-1/2 value is increased to 86.0 min (C).

generated using these three ROIs: (a) HEF and (b) hepatic excretion T-1/2. The ROI over the heart included both ventricles. Care was taken not to include any part of the liver within the heart ROI. The liver ROI was drawn over the peripheral right upper lobe, making sure not to include any ducts, the gallbladder, or the heart within the ROI, and it was evident that region bile canaliculi were included within the ROI. The HEF was calculated using the heart and liver ROIs and applying deconvolution analysis, described in detail elsewhere (*4,8–10*). The liver excretion T-1/2 was obtained by applying nonlinear least-square's fit using the liver and spleen ROIs as described elsewhere (*4*). Both HEF and excretion T-1/2 values were calculated using software (ADAC Lab, Milpitas, CA) developed and validated previously by us (*11*). The software allows selection of three ROIs over the liver and calculation of HEF and T-1/2 excretion value separately for each region, which is very essential in assessing the diseases that affect the liver regionally, e.g., sclerosing cholangitis. The software is semiautomatic and produces consistent results between and within individuals and institutions (*11*). For this study, we chose only one region over the right upper lobe. The software uses only the first 30 min of data for the calculation of HEF and all 60 data points for calculation of the excretion T-1/2 value and plots the results in a tabular form for final presentation. To check what effect the reduction of the duration of data collection would have on T-1/2 excretion values, each patient's data analysis was interrupted at 50, 40, and 30 min and the excretion T-1/2 values were recalculated and compared with values obtained using all 60 min of data (Fig. 2). The mean excretion T-1/2 values obtained using 30-, 40-, and 50-min data were each compared with values for 60 min using a paired t-test; p values $< 0.01$ were considered significant.

## RESULTS

In 18 control subjects, there was uniform uptake and excretion of $^{99m}$Tc-mebrofenin from all regions of the liver parenchyma without any evidence of defects or abnormal bile pooling. The CBD was seen with a mean ± s.e. time of 15.8 ± 1.5 min and a range of 8–34 min. The normal asymmetry between right and left hepatic ducts with more prominence of the left hepatic duct as seen in previous studies with other $^{99m}$Tc-IDA agents was again noticed in this study (*12*). The gallbladder was seen between 10 and 46 min with a mean time of 20.27 ± 2.7 min. The intestine was not seen by 60 min in two subjects. In the remaining 16 subjects, it was seen between 12 and 52 min with the mean time of 23.8 ± 3.0 min. The HEF was 100% in each of 18 control subjects. There was no significant difference among these excretion T-1/2 mean values ($p > 0.01$) at 30, 40, and 50 min when compared with the mean value at 60 min (Table 1).

In Group I patients (bilirubin <5 mg%), the serum bilirubin ranged from 1.4 to 4.9 with a mean value of 2.3 mg%. The CBD appearance time ranged from 12 to 210 min with a mean of 36.28 ± 13.99 min. The time of appearance of the gallbladder in 10 patients with intact gallbladders ranged from 14 to 210 min with a mean value of 65.70 ± 22.21 min (Table 2). The gallbladder was surgically removed in three patients and not seen in one patient. The small intestine appeared between 16 and 210 min with a mean of 42.14 ± 13.75 min. The HEF ranged from 65.2% to 100% with a mean value of 90.43% ± 2.88%. The liver excretion T-1/2 mean values at 30, 40, and 50 min were not significantly different from the mean value at 60 min when tested with the paired t-test (Table 2).

In Group II patients (bilirubin >5 mg;%), serum bilirubin ranged from 5.3 to 26.0 mg% with a mean value of 13.4 mg%. The CBD was seen within 60 min in three patients, and not seen at 60 min in the remaining seven patients. In four patients, the gallbladder was seen at 28, 144, 180, and 240 min and not seen in the remaining six patients (Table 3). The small intestine was seen at 60 min in four patients and not seen at 60 min in the remaining six patients. In six of seven patients whose gallbladder, CBD, and small intestine were not seen within 60 min, the HEF was below 40.8%

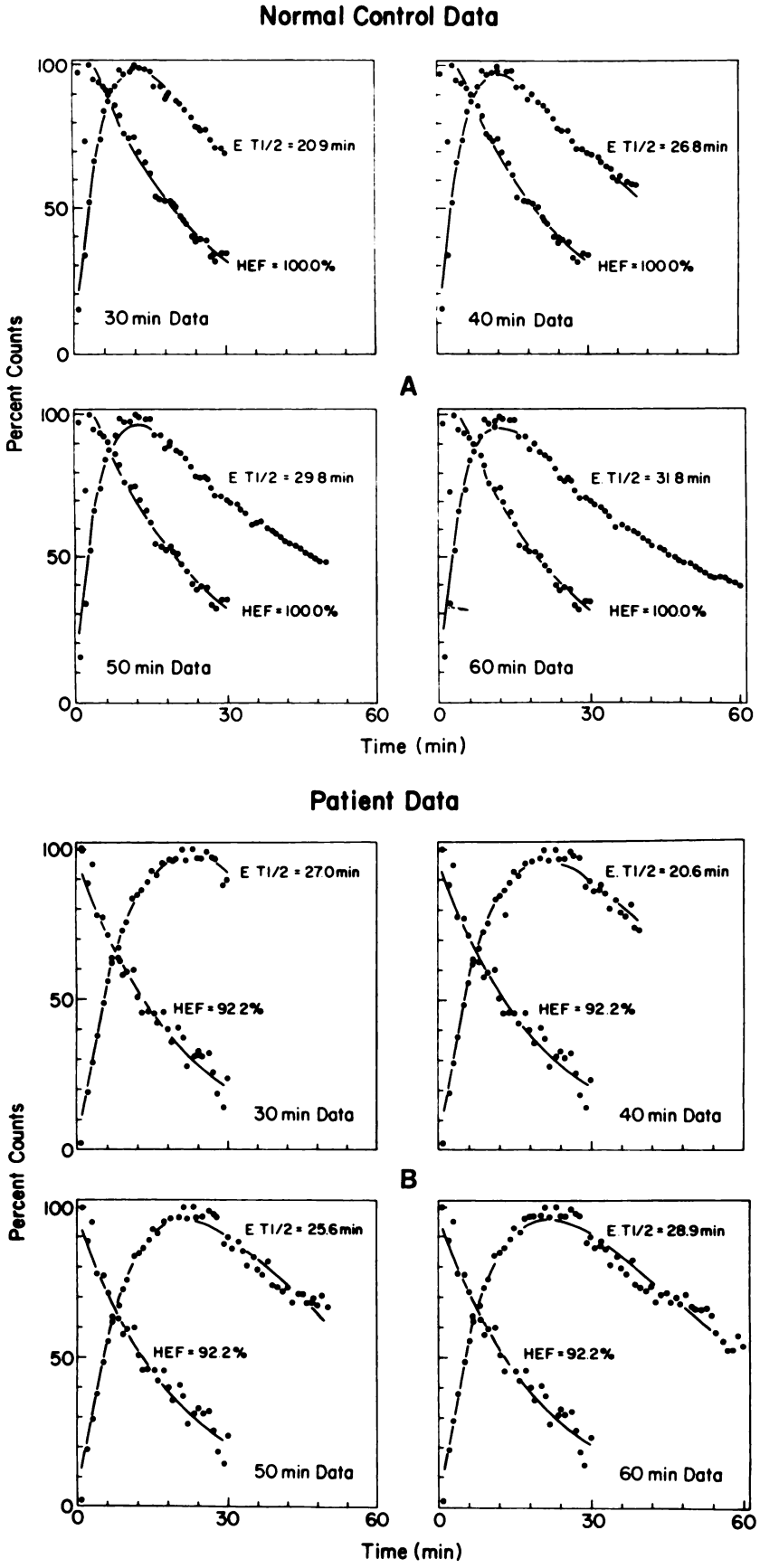


**FIGURE 2**
Semiautomatic computer calculation of HEF and ET 1/2 values in a normal control subject (A) and a Group I patient (B). Note that reanalysis of data at 30, 40, and 50 min has very little effect on T-1/2 excretion values when compared to values at 60 min (also see Table 2).

and in three it was as low as 2.9%, 6.9%, and 11.6%. The mean HEF for the group was 33.72% ± 10.88%. The mean excretion T-1/2 values at 30, 40, and 50 min were not significantly different ($p > 0.01$) from the 60-min value probably because of wide variations resulting in a large standard error (Table 3). The excretion T-1/2 showed a negative value (up slope curve) in three patients.

One patient with AIDS (No. 10 in Table 3) had the lowest HEF of 2.3%. He died within 2 wk of the study, and the liver biopsy taken before death showed marked bile stasis within the bile canaliculi without any evidence of fibrosis. Hepatobiliary images showed apparently good hepatic uptake of $^{99m}$Tc-mebrofenin, which mostly represented intrahepatic blood-pool activity and not true hepatocyte uptake (Fig. 1). In another patient with severe stricture of the distal CBD (Fig. 3A-B), the HEF was 97% and T-1/2 excretion 48.5 min (Fig. 4A). The CBD was dilated proximally on both ERCP and ultrasound (Fig. 3C-D), but the intrahepatic ducts were not dilated on computed tomography. Two weeks following choledochojejunostomy, there was prompt uptake and excretion of $^{99m}$Tc-mebrofenin (Fig. 5A) with the normal HEF of 100% and normal T-1/2 excretion of 20 min (Fig. 4B). The rising serum bilirubin values in Group I and II patients showed an inverse relationship with HEF (Fig. 6A) and a direct relationship with excretion T-1/2 values (Fig. 6B). A decrease in HEF, in general, was associated with an increase in T-1/2 excretion value (Fig. 6C).

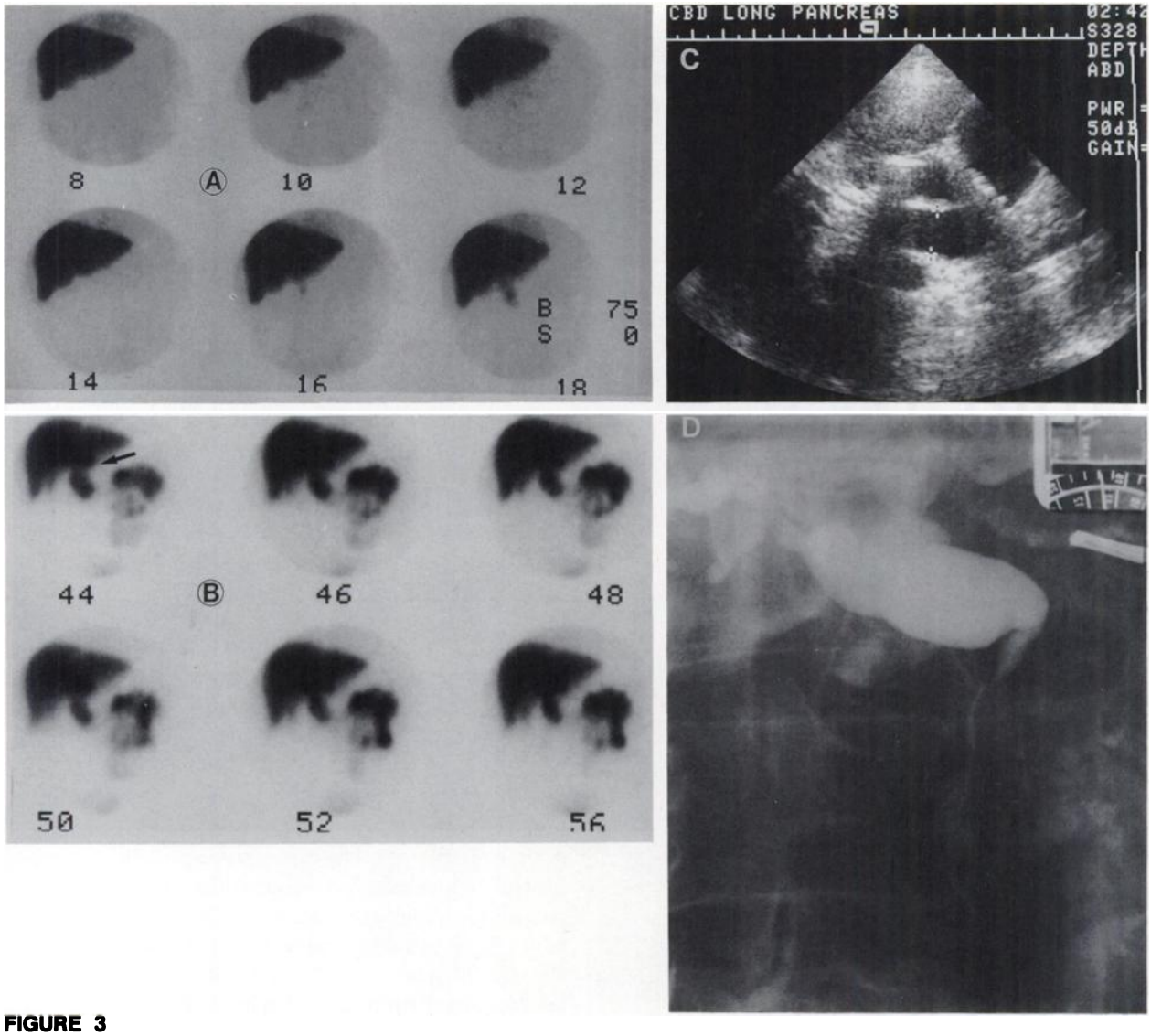


**FIGURE 3**
Biliary disease. A patient with tight stricture of the distal CBD shows prompt extraction of $^{99m}$Tc-membrofenin by the liver (A). Excretion into the proximal CBD (arrow) is delayed and distal CBD is not clearly visualized (B). Dilation of the proximal CBD is evident on both ultrasound (C) and ERCP (D). Severe stricture of the distal half of CBD is evident on ERCP (D) and corresponds to the segment not seen by scintigraphy (B).

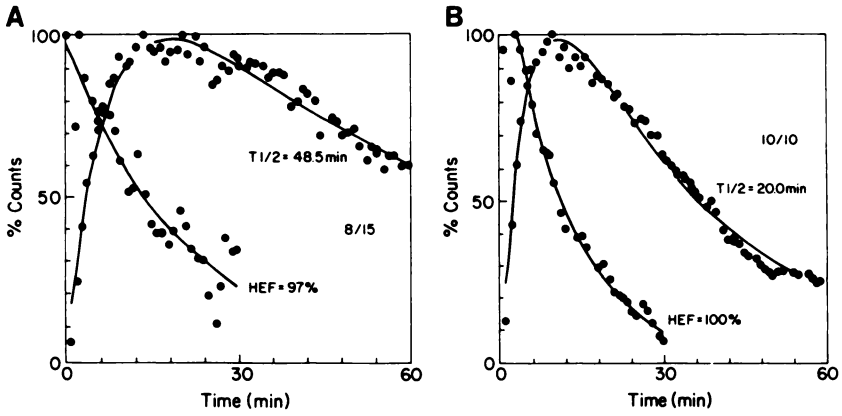


**FIGURE 4**
HEF and excretion T-1/2 values before (A) and after (B) relief of distal CBD obstruction in the patient shown in Figure 3. Excretion T-1/2 value decreases from 48.5 min before (A) to 20.0 min after (B) relief of CBD obstruction; HEF value remains essentially normal.

## DISCUSSION

Following intravenous injection, $^{99m}$Tc-IDA agents pass through five phases before their elimination into small intestine: (a) blood transport, (b) hepatocyte extraction, (c) secretion by hepatocytes into bile canaliculi, (d) flow through the bile ducts (excretion) into the gallbladder, and (e) elimination into small intestine through the sphincter of Oddi (*7*). Technetium-99m-IDA agents are transported in blood loosely bound to serum protein, mainly albumin. At the space of Disse, after disassociation from protein, $^{99m}$Tc-IDA is extracted by the hepatocyte (uptake) by a carrier-mediated non-sodium dependent membrane transport mechanism, a process also shared by bilirubin (*13*). A normal liver extracts 98.5% of the dose of mebrofenin and secretes it into bile, which is the primary route of excretion. The remaining 1.5% of the dose is excreted through the urine (*6*). As the serum bilirubin level rises, the hepatic uptake of $^{99m}$Tc-IDA compounds decreases (Fig. 6A) and the renal excretion increases. Of all $^{99m}$Tc-IDA agents, mebrofenin shows the greatest resistance to displacement by rising bilirubin. Cultured rat hepatocytes show 100% uptake of $^{99m}$Tc-IDA in a bilirubin-free medium. At serum bilirubin levels equivalent to 10 mg%, the uptake decreases to 36% with diisopropyl IDA and 71% with mebrofenin. Mebrofenin maintains the high hepatic uptake around 70% even at bilirubin levels of 20 mg% (*6*). In addition to using primarily the bilirubin path, $^{99m}$Tc-IDA agents are also known to use fatty acid and conjugated bile acid paths, explaining the observation that there is always some degree of hepatocyte uptake despite very high levels of serum bilirubin (*13,14*).

In all normal subjects and patients with near normal liver function, the HEF remains closer to 100% (Tables 1–2). In primary hepatocyte disease, the HEF decreases and the degree of HEF reduction is directly proportional to the severity of hepatocyte dysfunction (*4*). Three patients in Group I and one patient in Group II with serum bilirubin between 4.9 and 8.2 mg% were able to maintain normal HEF values of 100%, suggesting normal extraction efficiency of the hepatocytes despite high bilirubin. Using $^{99m}$Tc-DISIDA (diisopropyl iminodiacetic acid), we have shown that HEF remains normal in early biliary disease despite high bilirubin, suggesting that in some patients hepatocyte functional compromise is required before bilirubin begins to show its inhibitory effect (unpublished data). Ascher et al. reported (*15*) that high bilirubin did not have much inhibitory effect on $^{99m}$Tc-DISIDA uptake in a patient with no injury to hepatocytes. In late stages as the severity of biliary obstruction progresses, the hepatocyte function begins to compromise resulting in a secondary decline of HEF (*4*). The measurement of HEF not only provides a quantitative measure of hepatocyte function but also supplements images in separating primary biliary from primary hepatocyte disease (Figs. 1 and 3). Because of relatively high hepatocyte uptake, $^{99m}$Tc-labeled mebrofenin and arclofenin are considered as the preferred agents in both normal and severely jaundiced patients (*16*).

Visual inspection of the hepatic versus cardiac blood-pool images is often used to assess the relative hepato-

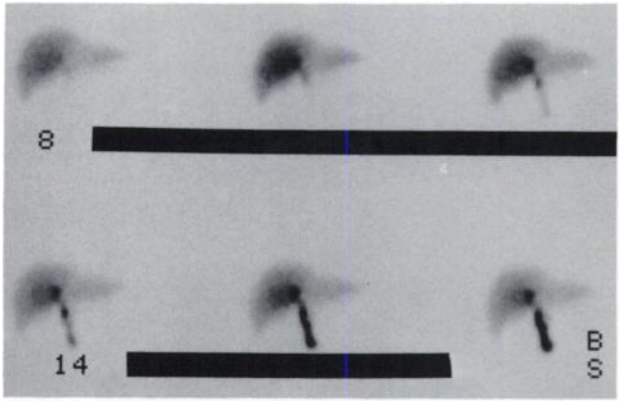


**FIGURE 5**
Scintigraphy two weeks after relief of distal CBD obstruction by choledochojejunostomy (in the patient shown in Figures 3 and 4) shows prompt uptake (8 min) and rapid excretion by the liver into the small intestine (14 min) of $^{99m}$Tc-mebrofenin.

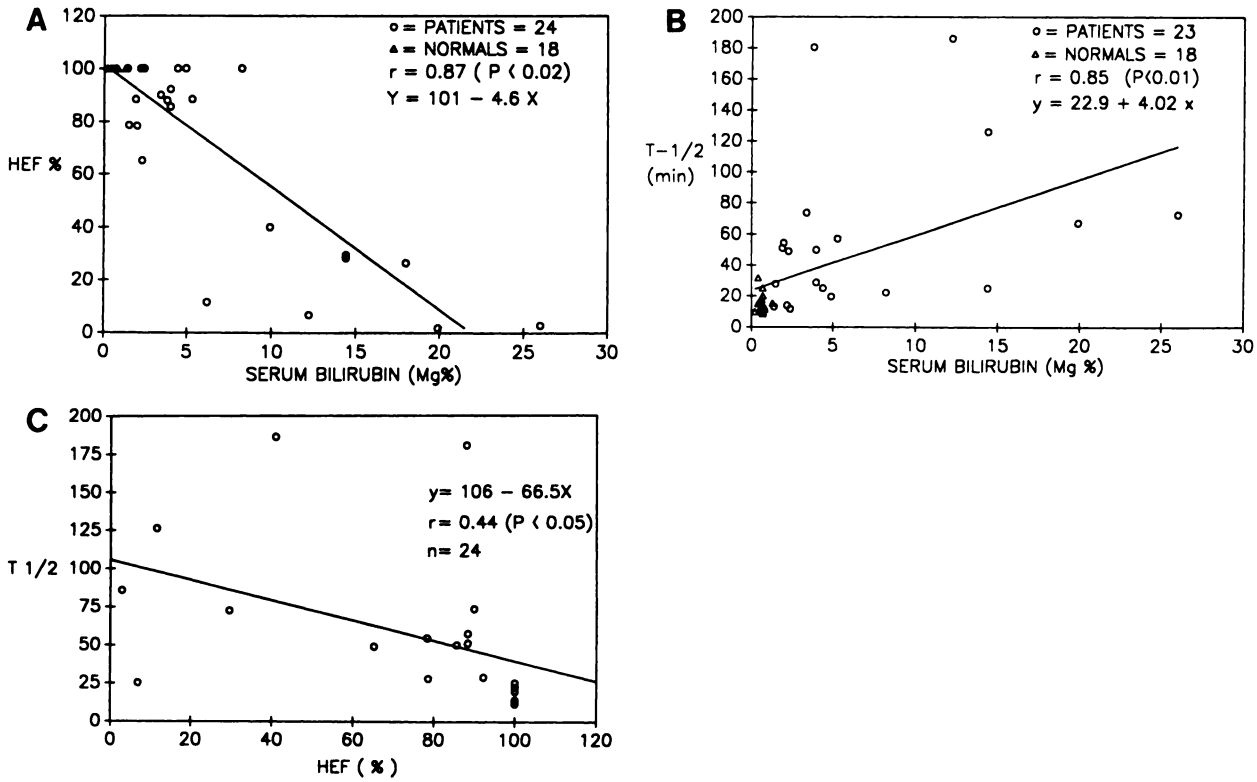


**FIGURE 6**
Effect of rising serum bilirubin on HEF and excretion T-1/2 of $^{99m}$Tc-mebrofenin by the hepatocyte. Note that as bilirubin increases the HEF decreases (A) and T-1/2 excretion value increases (B). Also note an inverse relationship between HEF and T-1/2 excretion values (C).

cyte function. Visual inspection, however, does not differentiate true hepatocyte uptake from the radioactivity within the hepatic blood pool. In the AIDS patient shown in Figure 1, the hepatic and the cardiac blood-pool intensity appear equal. From the images, it is not clear how much of the liver radioactivity is due to hepatocyte uptake and how much is due to hepatic blood pool. The patient's HEF of only 2.3% suggests that most of the liver activity is due to hepatic blood pool and very little is due to hepatocyte uptake. This patient's course was complicated by HbsAg hepatitis, cytomegalo virus infection, and *pneumocystitis carinii* pneumonia, and death within 2 wk of this study. Liver biopsy examination showed severe hepatocyte injury, confirming that HEF value reflected the true in vivo functional status of the hepatocyte.

*Secretion.* After their uptake, $^{99m}$Tc-IDA agents are secreted by hepatocytes into the hepatic bile in their native form (*2*). The T-1/2 value is a measure of how fast the $^{99m}$Tc-IDA is secreted from the hepatocyte and excreted through the bile canaliculi into major ducts. The effect of bilirubin on the rate of secretion of $^{99m}$Tc-IDA from the hepatocyte (after the uptake) has been difficult to measure in an in vitro model. Our in vivo results show that high serum bilirubin not only decreases HEF but also delays secretion resulting in prolongation of excretion T-1/2 value (Fig. 6B). This raises the possibility of a common secretory path for both bilirubin and $^{99m}$Tc-mebrofenin. However, it is more likely that increase in T-1/2 excretion value is a mere reflection of recirculation of the agent in hyperbilirubinemic states. In hepatocyte diseases, HEF decreases and T-1/2 excretion value increases (Fig. 1). In biliary disease, on the other hand, the T-1/2 excretion value alone increases and HEF remains normal (Fig. 3). An abnormal excretion T-1/2 value alone cannot distinguish between the hepatocyte and the biliary disease. The scintigraphic image pattern combined with HEF values are necessary to differentiate hepatocyte from biliary disease (*3,17,18*). The prolongation of excretion T-1/2 value in early ductal obstruction (Fig. 4A) is probably due to stagnation of bile within bile canaliculi (Fig. 4A) because the excretion T-1/2 value returns to normal when the obstruction is relieved (Fig. 4B). Unlike the HEF value which is primarily related to hepatic extraction, excretion T-1/2 value reflects recirculation of $^{99m}$Tc-mebrofenin in blood, bile secretion by hepatocyte, and bile flow (excretion) through the canaliculi and ducts before its elimination into the small intestine.

*Duration of $^{99m}$Tc-IDA Scintigraphy.* It has been routine practice for us to image the hepatobiliary system continuously for a minimum of 60 min. This practice began with the first $^{99m}$Tc-IDA agent (dimethyl IDA) and continued all through the succeeding agents pri-

marily because of their slow kinetics within the liver. Technetium-99m-mebrofenin clears from the liver rapidly with mean excretion T-1/2 of 15.25 min (Table 1). The T-1/2 excretion values calculated for data analyzed at 30, 40, and 50 min are similar to values obtained using 60-min data, suggesting that the normal values established using 60-min data could also be used for studies terminated at 30, 40, or 50 min in patients with bilirubin <5 mg% (Tables 1 and 2). The differences among mean values at 40, 50, and 60 min were <2 min (Table 2).

Gambhir et al. measured liver extraction, excretion, and mean residence time using $^{99m}$Tc-DISIDA and showed that quantification is easily adaptable to most nuclear medicine departments (*19*). Scintigraphy with $^{99m}$Tc-IDA has been used in the diagnosis of acute cholecystitis (*20*), CBD obstruction (*18*), primary sclerosing cholangitis (*21*), primary biliary cirrhosis (*22*), chronic cholecystitis, cystic duct syndrome (*23*), and a variety of other hepatobiliary diseases (*6*). Continuation of imaging into the gallbladder phase, using cholecystokinin or fatty meal stimulation provides additional quantitative parameters (gallbladder ejection fraction, ejection rate, bile reflux) which help in differential diagnosis (*7,17*). To carry out the gallbladder phase of the study accurately, it is essential to have an adequate number of counts within the gallbladder. A total of 50,000–100,000 cpm within the gallbladder are more than adequate to carry out the gallbladder phase (*18, 24–26*). In those patients with a bilirubin <5 mg% where the gallbladder and CBD have appeared, it may be possible to begin the gallbladder stimulation study as early as 30–40 min after injection. Normally once the gallbladder appears on the scintigraphy, it fills rather rapidly. In general, data collection for an additional 10–15 min after the gallbladder first appears, assures adequacy of counts for quantitation. In many patients, it is possible to complete the entire hepatobiliary imaging study (both liver and gallbladder phase) with quantification within 60 min. When the gallbladder does not visualize early, it may be necessary to conduct a post-CCK gallbladder dynamic study 2 to 4 hr later. This will free the gamma camera and computer for other studies between the liver and the gallbladder phase study.

In summary, measurement of quantitative physiologic parameters as an integral part of hepatobiliary imaging with $^{99m}$Tc-mebrofenin is feasible, practical, and provides additional information for diagnosis and for assessment of therapeutic benefits. In many patients with a bilirubin <5 mg%, the hepatic phase of study could be completed within 30–40 min, and both hepatic and gallbladder phases could be completed within 60 min. In patients with bilirubin >5 mg%, it appears essential to acquire the hepatic phase data for the entire 60 min.

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## SELF-STUDY TEST

# Radiobiology and Radiation Protection

### Questions are taken from the *Nuclear Medicine Self-Study Program I*, published by The Society of Nuclear Medicine

**DIRECTIONS**

**The following items consist of a heading followed by lettered options related to that heading. Select the options that you think are true and those that you think are false. Answers may be found on page 101.**

**1.** **Suppose that a nuclear medicine clinic's patients were almost exclusively geriatric, i.e., older than about 60 yr of age. Suppose further that the clinic's work load for skeletal imaging has been increasing steadily and throughput is now limited by available camera time during the work day. It occurs to the hospital administrator that the hospital could save the expense of buying a new camera ($200,000) and of hiring a new technologist ($25,000/yr) by simply increasing the usual 20-mCi dosage of $^{99m}$Tc-MDP to 50 mCi and reducing the time of imaging for any patient older than 60 yr of age. Although this action might cause a theoretically increased risk of cancer in these patients, this might not be a real concern because the latent period probably would be longer than their remaining life spans. The attitude of an NRC inspector to this policy is likely to be which one of the following?**

- **A.** It is acceptable because the NRC does not regulate dosage range.
- **B.** It is acceptable because this is an FDA responsibility and the FDA does not regulate dosage range.
- **C.** It is acceptable because the patients probably will excrete most of the excess radiopharmaceutical into the urine anyway.
- **D.** It is unacceptable because this policy is not conistent with the ALARA philosophy.
- **E.** It is unacceptable because this policy is not consistent with the de minimis philosophy.

**2.** **How does a nuclear medicine physician determine the maximum dosage of a radiopharmaceutical that can be administered to a patient for a routine clinical study?**

- **A.** FDA regulations contained in Title 21 of the Code of Federal Regulations
- **B.** NRC regulations contained in Part 35 of Title 10 of the Code of Federal Regulations (Medical Use of Byproduct Material)
- **C.** NRC regulations contained in Part 20 of Title 10 of the Code of Federal Regulations (Standards for Protection Against Radiation)
- **D.** NCRP Report No. 70 (Nuclear Medicine—Factors Influencing the Choice and Use of Radionuclides in Diagnosis and Therapy)
- **E.** Radiopharmaceutical package insert and clinical judgment

**3.** **Current radiation protection philosophy holds that efforts should be expended continually to reduce the radiation exposure of patients, radiation workers, the general public, and the environment, so long as the expenditure of resources to accomplish this reduction does not outweigh the incremental gain in radiation protection. This philosophy is known as**

- **A.** de minimis
- **B.** benefit–risk ratio
- **C.** ALAP
- **D.** ALARA
- **E.** relative biological effectiveness

*(continued on p. 101)*

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# Quantification of Hepatobiliary Function as an Integral Part of Imaging with Technetium-99m-Mebrofenin in Health and Disease

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