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Reply

The elimination kinetics of technetium-99m HIDA are altered in the hyperbilirubinemic, nonobstructed patient, resulting in decreased hepatobiliary clearance. In a recent *Journal* article (*1*) we demonstrated that bromsulfophthalein and, therefore, bilirubin were competitive inhibitors of Tc-99m HIDA's clearance. We further postulated that increased patient serum bilirubin levels would frustrate any linear pharmacokinetic approach to the measurement of liver function. In his letter, Dr. Popescu presents an alternative hypothesis—namely, that disease-related alterations in hepatocellular function are the primary determinate of Tc-99m HIDA's in vivo kinetics in the nonobstructed patient.

Dr. Popescu is correct in noting that the elimination of Tc-99m HIDA is a function of the biochemical integrity of the hepatocyte. A significant decrease in Tc-99m HIDA's liver uptake has been observed with experimentally induced liver cell damage in the absence of an elevated serum bilirubin level. Clinically, patients with severe drug-induced hepatitis frequently have much less Tc-99m HIDA liver uptake than is found in patients with primary hemolytic disease even though the latter have higher serum bilirubin. These results indicate that liver cell damage *per se* is a determinate of Tc-99m HIDA's liver uptake; they do not alter the conclusion of our recent paper, since the hepatocellular uptake and elimination rate constants can be a function of more than one variable. A relevant example of this process would be the active transport of pertechnetate into the thyroid, where the rate constant is a function of the integrity of the thyroid and the serum concentration of perchlorate (*2*). The inability to image the liver of the hyperbilirubinemic patient with Tc-99m HIDA is no more diagnostic for hepatocellular disease than is the inability of pertechnetate to image the thyroid in the presence of perchlorate diagnostic for thyroid disease.

These conclusions are further supported by the data in Table 1, which demonstrate that the uptake of various radiopharmaceuticals into isolated hepatocytes is inhibited by the addition to the reaction medium as either bilirubin or BSP. It is difficult to attribute this inhibition to drug-induced alterations in hepatocellular function, since BSP and bilirubin are relatively nontoxic at these concentrations and since the total exposure of the cells to these agents was less than 30 min (*3*).

Dr. Popescu also questions the use of radiolabeled bile salts as model compounds for the development of new hepatobiliary agents. His points are well taken, but the answers to many of his questions are best found using competitive in vitro analysis. The diagnostic utility of radiolabeled bile salts will depend upon their affinity for the carrier transport site (K_m), the capacity of their transport system (V_{max}), and the extent to which inhibitors reduce this capacity (K_I). These data are only now beginning to be collected in our laboratory (*3*) and elsewhere (*4,5*).

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TABLE 1. RADIOPHARMACEUTICAL UPTAKE INTO ISOLATED HEPATOCYTES

	Relative percent uptake*					
	Bilirubin (%)				BSP (μM)	
Agent	0	3.8	7.4	11.5	30	300
Rose Bengal	100(13.5)	73.1	57.7	43.7	60	28
HIDA	100(50.0)	87.6	51.2	34.6	62	23
DIDA	100(67.8)	86.9	72.7	57.3	90	50
PIPIDA	100(75.7)	93.7	83.1	70.3	88	63
BIDA	100(80.7)	95.0	91.1	82.7	94	50

*Uptake in absence of inhibitive set equal to 100%; absolute % uptake values are in parentheses.

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