PHYSICS AND RADIATION BIOLOGY

Tc-99m HIDA Dosimetry in Patients with Various Hepatic Disorders

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The pharmacodynamics of Tc-99m dimethyliminodiacetic acid were studied for normal subjects and for patients with a variety of hepatobiliary disorders. It was determined that, in normal subjects, ~65% of the gallbladder agent bypassed the gallbladder and was excreted directly from the liver into the small intestine. This bypassing of the gallbladder was even higher in patients with cystic-duct or common-duct obstruction. The radiation burdens to the gallbladder wall and other critical organs were calculated using the dynamic data obtained from patients with a variety of gallbladder disease. The dose to the gallbladder wall was found to be significantly lower than previously reported. Gallbladder ejection and clearance characteristics when stimulated by food intake were studied for normal subjects. Dosimetry calculations demonstrated a fivefold reduction of absorbed dose to the gallbladder wall when the gallbladder was stimulated to contract using a fatty meal. Accordingly, a fatty meal is recommended for patients at the end of all gallbladder imaging studies.

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Cholescintigraphy with the Tc-99m iminodiacetic (Tc-99m IDA) agents is now a standard technique for the evaluation of hepatobiliary disease. It is one of the procedures of choice in the diagnosis of acute cholecystitis (*1*,*2*), bile leakage (*3*), and enterogastric reflux (*4*). It is a similarly useful adjunct in the diagnosis of chronic cholecystitis (*5*) and in distinguishing medical from surgical jaundice (*6*).

Several technetium-based pharmaceuticals were developed for imaging the hepatobiliary system between 1970 and 1975 (*7–10*). Of these, Tc-99m HIDA (dimethyliminodiacetic acid), along with the more recently developed agents, PIPIDA (para-isopropyliminodiacetic acid), and DISIDA (di-isopropyliminodiacetic acid) have proved to be the most effective in this service.

Biokinetic data and estimates of radiation burden for these agents in animals and humans are available in the literature (*11–17*). There are some discrepancies among the reported data, but the differences are mostly within experimental error. The major controversy lies in the estimates of radiation burden to the gallbladder wall. Authors have reported that this dose, per injected mCi of HIDA, was as low as 110 mrad (*15*) or as high as 1880 mrad (*17*) for normal subjects without gallbladder stimulation. Whereas an underestimation of the radiation burden will subject the patients to unexpected risks, an overestimation will compromise both the quality and diagnostic value of this procedure.

The present work applied a recently developed method using a buildup-factor correction (*18*) to resolve the differences and to measure more accurately the biokinetic behavior of HIDA in vivo for normal subjects and for patients with a variety of hepatobiliary disorders. The approach indicates improved accuracy of the measured biological half-times of Tc-99m HIDA in various organs, and has led to the revision of previously published pharmacodynamic and dosimetric estimates (*11*).

MATERIALS AND METHODS

Following an overnight fast, an intravenous heparin lock was inserted in one forearm, and Tc-99m HIDA was administered in the opposite antecubital vein in an ac-

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TABLE 1. DEMOGRAPHIC DATA ON SUBJECTS

Group	Subject	Sex	Diagnosis	Bilirubin level mg%
1a and 1b	1	M	Normal volunteer	0.4
	2	M	Normal volunteer	0.5
	3	M	Normal volunteer	0.6
	4	M	Normal volunteer	0.6
	5	M	Normal volunteer	0.7
	6	M	Normal volunteer	0.5
	7	F	No hepatobiliary disease, normal patient	0.3
	8	F	No hepatobiliary disease, urinary tract infection	0.6
	9	F	Bile reflux, pyloric channel ulcer	0.8
	10	F	No hepatobiliary disease, esophagitis	0.6
2	11	F	Acute cholecystitis, complete obstruction of common duct	0.6
	12	M	Alcoholic cirrhosis, chronic cholecystitis, pancreatitis, no obstruction proven by surgery	0.5
	13	F	Chronic cholecystitis, possible gallstone	0.2
3	14	F	Chronic cholecystitis, gallstone, common bile duct obstruction	4.5
	15	M	Chronic cholecystitis, cirrhosis	2.5

tivity of 0.07 mCi per kilogram of body weight, or approximately 5 mCi per patient. Sequential blood samples of 1 ml each were drawn through the intravenous cannula at 1, 3, 5, 15, 30, 60, 90, and 120 min.

Total urine excretion was collected for 24 hr in separate pooled samples from 0–30 and 30–60 min, and 1–2, 2–8, 8–16, and 16–24 hr. Blood chemistry determinations were obtained within 48 hr before and after each study.

The method for the measurement of activity in the organs of interest follows the two-view (anterior and posterior) technique described by Fleming (*19*), improved upon by introducing the buildup factor in order to account for the considerable contribution of scatter to measured gamma-camera count rates (*18*). The method was shown to result in less than 1% error for activity quantification at depths of clinical interest. The patient was placed under the diverging collimator of a gamma camera using a 30% window centered at 140 keV. The camera was interfaced to a digital computer in which data were stored for subsequent analysis. Cotton patches of known activity were placed in a phantom of tissue-equivalent material at known depths, and images were obtained to provide a calibration reference in cpm/μCi so that the absolute activity in a region of interest could be calculated from the recorded camera count rate. The activity on the patch was chosen to give counts of the same order of magnitude as the counts from the radiopharmaceutical in the organs studied. 1-min images for the subjects were obtained over the liver and abdominal areas of interest at 5, 15, 30, 60, 90, 120, and 180 min, in the supine position for all the patients and also in the prone position for most of the normal subjects. The anteroposterior thickness of the abdomen was measured for all normal volunteers and patients.

Fifteen subjects were studied, including six normal volunteers. Demographic data on these subjects are shown in Table 1. Group 1 consisted of the six normal volunteers and four patients with mild gastrointestinal dysfunction, all having normal bilirubin levels. One had a pyloric ulcer and bile reflux, and the other three had normal hepatobiliary functions. In order to study the gallbladder contraction and the subsequent changes in gallbladder clearance when the gallbladder is stimulated by food intake, two normal volunteers were given a glass of protein-vitamin-mineral liquid at 1 hr after injection. This group of two subjects is identified as Group 1b, whereas those without gallbladder stimulation are referred to as Group 1a. Group 2 consists of patients with moderate hepatobiliary dysfunctions, and Group 3 with more severe dysfunctions. The three patients in Group 2 were suffering from either acute or chronic cholecystitis but all had normal bilirubin levels (0.2 to 0.6 mg%). Of the two patients included in Group 3, one had common-duct obstruction and the other had cirrhosis. Both had chronic cholecystitis and elevated bilirubin levels (4.5 and 2.5 mg%). No gallbladder stimulants were given to Group 2 and Group 3 patients.

RESULTS

Although the number of patients examined in this study is small, the results are from patients who were specifically selected to be representative of the three patient groups described.

Blood pool. The time-activity curve for the blood pool was obtained by counting the blood samples in a well scintillation counter. The results are shown in Fig. 1. There is only a slight difference in blood clearance rates among patients in Groups 1 and 2, whereas for patients

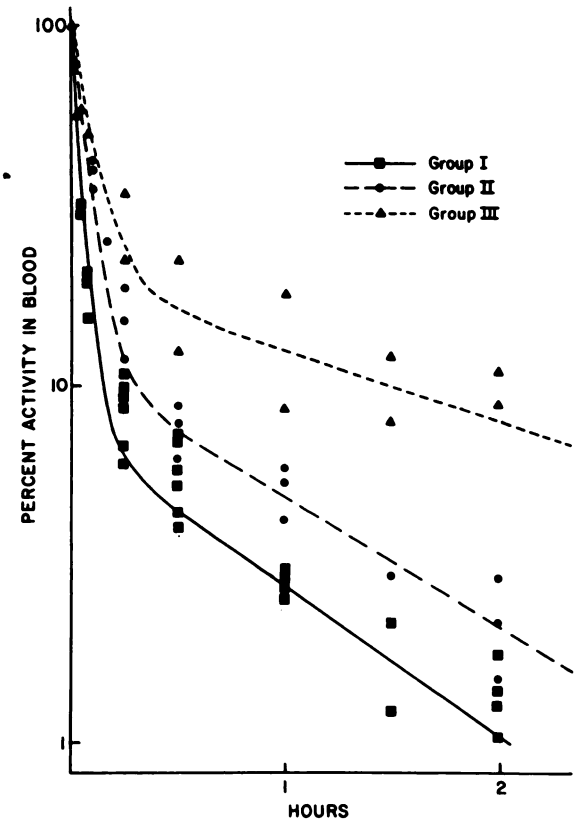


FIG. 1. Time-activity curve for Tc-99m HIDA in blood pool, as percentage of injected dose, for all 3 patient groups. Curves are least-squares exponential fits.

with severe disease (Group 3), the activity clears the blood pool at a slower rate. The decay-corrected activity in the blood pool at various times A(t) may be approximated by a double exponential curve with a fast and a slow component:

$$A(t) = A_0(P_f e^{-0.693t/T_{Bf}} + P_s e^{-0.693t/T_{Bs}}),$$

where the subscripts f and s represent the fast and slow components, respectively, and A_0 is the injected activity. T_{B_f} is the biological half-time of the rapidly clearing blood-pool component. In Groups 1, 2 and 3 it was found to be 2.2 ± 1.2, 3.1, and 4.3 min, respectively. T_{B_s} is the biological half-time of the slow component, and was determined to be 50 ± 7 min for patients with mild hepatobiliary disease (Groups 1 and 2) and 1.5 hr for patients suffering from severe disease (Group 3). P_f and P_s were 0.93 and 0.07, respectively, for patients in Group 1, 0.89 and 0.11 for patients in Group 2, and 0.8 and 0.2 for patients in Group 3.

Essentially, 80–93% of the injected tracer clears the blood pool very quickly with a half-time of 2 to 4 min, while the remaining 7–20% clears with a longer half-time of 50 min to 1.5 hr, depending on the bilirubin level and the degree of hepatobiliary dysfunction. The exponential equations, which are represented by the three curves in Fig. 1, agree very well with the measured data. The curve for normal subjects is in good agreement with that of Loberg et al. (*15*). The decreased blood-clearance rates with elevated bilirubin levels have been found by Jansholt et al. (*12*) in animal studies.

Kidneys. The urine samples and gamma images of the kidneys taken in the prone position showed that the kidneys excrete about 15% of the tracer, with a biological half-time of 20 minutes in normal subjects. The uptake increases with the bilirubin level and the degree of obstruction of the biliary tree, in agreement with the literature (*13,14*). For patients in Group 2, the kidneys clear about 30% of the injected activity, and for Group 3, about 65%. The biological half-times in both groups are normal.

Liver. Images were obtained with the patient lying prone and supine. Regions of interest were drawn manually to obtain the anterior- and posterior-view count rates. The activity in the liver was then determined, based on the buildup-factor scheme developed by our group (*18*).

The liver excretes between 35% to 85% of the injected activity, depending on the bilirubin level and the degree of obstruction. About 85% of the injected activity clears through the liver in Group 1 subjects with a biological

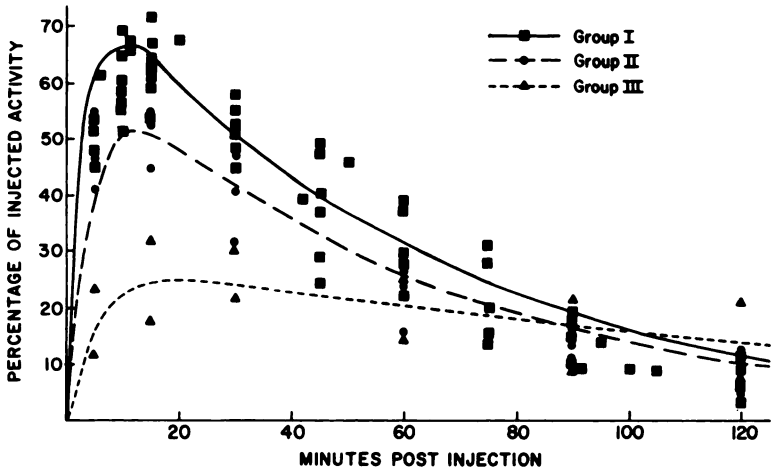


FIG. 2. Instantaneous activity of Tc-99m HIDA in liver at various times after injection, for all 3 patient groups. Curves (least-squares exponential fits) are based on biological parameters shown in Figs. 4 to 6.

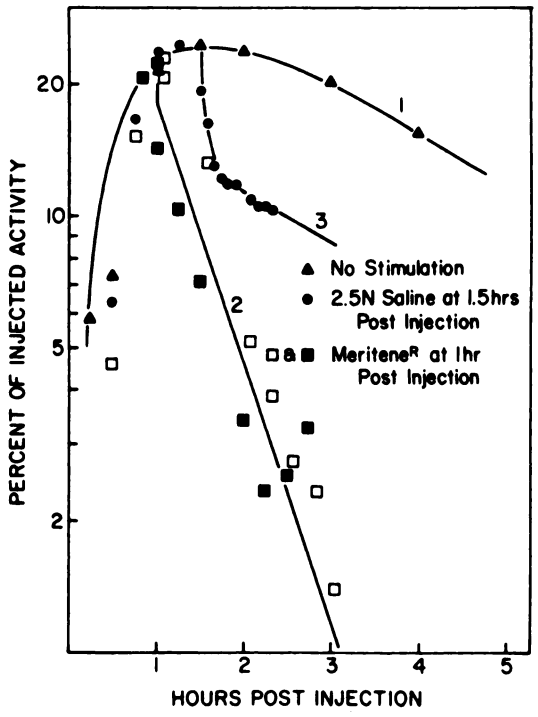


FIG. 3. Instantaneous activity of Tc-99m HIDA in gallbladder in Group 1 subjects, with and without gallbladder stimulation. Curves 1 and 2 are based on biological parameters summarized in Fig. 4. Curve 3 is empirical. (All are least-squares exponential fits.)

half-time of 45 min, in agreement with reported values (*13,14*). The time-activity curve is represented by the solid curve in Fig. 2. In Group 2 patients the liver takes up less of the injected activity (70%), but the clearance rate is about the same. For patients suffering from severe hepatobiliary dysfunction (Group 3), the liver uptake is reduced to 35% and the biological half-time in the liver becomes much longer (2 hours). The percent uptake values shown in Fig. 2 refer to individual curve peaks for each of the three patient groups, and are seen to be less than indicated above due to simultaneous liver clearance.

Gallbladder. The tracer uptake and clearance characteristics for the gallbladder have been studied carefully in order to obtain a more accurate estimate of the radiation dose to the gallbladder wall. In our earlier preliminary work, we reported that 20% of the Tc-99m HIDA that passes through the liver will enter the gallbladder on its way to the intestine (*11*). Later, when more patients were included in the study, we found that this value varied from 20% to 50%. In the dosimetry calculation that follows, we assume an average value of 35%, in contrast to the value of 50% used by Brown et al. (*5*). We feel that the lower figure is more realistic for dosimetry calculation purposes. We have been able to determine the tracer activity in the gallbladder to within 10% by refining the measurement technique (*18*).

Figure 3 shows the time-activity curves for four normal subjects. Curve 1 represents the uptake and clearance characteristics of a typical Group 1a subject. The biological half-time of the nuclide in the gallbladder is about 4 hr. However, when a glass of protein drink was given at 1 hr after injection, the results as shown in Curve 2 for two patients (Group 1b) were quite different. The gallbladder ejected about 10 to 30% of its contents immediately, then excreted the remaining contents with a biological half-time of ~20 min. The fourth subject was given a 250-cc glass of 2.5*N* NaCl, which caused the immediate ejection of about half of the gallbladder contents (Curve 3). The remaining radioactivity was excreted with a biological half-time of 4 hr, the same rate as the subject who did not receive any gallbladder stimulation.

The tracer uptake by the gallbladder for patients in Groups 2 and 3 is very low, so we assume no gallbladder uptake in the dosimetry calculations.

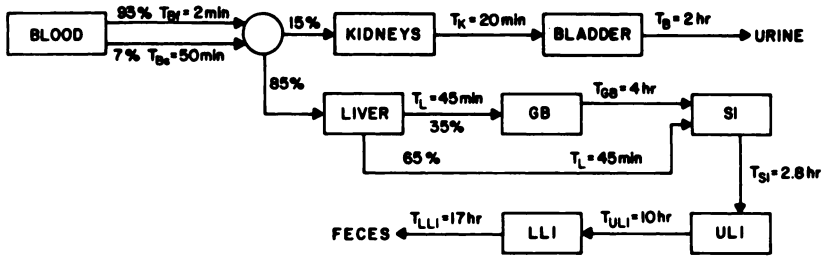
Intestine. The tracer was found to leave the small intestine with a biological half-time of about 2–3 hr, which is consistent with the data of Eve (*20*), who concluded that the mean transit time through the small intestine was 4 hr, assuming that the bolus of food material goes through the GI tract at a constant rate. This value corresponds to a biological half-time of 2.8 hr (*21*) if the radiotracer clears the small intestine in an exponential pattern. This result is obtained by setting the cumulated activity integral equal to the 4-hr transit time reported by Eve. In our dosimetry calculation, we used this value of 2.8 hr.

The mean transit times in the upper and lower large intestine, according to Eve (*20*), are 14 hr and 24 hr, respectively, corresponding to half-times of 10 hr and 17 hr, in an exponential excretion model.

Summary of pharmacodynamics. The uptake and clearance patterns for the three groups are summarized in Figs. 4 to 6. The radiopharmaceutical is assumed to leave each organ exponentially, with the biological half-time indicated. Whenever there are two possible pathways (e.g., the gallbladder or small-intestine pathways in Fig. 4, upper), the fraction of the radiopharmaceutical clearing into each pathway is the indicated percentage (35% and 65%, respectively) of the activity in the originating organ (liver) *at that moment*, except in the case of the blood clearance. In the case of the blood clearance, we assume that a fraction P_f of the *injected activity* clears with a biological half-time of T_{B_f} and the remaining fraction clears with a biological half-time of T_{B_s} as described by Eq. (1).

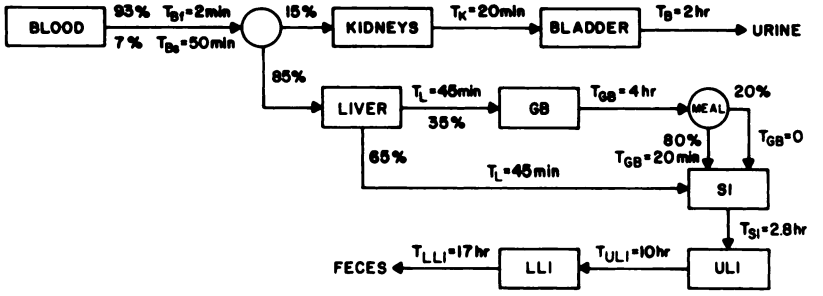
Among the first group of ten subjects with normal hepatobiliary function, eight did not receive gallbbladder stimulation, two were given a fatty meal at 1 hr after injection. Their corresponding uptake and clearance patterns are shown in Fig. 4.

Figures 5 and 6 outline the uptake and clearance patterns for Group 2 and Group 3 patients, showing a small difference in blood clearance but significant dif-



DOSIMETRY MODEL FOR Tc-99m-HIDA

FIG. 4. Pharmacodynamics of Tc-99m HIDA in Group 1a (upper) and Group 1b (lower) subjects, showing biological half-lives in various organs.



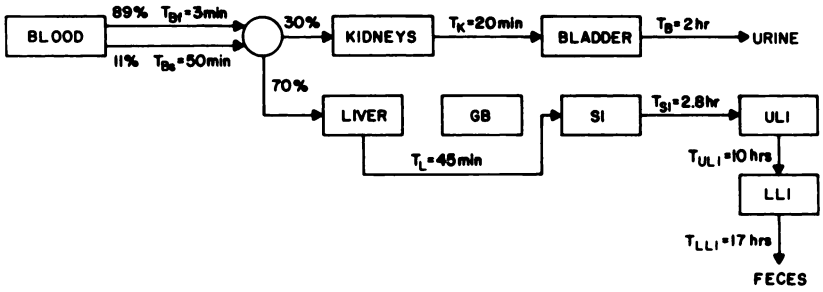


FIG. 5. Pharmacodynamics of Tc-99m HIDA in Group 2 patients, showing biological half-lives in various source organs.

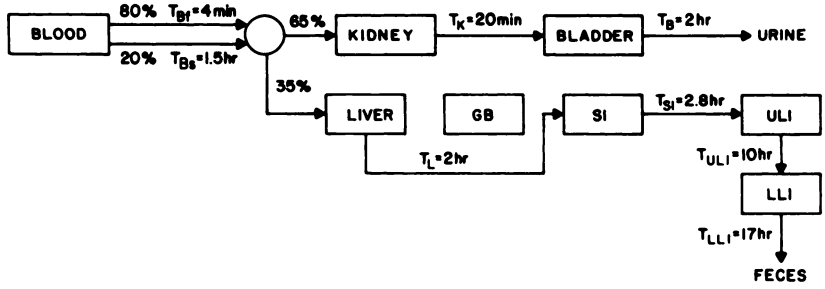


Fig. 6. Pharmacodynamics of Tc-99m HIDA in Group 3 patients, showing biological half-lives in various source organs.

ferences in liver retention and in the amount excreted through the urinary tract and the liver-GI tract.

Dosimetry calculation. The cumulated activities in various source organs for each of the three groups were calculated using the uptake and clearance parameters as summarized in Figs. 4 to 6. For the bladder we assume that the biological half-time of the tracer is 2 hr, this being shortened if the subject voids more frequently. The activity in each organ as a function of time was first obtained by computer processing of the pharmacodynamic data. The cumulated activity was then obtained by numerical integration, and was also calculated analytically by the method of Bernard and Hayes (*22*). The values are in agreement in all cases. Numerical integration was necessary for the case of gallbladder stimulation (Group 1b). The results are listed in Table 2.

The dose to the target organs per unit administered activity can be expressed, following the MIRD method (*19*) as:

$$D_{k\leftarrow h} = S_{k\leftarrow h}\tilde{A}_h,$$

where $D_{k\leftarrow h}$ denotes the absorbed dose (mrad) to target organ k due to source organ h, $S_{k\leftarrow h}$ is the S-factor for organ h to organ k (mrad/μCi-hr), and $\tilde{A}_h$ is the cumulated activity in organ h (mCi-hr).

The S-factors for the various source and target organs of interest were taken from MIRD Pamphlet No. 11 (*23*), with the exception of the S-factors for the gallbladder (*24*). These S-factors, shown in Table 3, are different from previously reported values, e.g., S (liver

TABLE 2. RESIDENCE TIMES (hr) IN VARIOUS ORGANS

Organ	Group 1a	Group 1b	Group 2	Group 3
Liver	0.81	0.81	0.66	0.72
Gallbladder	0.90	0.18	0	0
Small intestine	1.8	2.0	1.7	0.69
Upper large intestine	2.4	2.7	2.2	0.92
Lower large intestine	1.0	1.2	1.0	0.41
Kidneys	0.07	0.07	0.13	0.28
Bladder	0.30	0.30	0.60	1.3
Total body	0.12	0.12	0.18	0.42

← gallbladder contents) has been reported as 25 mrad/mCi-hr (*17*), whereas we find a value of 10.1 mrad/mCi-hr (*24*).

The total dose to target organ k (D_k) is given as:

$$D_k = \sum_h D_{k \leftarrow h}.$$

The results are shown in Table 4 and are in good agreement with previously published dosimetry values (*11-15*).

DISCUSSION

We have found that the dynamic behavior of Tc-99m HIDA depends on several factors, including the bilirubin level in the blood pool, the degree of obstruction in the cystic duct and the common bile duct, and the degree of hepatobiliary dysfunction. The tracer initially clears the blood stream at roughly the same rapid rate among the different groups of patients, but after about half an hour, the remaining activity clears much more slowly, with the slowest rate found in patients with the highest bilirubin levels.

TABLE 3. GALLBLADDER-TO-ORGAN S VALUES FOR Tc-99m IN ADULTS (mrad/mCi-hr) (*24*) (SOURCE ORGAN = GALLBLADDER CONTENTS)

Target organ	Source organ
Liver	10.1
Gallbladder	506.0
Small intestine	4.4
Upper large intestine	6.7
Lower large intestine	0.74
Kidneys	5.4
Bladder	0.45
Ovaries	1.3
Testes	0.10
Uterus	1.2
Total body	2.0

The tracer normally clears into the liver-GI pathway, with only a small fraction clearing into the urinary tract. However, in patients with higher bilirubin levels, more activity is observed in the urinary tract and less in the liver. The result is an increasing radiation burden to the kidneys without the benefit of a decrease in radiation burden to the liver, because the rate of excretion from the liver is much slower in patients with hepatobiliary dysfunction.

For normal subjects who do not have fatty-meal stimulation, the radiation burden to the gallbladder wall is 490 mrad/mCi. This value is higher than the 110 mrad/mCi reported by Loberg et al. (*15*), but is considerably lower than the 1880 mrad/mCi value reported by Brown et al. (*17*). The reasons for the higher value in the Brown report are threefold (*1*). They assumed that 56% of the activity from the liver goes to the gallbladder, whereas we used a figure of 35%, based on in vivo measurements using the buildup-factor correction. The scatter contribution, if not corrected, tends to exaggerrate the activity localized in an organ like the gallbladder (*2*). The S-factor ($S_{GBW \leftarrow GBC}$) derived by Brown et al. is about 33% higher than the value used in this work, which was obtained by Bernard and Chen (*24*). The calculation was based on the Monte Carlo transport code using a mathematical phantom including the gallbladder, which is the same method by which all the other S-factors were obtained. Brown et al. calculated the S-factor of the gallbladder using the tabulated absorbed fraction for the liver as an approximation (*3*). The biological half-time of the agent in the gallbladder used in this work is 4 hr. This was obtained from measured data shown in Fig. 3, and is in agreement with the literature (*13,14,16*). Brown et al. (*17*) used a higher value of 6.8 hr, thus finding a higher cumulated activity and absorbed dose in the gallbladder.

The radiation burden to the gallbladder wall is contributed mainly by the quantity of the radioactivity collected in the gallbladder itself, and therefore is in general quite low in patients suffering from cystic duct or common duct obstruction. For other patients, the

TABLE 4. ESTIMATED ORGAN DOSE (mrad) PER mCi OF INJECTED Tc-99m HIDA, FOR ALL PATIENT GROUPS

Organ	Total organ dose (mrad/mCi)			
	Group 1a	Group 1b	Group 2	Group 3
Liver	56.4	50.3	40.5	39.1
Gallbladder wall	490.0	125.3	31.0	19.6
Small intestine	194.2	215.8	182.3	80.0
Upper large intestine	363.0	405.2	340.7	144.5
Lower large intestine	223.0	251.5	214.0	96.4
Kidneys	34.2	32.1	41.1	62.8
Bladder	65.8	67.8	113.2	210.8
Ovaries	70.7	78.6	68.7	36.9
Testes	4.8	5.2	6.1	8.0
Uterus	43.7	47.7	45.8	36.4
Total body	16.4	16.5	14.5	10.1

absorbed dose to the gallbladder wall is 0.49 rad per administered mCi if the content of the gallbladder is not drained after the camera images are obtained. The radiation burden to the gallbladder wall is reduced by a factor of five if a glass of protein drink is taken by the patient at 1 hr after injection. For this reason, we recommend that a fatty meal be taken by patients at the completion of gallbladder imaging studies whenever induced emptying of the gallbladder is not part of the study.

Due to the lower uptake and delayed clearance by the liver in Group 3 patients, the cumulated activities in the intestines are significantly lower, resulting in lower radiation burdens to the intestines as well as to the ovaries or testes.

The radiation burden to the kidneys and bladder increases with the bilirubin level because of increased HIDA clearance through the urinary tract, but the levels are quite low (Table 4). The urinary bladder dose may be further decreased if the patient is instructed to void frequently, particularly within the first 2 hr after injection.

The radiation burdens to the whole body and other reproductive organs are very low.

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