Scintigraphic Variations of Normal Biliary Physiology

Walter Williams, G. T. Krishnamurthy, Harinder S. Brar, and V. R. Bobba

VA Medical Center and Oregon Health Sciences University, Portland, Oregon

We studied 115 healthy adult volunteers, fasting overnight, to establish the normal scintigraphic variability. Five Tc-99m IDA agents with liver excretion half-times ranging from 18 to 108 min were used. The time of appearance of the common bile duct correlated directly with the liver's excretion half-time. The appearance of the gallbladder and the small intestine were independent of the excretion half-time and showed a reciprocal relationship suggesting a major role for the sphincter of Oddi. In 22% of the subjects, the sphincter tonus was tight enough to divert all of the hepatic bile into the gallbladder, allowing none into the intestine. All of such subjects showed normal dynamic response to intravenous cholecystokinin. The pattern of the bile drainage from the two lobes differed, resulting in asymmetry of the right and left hepatic ducts. It is concluded that the selection of a Tc-99m IDA agent should be based on the clinical problem at hand and that a clinician's understanding of the scintigraphic variability in normal subjects is critical before attempting diagnosis.

J Nucl Med 25: 160–165, 1984

Hepatobiliary imaging with Tc-99m-labeled iminodiacetic acid (IDA) analogs is now a well-established test in the diagnosis of acute cholecystitis (*1–3*). Other areas of application of these agents include quantitative biliary dynamics (*4*), differential diagnosis of jaundice (*5*), segmental intrahepatic obstruction, and a variety of other biliary and nonbiliary disorders (*6–11*).

Despite the availability of Tc-99m IDA agents since 1975, normal variations in biliary imaging parameters have not been established in a large number of normal subjects studied under a uniform protocol. For example, it is not clear how much importance should be given to the early appearance (within 30 min) of the gallbladder and the common bile duct (CBD) and the late appearance (60 min) of the intestinal activity. Does this mean partial CBD obstruction, or spasm of the sphincter of Oddi? Tc-99m IDA agents clear from the liver at varying rates, with excretion half-times ranging from 18 to 108 min (*12–14*). Do the appearance times for the gallbladder, common bile duct, or the intestine depend upon either the rapidity of excretion of Tc-99m agent by the liver, or the tonus of the sphincter of Oddi, or both? What is the importance of the nonappearance of the intrahepatic segmental and area bile ducts? The diagnosis of obstruction of these ducts (*9–11*) requires the full knowledge of the normal pattern of bile flow and extremes of variation. The accuracy of confirmation of the diagnosis of acute cholecystitis by imaging is clearly established (*1,2*), but the importance of exclusion of the diagnosis is not fully appreciated. The current project was undertaken to answer the above questions, and we report the results.

MATERIAL AND METHODS

Subject selection. A total of 115 healthy adult volunteers (64 men, 51 women), ranging in the age from 22 yr to 54 yr (mean age 38), was chosen from the general population. The status of their good health was confirmed by obtaining normal liver function tests (total protein, albumin, alkaline phosphatase, bilirubin, lactic

Received June 20, 1983; revision accepted Sept.7, 1983.

For reprints contact: G. T. Krishnamurthy, MD, VA Medical Center (115P), 3710 SW U.S. Veterans Hospital Rd., Portland, OR 97201.

dehydrogenase, and transaminase) and urinalysis. An ultrasound study confirmed normal anatomy of the liver and gallbladder. The subjects were taking no medication.

Data collection. After an overnight fast, each subject received 2-5 mCi (74-185 MBq) of one of five Tc-99m IDA agents intravenously while lying supine under a gamma camera fitted with low-energy, all-purpose, parallel-hole collimator. Di-isopropyl IDA (DISIDA) was used in 29 cases, dimethyl (HIDA) in 59, diethyl (EIDA) in nine, parabutyl (PBIDA) in six, and para-isopropyl (PIPIDA) in 12 subjects (Table 1). The spectrometer was set for 140 keV with a 20% window. The analog images were obtained at 2-min intervals for 60 min and recorded on either Polaroid or 8- by 10-in. x-ray film (Fig. 1, upper left). The data were simultaneously collected in 64- × 64-computer matrix at 1 frame/min for 60 min, which allowed determination of the liver's excretion half-time by a nonlinear least-squares method (*12,14*). A 2.5-cm radioactive reference marker was included with the image between 58–60 min. Finally a right lateral view of the liver was obtained for 2 min. In those subjects whose intestinal radioactivity did not appear by 60 min, imaging was continued for an additional 30 min with an infusion at 70 min of 5 to 10 ng/kg octapeptide of cholecytokinin (OP-CCK).

Data analysis. The times of appearance of the gallbladder (GB), small intestine (SI), and the common bile duct (CBD) were noted from the serial analog images. The right and left hepatic ducts were compared as to their relative prominence. The length of the common duct from the union of the right and left hepatic duct to its termination at the duodenum was measured using the 2.5-cm reference marker. The liver was divided into physiological right and left lobes, based on the formation and course of this common duct (Fig. 1). The anterior and posterior halves of the right lobe of the liver were compared on the right lateral view to check for any difference in bile flow. The entry of radioactivity from the GB into the SI was confirmed on images in all 22 subjects who received OP-CCK.

RESULTS

All of the 115 GBs and CBDs, but only 93 (80%) SIs were seen within 60 min. In the remaining 22 subjects, the SI was seen promptly after OP-CCK infusion (Table 2), and in all of them the gallbladder was seen within 30 min and in 19 within 20 min. The left hepatic duct (LHD) was more prominent in 63 (55%), the right hepatic duct (RHD) in 15 (13%), and the two showed equal prominence in 12 (10%). In 25 subjects (22%), neither duct was seen (Table 3), but in all of these the SI appeared within 30 min. Nonvisualization of ducts occurred with all five agents, mostly in association with early intestinal activity. In 93 subjects the GB and SI were seen within 60 min, and in 55 of these both appeared within 30 min. In the remaining 38 subjects a reciprocal relationship was noted (Fig. 2). The GB appearance after 30 min was accompanied by an early SI appearance, and vice versa. In all nine subjects whose GB appeared after 30 min, the SI was seen within 25 min. Likewise, in all 29 subjects whose SI was seen after 30 min, the GB was seen within 25 min. About 50% of the GBs were seen within 15 min, 90% within 30 min, and 100% within 55 min (Fig. 3). The mean length of the common duct from the junction of RHD and LHD to its termination in the duodenum was 6.6 ± 1.3 cm.

The emptying of the gallbladder was normal following OP-CCK infusion. There was no difference between the anterior and posterior halves of the right lobe (right lateral view), suggesting equal rates of bile flow. There

TABLE 1. LIVER EXCRETION HALF-TIME AND TIMES OF APPEARANCE OF CBD, GB, AND INTESTINE IN 115 NORMAL SUBJECTS WITH FIVE Tc-99m IDA AGENTS (MEAN ± s.e., AND RANGE)*

Tc-99m IDA agent	Liver $T_{1/2}$ min (14)	Appearance time (min)		
		Common bile duct	Gallbladder	Intestine (n = 93)
DISIDA (n = 29)	18.8 ± 2.5	9.6 ± 0.7 (6–20)	14.2 ± 2.2 (6–50)	22.1 ± 2.4 (6–50)
EIDA (n = 9)	37.3 ± 11.8	13.8 ± 1.2 (8–18)	15.5 ± 1.1 (12–20)	27.3 ± 4.7 (12–50)
HIDA (n = 59)	42.3 ± 5.4	14.4 ± 0.6 (6–28)	17.4 ± 0.8 (8–34)	31.9 ± 1.9 (10–60)
PIPIDA (n = 12)	59.3 ± 5.0	16.0 ± 1.0 (10–22)	23.7 ± 4.3 (10–60)	32.8 ± 4.8 (20–60)
BIDA (n = 6)	107.6 ± 14.1	25.3 ± 2.2 (18–32)	21.8 ± 1.8 (16–28)	30.5 ± 4.4 (22–42)

* Values within a bracket do not differ significantly, and those outside brackets differ from each other at $p < 0.05$. IDA agents: DISIDA = di-isopropyl, EIDA = diethyl, HIDA = dimethyl, PIPIDA—paraisopropyl, and BIDA = parabutyl.

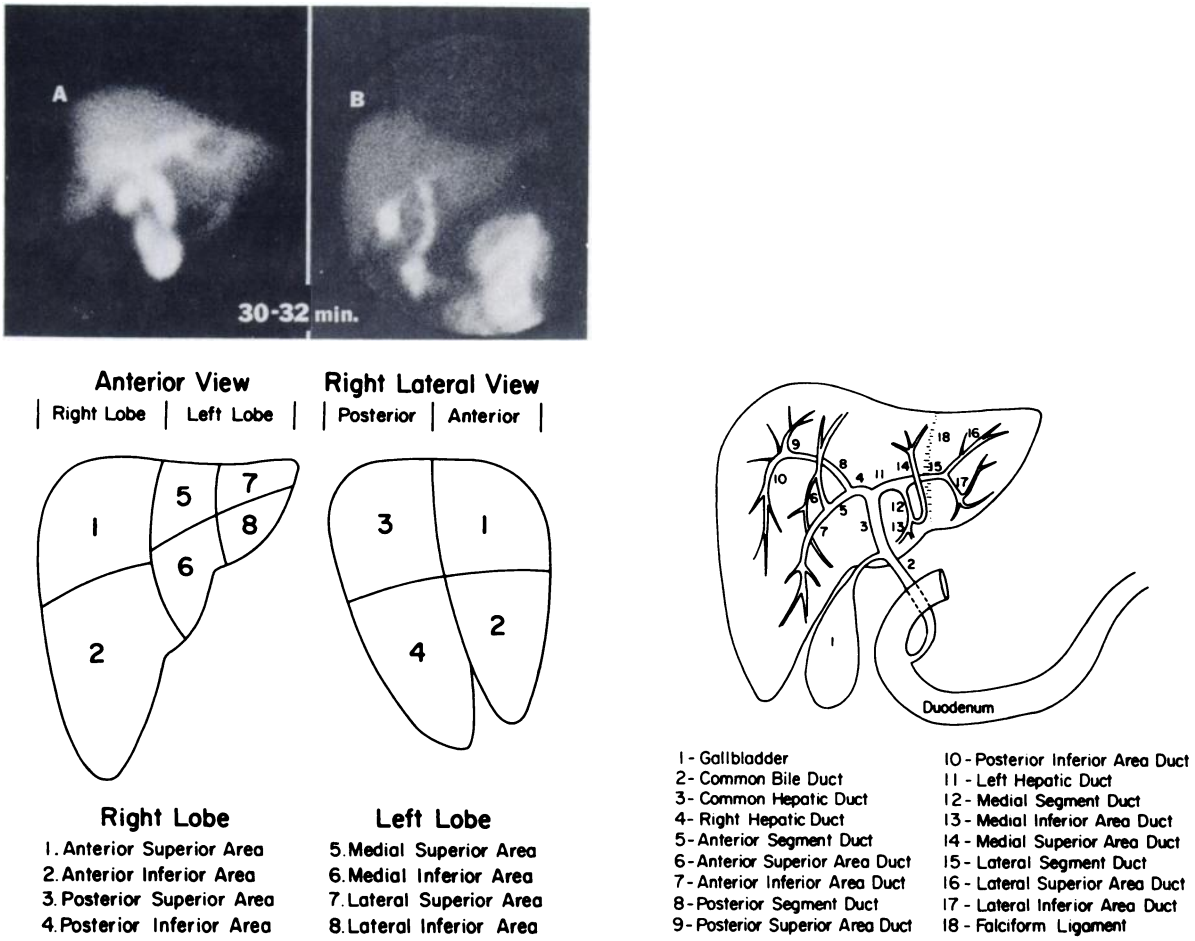

FIG. 1. Normal variations in pattern of bile flow from right and left lobes (upper left). Note LHD prominence with clear separation of medial- and lateral-segment ducts in Subject A, and nonvisualization of both RHD and LHD in Subject B, in whom most of bile enters intestine quickly (lax sphincter). Diagram of division of liver physiologically into two lobes, four segments, and eight areas (lower left). These regions are drained by corresponding ducts (see lower right). Two posterior areas of right lobe are seen better in right lateral view. Diagram of normal biliary anatomy on scintigraphy (lower right). Ducts are named after areas, segments, and lobes they drain. Note that anatomical line of demarcation (falciform ligament, 18) is to left of physiological division (union of RHD and LHD and course of common hepatic duct), and that medial segment duct (12) drains bile from area between these two demarcations.

was no statistically significant difference among the five agents in the mean-time of appearance of the gallbladder and the small intestine. The mean-time of appearance of CBD, on the other hand, correlated directly ($r = 0.99$, $p < 0.001$) with the half-time of the agent's liver excretion (Table 1).

DISCUSSION

Division of liver. The division of the liver into right and left lobes is based on either anatomical or physiological markers. It is felt that the anatomical division (attachment of the falciform ligament) is convenient but does not serve any useful purpose, since it follows no embryological separation (*15*). The physiological division, on the other hand, is more meaningful since it follows the development and is marked by a deep lobar fissure posteriorly in line with the fossa for the gallbladder and fossa for inferior vena cava (*15*). This information is essential prior to or during biliary surgery (Fig. 1, upper left).

In 1953, Healey and Schroy made a detailed study of 100 adult human livers obtained at autopsy and named the ducts according to a recommendation made by an international nomenclature committee (*15*). This nomenclature is adopted in our discussion of the biliary structures as they appear on Tc-99m IDA scintigrams.

Biliary anatomy. For scintigraphic purposes, the liver can be divided into two lobes, four segments, and eight areas (Fig. 1). The ducts are named corresponding to areas, segments, and lobes, and they drain as shown in Fig. 1 (lower right). Note that a part of the medial segment of the physiological left lobe forms a part of the "anatomical" right lobe. Caudate and quadrate lobes do not appear as separate entities on scintigraphy. In 72% of the subjects, the RHD and LHD are formed by the

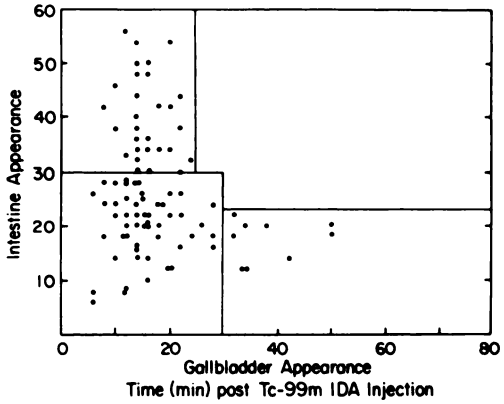

FIG. 2. Relation between appearance times of gallbladder and small intestine. Note that in most subjects both appear within 30 min (lower left square). In all nine subjects whose gallbladders appeared after 30 min, SI was seen within 25 min (lower right rectangle), and in all 28 subjects whose SI appeared after 30 min, GB was seen within 25 min (upper left rectangle).

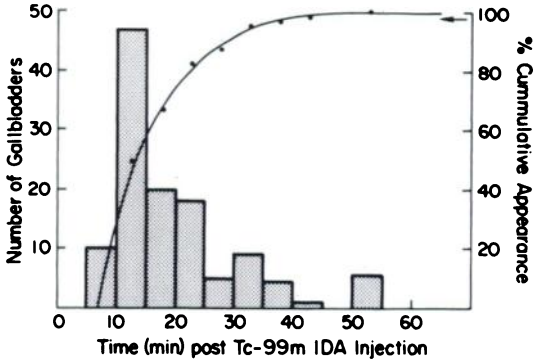

FIG. 3. Time of appearance of 115 normal gallbladders with Tc-99m IDA. Note that 50% appear within 15 min, 80% within 25 min, and 100% within 60 min. Appearance time is shown on x-axis and number of visible gallbladders on y-axis. Cumulative percent appearance is shown at right.

union of their respective segmental ducts. The posterior and anterior segment ducts of the right lobe join the LHD in 22% and 6% of the subjects, respectively (*15*).

Intra- and extrahepatic ducts. The terminal portions of both RHD and LHD, and the entire course of the common hepatic duct and common bile duct, are extrahepatic in location, despite the opposite impression by scintigram (Fig. 1). This is because the inferior liver border extends anterior to these structures. Proximal RHD and LHD and the rest of the segmental and area ducts are intrahepatic. The terminal part of RHD and LHD join to form the common hepatic duct about 0.5 to 1 cm away from the deep fissure over the posterior surface of the liver. The common hepatic duct is ~3 cm long and the common bile duct ~5 cm, for a total of 8 cm from the union of RHD and LHD to the ductal entry into the duodenum (*16*). On our scintigrams this entire length measured 6.6 ± 1.3 cm (mean ± s.d.). The ducts proximal to RHD and LHD are sometimes not seen on scintigraphy (Fig. 1) and become prominent when there is partial obstruction, with pooling of bile over the corresponding area (*9,11*). Depending upon the location of bile pooling, one may infer which area, segmental, or lobe duct is involved, a situation like that in lung perfusion studies where the lobes and segments are identified from the image pattern. Complete CBD obstruction of less than 24 hr duration is characterized in experimental animals by good hepatic uptake and excretion of Tc-99m IDA, with clear gallbladder visualization. An obstruction lasting more than 24 hr is characterized by nonvisualization of the gallbladder and the extrahepatic ducts, with a relatively good hepatic uptake (*17*).

Duct asymmetry. In our study, the LHD prominence was seen more often (55%) than the RHD (Table 3). The reasons for the LHD prominence are not all known but may include the following: (a) less photon attenuation due to thin liver tissue overlying the LHD; (b) LHD more anterior in position than RHD; (c) the posterior or anterior segmental duct from the right lobe draining bile into LHD instead of its usual RHD; (d) the undivided portion of the LHD is twice as long as RHD and is more prone to tortuosity that impedes free bile flow into the common hepatic duct (CHD). The RHD course is shorter and more directly in line with CBD (*15,18,19*). Since many types of drainage procedures are now available for therapy (*20,21*), the detection of segmental and area ductal obstruction noninvasively attains more importance (*10–11*).

Sphincter role. The fractional hepatic bile flow after an overnight fast is variable, depending upon the tonus of sphincter of Oddi, with a mean of 70% into GB and 30% into SI (*4*). If the sphincter tonus is increased, all

TABLE 2. FREQUENCY OF VISUALIZATION OF CBD, GALLBLADDER AND INTESTINE BY 60 min IN 115 NORMAL SUBJECTS

	No.	(%)
Visualization of GB by 60 min	115	100%
Visualization of CBD by 60 min	115	100%
Visualization of intestine by 60 min	93	80%
Nonvisualization of the intestine by 60 min	22	20%

TABLE 3. RELATIVE PROMINENCE OF RIGHT AND LEFT HEPATIC DUCTS WITH Tc-99m IDA IN 115 NORMAL SUBJECTS

	No.	(%)
Left hepatic duct prominence	63	55%
Right hepatic duct prominence	15	13%
Left hepatic duct = right hepatic duct	12	10%
Neither duct visualized	25	22%

of the hepatic bile formed during fast may enter GB and none into SI. This happened in 20% of our subjects (Table 2). A reciprocal relationship between GB and SI bile flow is evident when the GB appears within 30 min (suggesting increased sphincter tone) and the SI appears beyond 30 min (Fig. 2). No reciprocal relationship is seen when both of them appear within 30 min. Therefore, nonvisualization of the SI at 60 min usually indicates increased sphincter tonus and does not necessarily mean an anatomic abnormality. Dynamic studies with cholecystokinin or fatty meal are needed to differentiate the spasm and fixed anatomical lesions from a normally tight sphincter (*4*). Unlike the GB and SI, the time of appearance of CBD depends on the rapidity of excretion of Tc-99m IDA from the liver; it appears early with an agent that clears rapidly, and vice versa (Table 1).

A confirmatory test documenting cystic duct obstruction as a sign of acute cholecystitis requires imaging up to 3–4 hr (*1*,*2*). On the other hand, the documentation of patency of cystic duct can be accomplished much sooner, usually within an hour (Fig. 3). Our results show that 50% of the normal gallbladders will appear within 15 min, 90% within 30 min, and 100% within 55 min. A delayed GB appearance between 1 and 3 hr is a feature of chronic cholecystitis (*1*,*2*).

Advantages and disadvantages of fast and slow agents. The rapidity of clearance of Tc-99m IDA agents from the liver is dependent upon the integrity of the hepatocytes, and the structural difference among agents plays a role in determining how fast an agent is excreted from the hepatocytes into bile (*12*). Once the agent is cleared into bile, however, the flow of bile into the GB compared with SI is controlled primarily by the tonus of the sphincter of Oddi and the concentrating capacity of the gallbladder. Often it is possible for the hepatocyte function to remain entirely normal while gallbladder function alone is abnormal, as is often the case in chronic cholecystitis and in patients on long-term parenteral nutrition (*22*). Therefore, a combination of a normal liver but abnormal GB function may result in nonvisualization of the GB if a rapidly clearing Tc-99m IDA agent is chosen for imaging. The mean excretion half-times of Tc-99m IDA agents range from 18.8 to 108 min (Table 1). This information was not available when the claims of "best overall agent" were made (*23*).

In the earlier studies, using mainly the slow-clearing agents, the overall diagnostic accuracy (97.5%), specificity (99.2%), and sensitivity (95.2%) for acute cholecystitis were high with a low false-positive incidence (gallbladder nonvisualization) (*1*). In recent years, however, the incidence of false-positve GB imaging has increased, and in such studies more often a rapidly clearing agent has been used (*24*). In six of ten patients studied by Kalff et al., the serum bilirubin was entirely normal (<1.3 mg/dl) and the patients were fasting longer than 2 days and some up to 30 days. Biliary imaging at 2 or 2.5 hr with DISIDA means imaging after six to eight liver excretion half-times of the agent. After six half-times, less than 1.5% of the liver activity at injection time is retained in the liver (*14*). In the presence of normal liver function, there appears to be no point in imaging beyond 2 hr with agents that clear with an excretion half-time less than 20 min. Since the gallbladder may fill slowly in such conditions, the agents that clear from the liver at a much slower rate appear most suitable if we are to maintain the high level of diagnostic accuracy that has already been achieved (*1*,*2*). Rapidly clearing agents are ideal for the assessment of the common bile duct and the intrahepatic ducts, but there is no theoretical reason why these agents should be better for visualizing the gallbladder, especially when its function is compromised. In patients with abnormal liver function, the agents of choice are those that resist displacement by high serum bilirubin (*13*,*25–27*).

The clear visualization of the entire biliary system was easily accomplished, since all of our subjects were normal healthy volunteers from the general population. The question arises about the constancy of the biliary physiology in a subject on a day-to-day basis. In a paired study, using HIDA on both occasions in normal subjects, the biliary physiology is shown to be predictably constant from day to day (*28*). However, we do not know whether this constancy is maintained in disease.

ACKNOWLEDGMENT

We thank Dr. Paul Brown for providing statistical analysis and for suggestions and review of the manuscript, and Mrs. Barbara Wright for manuscript preparation.

This project is supported by the Veterans Administration.

REFERENCES

1. KRISHNAMURTHY GT: Acute cholecystitis: The diagnostic role for current imaging tests. *West J Med* 137:87–94, 1982
2. WEISSMANN HS, BADIA J, SUGARMAN LA, et al: Spectrum of 99m-Tc-IDA cholescintigraphic patterns in acute cholecystitis. *Radiology* 138:167–175, 1981
3. SAMUELS BI, FREITAS JE, BREE RL, et al: A comparison of radionuclide hepatobiliary imaging and real-time ultrasound for the detection of acute cholecystitis. *Radiology* 147:207–210, 1983
4. KRISHNAMURTHY GT, BOBBA VR, MCCONNELL E, et al: Quantitative biliary dynamics: Introduction of a new non-invasive scintigraphic technique. *J Nucl Med* 24:217–223, 1983
5. FONSECA C, ROSENTHAL L, GREENBERG D, et al: Differential diagnosis of jaundice of Tc-99m-IDA hepatobiliary imaging. *Clin Nucl Med* 4:135–142, 1979
6. WEISSMANN HS, SUGARMAN LA, FRANK MS, et al: Serendipity in technetium-99m dimethyl iminodiacetic acid cholescintigraphy. *Radiology* 135:449–454, 1980
7. FREITAS JE, FINK-BENNET DM, THRALL JH, et al: Efficacy of hepatobiliary imaging in acute abdominal pain: Concise communication *J Nucl Med* 21:919–924, 1980

8. EIKMAN EA: Radionuclide hepatobiliary procedures: when can HIDA help? *J Nucl Med* 20:358-361, 1979
9. KUNI CC, KLINGENSMITH WC III: *Atlas of Radionuclide Hepatobiliary Imaging.* Boston, G. H. Hall Medical Publishers, 1983, pp 63-120
10. GUPTA S, OWSHALIMPUR D, COHEN G, et al: Scintigraphic detection of segmental bile-duct obstruction. *J Nucl Med* 23:890-891, 1981
11. YEH S-H, LIU O-K, HUANG M-J: Sequential scintigraphy with technetium-99m pyridoxylideneglutamate in the detection of intrahepatic lithiasis: Concise communication. *J Nucl Med* 21:17-21, 1980
12. BOBBA VR, KRISHNAMURTHY GT, KINGSTON E, et al: Comparison of biokinetics and biliary imaging parameters of four Tc-99m iminodiacetic acid derivatives in normal subjects. *Clin Nucl Med* 8:70-75, 1983
13. KLINGENSMITH WC III, FRITZBERG AR, SPITZER VM, et al: Work in progress: clinical evaluation of Tc-99m-trimethylbromo-IDA and Tc-99m-diisopropyl-IDA for hepatobiliary imaging. *Radiology* 146:181-184, 1983
14. BROWN PH, KRISHNAMURTHY GT, BOBBA VR, et al: Radiation dose calculation for five Tc-99m-IDA derivatives. *J Nucl Med* 23:1025-1030, 1982
15. HEALEY JE JR, SCHROY PC: Anatomy of the biliary duct within the human liver. *Arch Surg* 66:599-616, 1953
16. SCHOENFIELD LJ: *Diseases of the Gallbladder and Biliary System.* New York, John Wiley and Sons, 1977, pp 1-43
17. KLINGENSMITH WC III, WHITNEY WP, SPITZER VM, et al: Effect of complete biliary-tract obstruction on serial hepatobiliary imaging in an experimental model: Concise communication. *J Nucl Med* 22:866-868, 1981
18. SCHEIN CJ, STERN WZ, JACOBSON HG (eds): *The Common Bile Duct.* Springfield, IL, Charles C. Thomas, 1966, pp 33-66
19. STERN WZ, SCHEIN CJ, JACOBSON HG: The significance of the lateral view in T-tube choleangiography. *Am J Roentgenol* 87:764-771, 1962
20. MUELLER PR, FERRUCCI JT, JR, VAN SONNENBERG E, et al: Obstruction of the left hepatic duct: diagnosis and treatment by selective fine-needle choleangiography and percutaneous biliary drainage. *Radiology* 145:297-302, 1982
21. MCLEAN GK, RING EJ, FREIMAN DB: Therapeutic alternatives in the treatment of intrahepatic biliary obstruction. *Radiology* 145:289-295, 1982
22. ROSLYN JJ, PITT HA, MANN LH, et al: Gallbladder disease in patients on long-term parenteral nutrition. *Gastroenterology* 84:148-154, 1983
23. WEISSMANN HS, BADIA JD, HALL T, et al: Tc-99m-diisopropyl iminodiacetic acid (DISIDA): The best overall cholescintigraphic radionuclide for the evaluation of hepatobiliary disorders. *J Nucl Med* 21:P18, 1980 (abst)
24. KALFF V, FROELICH JW, LLOYD R, et al: Predictive value of an abnormal hepatobiliary scan in patients with severe intercurrent illness. *Radiology* 146:191-194, 1983
25. BROWN PH, KRISHNAMURTHY GT, BOBBA VR, et al: Radiation dose calculation for Tc-99m-HIDA in health and disease. *J Nucl Med* 22:177-183, 1981
26. KLINGENSMITH WC III, FRITZBERG AR, SPITZER VM, et al: Clinical comparison of ^{99m}Tc-Diethyl-IDA and ^{99m}Tc-PIPIDA for evaluation of the hepatobiliary system. *Radiology* 134:195-199, 1980
27. NUNN AD, LOBERG MD, CONLEY RA: A structure-distribution-relationship approach leading to the development of Tc-99m-mebrofenin: an improved cholescintigraphic agent. *J Nucl Med* 24:423-430, 1983
28. BOBBA VR, KRISHNAMURTHY GT, KINGSTON E: Consistent parameters of normal biliary imaging. The role in the comparative assessment of Tc-99m-labeled IDA derivatives. *Nucl Med Comm* 2:9-14, 1981