17-Iodine-123 Iodoheptadecanoic Acid for Metabolic Liver Studies in Humans

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(17-^{123}I)-Iodoheptadecanoic acid ([^{123}I]HA) was used for dynamic planar scintigraphy of the liver in normal individuals (control I), in patients without liver disease but with elevated serum cholesterol and/or triglycerides (control II), and in patient groups with (a) alcohol-induced fatty liver (PG I), (b) fatty liver not due to alcohol (PG II), (c) alcohol-induced liver cirrhosis (PG III), or (d) liver cirrhosis of the posthepatitic type (PG IV). Tracer uptake and elimination time were assayed in different liver regions; mean elimination time was expressed for total liver. In control I, tracer uptake was homogeneous, and mean elimination time was 20.7 ± 5.3 min without significant local variations. In control II, tracer uptake was reduced but homogeneous and mean elimination time was 59.4 ± 35.8 min with some local variations. In PG I, uptake was reduced and inhomogeneous and elimination time was the same as in control I, irrespective of cholesterol and triglyceride values. In PG II, uptake was the same as in PG I but mean elimination time was 48 ± 8.1 min with some local variations. In PG III, uptake was extremely reduced and spotty and elimination time correlated with the severity of disease from 19 to 881 min in different liver regions.

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Several metabolic investigations of free fatty acids (FFA) in various organs of animals have been described both in vivo and in vitro (*1–6*). Most of those studies involved heart, liver, and brain tissue and included observations of the fatty acid uptake by brain (*6*), heart (*5,7*), and liver (*8*) of mouse and rat in vivo and in vitro, effects of fatty acids on energy metabolism in the perfused rat liver (*9*), metabolism of free fatty acids by isolated rat liver cells (*8*), incorporation of fatty acids into rat liver glycerolipids (*10*), and fatty acid uptake by liver cells (*11*). However, studies of perfused organs and isolated cells are quite different from those done under normal physiological conditions. If fatty acids are administered orally or intravenously, they circulate throughout the whole body and it is therefore necessary to consider the effects of other organs on the metabolism of these fatty acids.

Liver metabolism of fatty acids may be studied noninvasively with labeled fatty acids using 17-iodine-123 iodoheptadecanoic acid ([^{123}I]HA), and tracer accumulation and turnover of fatty acids can be assayed separately (*12*). This study is an attempt to describe accumulation and turnover of labeled fatty acids in patients without liver disease and will further describe the first clinical results to whether [^{123}I]HA may be used as an indicator for the noninvasive evaluation of normal and disturbed hepatocellular metabolism.

PATIENTS AND METHODS

The study included: 16 patients without liver disease and with normal serum cholesterol (C) and triglycerides (T) (control I); six patients without liver disease but with elevated C and/or T (control II); ten patients with alcohol-induced fatty liver (PG I); four patients with fatty liver but without history of alcoholism (PG II); five patients with cirrhosis due to chronic alcohol consumption (PG III); and four patients with cirrhosis following hepatitis B (PG IV). Characterization of control subjects included normal clinical history and normal liver function tests (total protein, albumin, globulin, alkaline phosphatase, bilirubin, lactic dehydrogenase, and transaminases). An ultrasound study confirmed normal anatomy of the liver and gallbladder. The subjects were taking no medication. Patients were diagnosed on the basis of clinical history, pathological

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liver function tests, diagnostic ultrasound, laparascopy, and liver biopsy in all cases. Neither control patients nor any individual in the different patient groups had symptoms of cardiac disease. This was confirmed by patient history, physical examination, rest and exercise ECG, chest x-ray, and thallium scintigraphy.

After overnight fasting each individual received intravenously 2–3 mCi [^{123}I]HA. Dynamic images of the liver including the heart region were taken in the anterior projection under the head of a large field-of-view Anger scintillation camera, equipped with a low-energy parallel-hole collimator. The measurement was started immediately with the injection of the tracer. One millicurie of carrier-free sodium-^{123}I was administered i.v. 30 min after injection of [^{123}I]HA to derive a correction for ^{123}I in the blood pool and interstitial space as previously published (*13*). A total of 40 images—one per minute—were registered. Accumulation of [^{123}I]HA was assayed qualitatively, whereas turnover rates were given quantitatively as elimination half-times (ET). For this purpose, regions of interest were selected for the superior and inferior area of the right lobe (regions A and B) and for the left lobe (region C) of the liver as well as for the total left ventricular wall. Mean elimination times—representing the total liver—were calculated from the three liver regions. Mean activity per pixel in the heart region and in the three liver regions was used for calculating heart/liver ratios. The demonstrated images were obtained from the ^{123}I corrected images, collecting data from the time of peak accumulation over a period of 7 min. For comparison, all patients had technetium-99m (^{99m}Tc) sulfur colloid scans 3 days after the [^{123}I]HA study.

RESULTS

Patients without liver disease and normal serum cholesterol and triglycerides (Table 1) showed a homogeneous distribution of [^{123}I]HA within the liver (Fig. 1A). Besides the liver, the left ventricular wall was clearly delineated. In contrast to the liver sulfur colloid scan (Fig. 1B) there was no tracer accumulation in the spleen. Heart/liver ratios of tracer uptake ranged between 1.0 and 1.31 with an average of 1.25. The mean elimination time for the total liver was 20.7 min ± 5.25. The ET from different liver regions did not differ significantly ($p < 0.05$) (Table 2).

Control II patients without liver disease but with elevated serum cholesterol and/or triglycerides (Table 3) had normal colloid scans but a homogeneous reduced uptake of [^{123}I]HA in the liver, whereas the heart showed a normal accumulation (Fig. 2). Heart/liver ratios were 1.42 and, therefore, elevated compared with control I patients, who had normal values for serum cholesterol and triglycerides. The mean ET for the total liver was 59.4 ± 35.7 min (Table 4) and, therefore, significantly longer ($p < 0.05$) than that in control I, whereas the ET for the total heart was in the normal range. The prolongation of ET did not relate to the degree of elevation for C and/or T. Elimination times varied within single

TABLE 1
Plasma Concentrations of Liver Enzymes and Lipids in Normals (Control I)*

Patient no.	GOT mU/ml	GPT mU/ml	GGT mU/ml	Alkal. phosph. mU/ml	Triglyc. mg (%)	Cholest. mg (%)
1	12	11	14	75	119	179
2	10	13	9	82	109	150
3	14	11	7	66	33	194
4	11	11	6	99	43	217
5	12	18	21	125	78	217
6	11	11	6	77	66	229
7	10	14	12	75	148	139
8	12	8	7	87	92	183
9	13	16	16	119	153	194
10	10	14	16	103	141	198
11	7	10	13	56	100	203
12	14	17	18	102	98	141
13	17	14	15	110	115	131
14	12	15	7	66	111	205
15	10	14	7	76	53	240
16	12	18	12	78	138	232

*GOT: Glutamate oxalacetate transaminase; GPT: Glutamate pyruvate transaminase; GGT: α-Glutamyl transpeptidase.

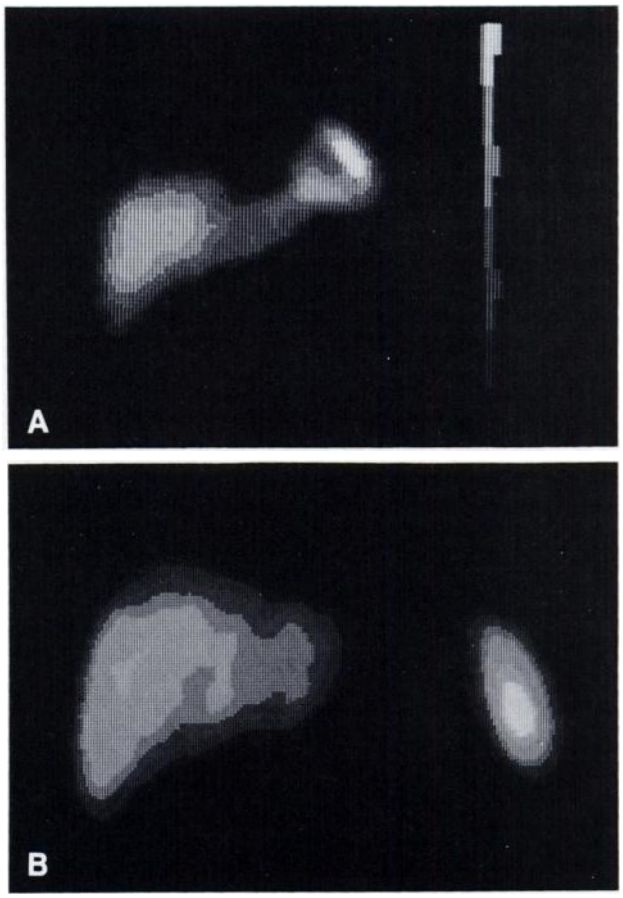

FIGURE 1
A: Iodine-123 HA liver image of normal subject with normal values for cholesterol and triglycerides in serum. B: Technetium-99m colloid scan of same patient as in Fig. 1A

TABLE 2
Elimination Half Times of ω-Iodine-123 Heptadecanoic Acid in Normals (min)

Patient no.	A*	B*	C†	Mean
1	27.6	26.8	26.6	27.0
2	22.2	24.0	23.1	23.1
3	8.7	12.1	11.2	10.7
4	12.6	10.8	11.2	11.5
5	27.5	19.7	20.0	22.4
6	16.4	17.7	13.9	16.0
7	12.3	15.6	11.0	13.0
8	26.4	25.3	26.9	26.2
9	18.1	20.3	19.2	19.2
10	20.1	22.0	21.8	21.3
11	27.6	26.6	27.9	27.3
12	23.8	23.8	17.2	21.6
13	23.1	23.6	24.7	23.8
14	24.4	23.2	25.3	24.3
15	25.3	25.2	26.2	25.6
16	18.0	20.2	18.8	19.0
$\bar{x}$	20.88	21.06	20.31	20.75
$S\bar{x}$	5.80	4.72	5.79	5.25

* A and B: Regions of right lobe.
† C: Region of left lobe.

liver areas with a minimal variation of 8 (Patient 3, Table 4) and a maximal difference of 26% (Patient 5, Table 4).

Patients with alcoholic fatty liver showed reduced inhomogeneous uptake of [^{123}I]HA (Fig. 3A), whereas the sulfur colloid scans were nearly normal (Fig. 3B).The mean heart/liver ratio was 1.47. The ETs (Table 5) of these patients were in the range of control I patients independent of normal or elevated values for C and/or T and also independent of the degree of abnormalities found by liver function tests. Furthermore, the inhomogeneity of uptake in different liver regions was not accompanied by a significant variation in elimination times.

Patients with fatty liver not due to alcohol showed a reduced inhomogeneous distribution pattern of [^{123}I] HA and were not distinguishable from patients with alcohol-induced fatty liver, even if serum lipids were in the normal range. Generally, colloid scans did not indicate liver disease. Iodine-123 HA heart/liver ratios

TABLE 3
Plasma Concentrations of Liver Enzymes and Lipids in Normals (Control II)

Patient no.	GOT mU/ml	GPT mU/ml	GGT mU/ml	Alkal. phosph. mU/ml	Triglyc. mg (%)	Cholest. mg (%)
1	14	17	26	106	292	277
2	10	22	25	115	270	194
3	12	21	20	76	178	288
4	11	18	23	99	76	291
5	13	22	10	106	199	203
6	12	21	16	102	367	189

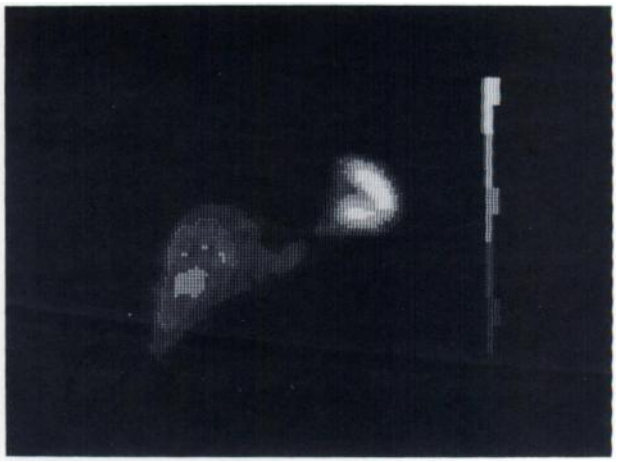

FIGURE 2
Iodine-123 HA liver image of normal subject with elevated triglycerides and/or cholesterol in serum

ranged between 1.49 and 1.68. The ETs had a mean of 48.0 ± 8.06 min (Table 6) for the total liver and were therefore prolonged compared with control I patients and also compared with patients with alcoholic fatty liver. The ETs for different liver regions varied significantly ($p < 0.005$).

In patients with alcohol-induced cirrhosis (Fig. 4A) the uptake of [^{123}I]HA was extremely reduced with a mean heart/liver ratio of 5.2. The diminution in uptake was more pronounced than in sulfur colloid scans (Fig. 4B) but the tracer pattern within the liver was comparable for both scans. It was difficult to properly assess size and enlargement of the liver in the [^{123}I]HA or sulfur colloid images. The ETs with a mean of 120.1 ± 71.5 min for the total liver were prolonged and ranged between 19.9 and 881.6 min in different liver regions (Table 7). The overall mean of ET was 212.8 min for the right and 50.0 min for the left lobe. This was consistent with difference of initial distribution between right and left liver lobes with relatively higher uptake in the left lobe (except Patient 5, Table 7). The prolongation in ET correlated with the stage of cirrhosis, i.e.,

TABLE 4
Elimination Half Times of ω-Iodine-123-Heptadecanoic Acid in Normals with Elevated Cholesterol and/or Triglycerides (min)

Patient no.	A*	B*	C†	Mean
1	58.6	72.9	46.4	59.3
2	38.9	41.0	29.0	36.3
3	38.0	34.8	32.1	35.0
4	118.0	137.2	157.1	137.4
5	38.6	45.6	52.4	45.5
6	38.7	42.3	47.6	42.9
$\bar{x}$	55.13	62.30	60.77	59.40
$S\bar{x}$	29.05	35.62	43.90	35.77

* A and B: Regions of right lobe.
† C: Region of left lobe.

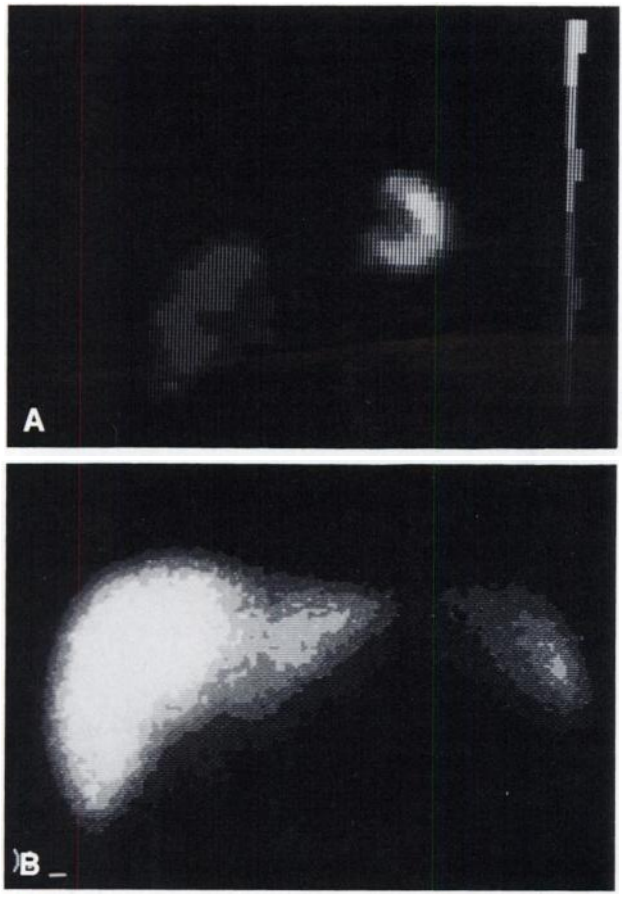

FIGURE 3
A: Iodine-123 HA image of patient with alcoholic fatty liver. Morphological features included fatty liver without cell degeneration or necrosis. B: Technetium-99m colloid image of same patient as in Fig. 3A

patients with advanced liver disease had longer ET than patients in the intermediate stage.

Three of the four patients with posthepatitic cirrhosis had normal values for serum cholesterol and triglycerides. Liver uptake of [^{123}I]HA was extremely reduced, as in patients with alcoholic liver cirrhosis with a patchy distribution and/or defects in uptake throughout the organ (Fig. 5). Again, the reduction in uptake was more pronounced than in the colloid scans. The ETs varied (Table 8) and were relatively short in patients with compensated cirrhosis (Patients 1 and 2, Table 8). In contrast, the ETs were not measurable in Patient 4, Table 8; this patient died in hepatic coma 8 days after investigation.

TABLE 5
Elimination Half Times of ω-Iodine-123-Heptadecanoic Acid in Patients with Alcoholic Fatty Liver (min)

Patient no.	A*	B*	C†	Mean
1	25.4	27.4	23.0	25.3
2	28.8	28.4	21.7	26.3
3	21.7	19.1	16.6	19.1
4	21.2	24.5	15.4	20.4
5	41.8	26.0	29.8	32.5
6	24.3	22.5	20.3	22.4
7	21.7	22.3	24.6	22.9
8	26.9	31.4	28.0	28.7
9	19.4	21.6	23.8	21.6
10	26.4	23.9	25.0	25.1
$\bar{x}$	25.8	24.7	22.8	24.4
$S\bar{x}$	±6.0	±3.5	±4.3	±3.8

* A and B: Regions of right lobe.
† C: Region of left lobe.

TABLE 6
Elimination Half Times (Min) of Patients with Fatty Liver but Without History of Alcoholism

Patient no.	A*	B*	C†	Mean
1	66.1	42.5	52.8	51.7
2	52.4	35.0	28.3	38.6
3	38.7	42.3	47.6	42.5
4	58.7	72.9	46.4	59.3
$\bar{x}$	53.98	64.23	43.78	48.03
$S\bar{x}$	10.06	21.70	9.25	8.06

* A and B: Regions of right lobe.
† C: Region of left lobe.

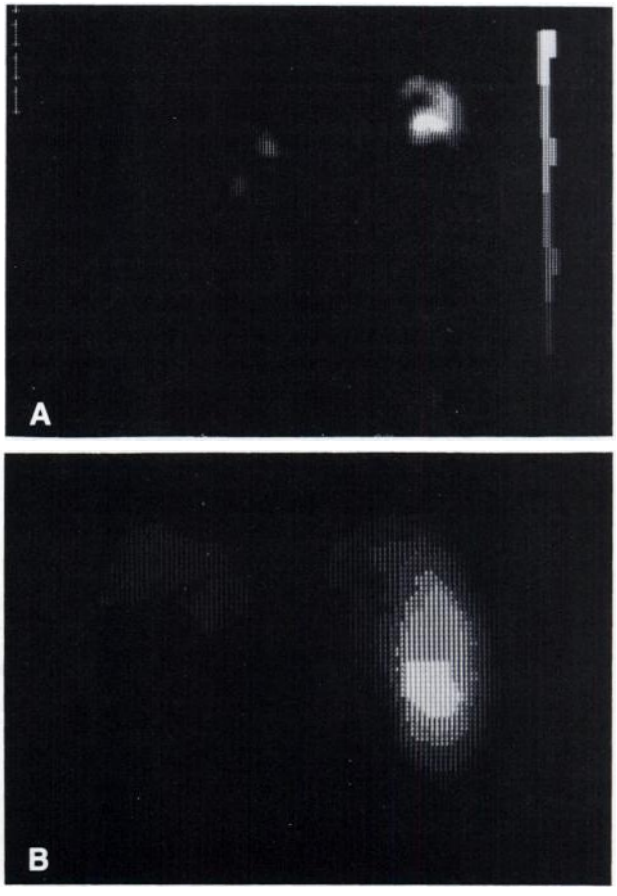

FIGURE 4
A: Iodine-123 HA image of patient with decompensated alcoholic liver cirrhosis. B: Technetium-99m colloid scan of same patient as in Fig. 4A

TABLE 7
Elimination Half Times of ω-Iodine-123-Heptadecanoic Acid in Patients with Alcohol Induced Liver Cirrhosis (min)

Patient no.	A*	B*	C†	Mean
1	57.8	166.4	29.3	84.5
2	669.4	54.0	33.9	252.4
3	19.9	78.4	44.3	47.5
4	881.6	44.8	48.3	132.6
5	68.2	87.5	94.3	83.3
$\bar{x}$	339.4	86.2	50.0	120.1
$S\bar{x}$	362.7	43.0	23.2	71.5

*A and B: Regions of right lobe.
†C: Region of left lobe.

TABLE 8
Elimination Half Times (Min) in Patients with Posthepatic Cirrhosis

Patient no.	A*	B*	C†	Mean
1	27.1	25.3	20.0	27.4
2	39.1	18.1	47.8	35.0
3	57.4	65.9	58.4	60.5
4	‡	‡	‡	—
$\bar{x}$	41.20	36.43	45.40	40.97
$S\bar{x}$	12.46	21.04	11.72	14.16

*A and B: Regions of right lobe.
†C: Region of left lobe.
‡Not measurable.

DISCUSSION

Free fatty acids (FFA) disappear from the blood stream quite rapidly into heart and liver normally, as a result of the product of the concentration of FFA in the perfusing serum, the duration of perfusion, and the fractional extraction ratio (*14–17*). As seen with labeled FFA, the extraction is influenced for both heart and liver by the type of fatty acid and position of labeling (*7,18*). Both organs show a closely similar peak time of accumulation for natural and iodo-labeled fatty acids, but the rates of FFA uptake and catabolism are different for the two organs (*7,18*). Various natural fatty acids are taken up by the liver at identical rates (*19,20*), whereas heart uptake depends on chain length (*21,22*). Furthermore, the data reported here allow the conclusion that liver uptake of FFA is influenced by elevated serum lipid levels (probably including that of FFA itself), whereas the amount of uptake by the heart is independent of plasma lipid concentrations. Moreover, all patients with elevated serum lipids had normal ETs for the heart. Curiously, the catabolism of FFA depends on chain length both for heart (*21,23*) and liver (*18,19*) and increasing plasma lipid levels are usually associated with a prolongation in elimination times of FFA in the liver and not in the heart, even if no common signs of parenchymal liver disease are present. Thus, in normals (control II) an excess of serum lipids may result in homogeneously reduced uptake of FFA and also may relate to slowed turnover rates.

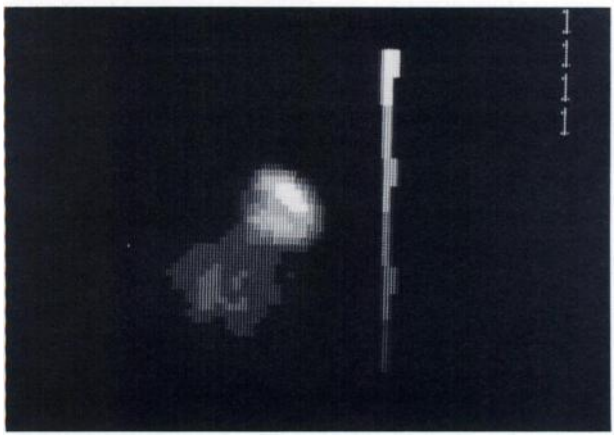

FIGURE 5
Iodine-123 HA image of patient with posthepatitic cirrhosis

The steps involved in the metabolic interrelationships between the various intracellular compartments of liver free fatty acid oxidation, lipid and lipoprotein metabolism cannot be assayed from the present data, but the homogeneity in uptake in control II subjects (high serum cholesterol and/or triglycerides) may indicate the functional patency of cellular membranes to take up FFA from the peripheral plasma into elevated intracellular lipid pools. In contrast, the difference in elimination times within single liver areas emphasizes the concept of a disturbed continuous flux of intermediates of lipid and lipoprotein metabolism in the various lipid compartments. Further observation is needed to ascertain whether these patients are in a preliminary state of fatty liver.

Those patients with fatty liver are distinguished from patients with hyperlipemia but without liver disease by an inhomogeneous (besides generally reduced) uptake. The elimination times for nonalcoholic fatty liver are in the range of the nonliver-diseased patients with hyperlipema. Therefore, not only is the subsequent translocation of FFA between the intracellular lipid and lipoprotein compartments disturbed and the uptake of FFA generally reduced, but there is also an irregular block within different liver regions for the influx rate of FFA in these patients with nonalcoholic fatty liver. Regional variation in perfusion may also cause this heterogeneous uptake. This metabolic situation points to the need to judge both FFA uptake and metabolic turnover rates, and it should be the aim of further studies to quantify the rates of influx of FFA into the liver.

Surprising results were obtained in patients with alcoholic fatty liver. As in patients with nonalcoholic-induced fatty liver, the uptake of [^{123}I]HA was inho-

mogeneously reduced, but the ETs were significantly shorter than those in the latter group. Comparable data from in vivo studies in humans are not available. Shreeve et al. (*18*) observed in chronic ethanol-fed mice an outstanding increase of percent dose of natural or iodinated fatty acids in hepatic triglycerides for those fatty acids which show normally a relatively low percentage conversion to triglycerides. This was found, for example, for iodinated heptadecanoic acid and stearic acid but not for palmitic or paraiodophenylpentadecanoic acids. Therefore, the biochemical mechanism underlying different long-chain fatty acids in normal and diseased liver is to be considered in comparative studies with different labeled fatty acids. Unlike the present findings with alcoholic fatty liver in humans, elimination time for some fatty acids (including [^{123}I]HA) appeared to be prolonged in the ethanolic mice.

Various reports suggest that both acute and continuous administration of alcohol produce an increase of hepatic triglycerides and of lipoprotein lipase activity in adipose tissues (*18,24–31*). Blomstrand found in human liver slices incubated with ethanol and with albumin-bound long-chain fatty acids a decreased beta-oxidation of FFA (*32*). This reduced oxidation of FFA in patients with alcoholic fatty liver is considered to be a major factor in the availability of fatty acids for triglyceride synthesis and the development of alcohol fatty liver. Our data on prolonged elimination times could be due merely to an isotopic dilution of labeled fatty acids by the fat accumulated in the liver. The observation of differing elimination times may be compatible also with the existence of at least two triglyceride pools in the liver (*18,29,33*): a storage pool with slow turnover in which only a fraction of the label is diluted, and a more rapidly exchangeable pool which becomes much more highly labeled. The labeled lipoproteins in experimental data and the relative short elimination times of [^{123}I]HA in patients with alcoholic fatty liver probably reflect the activity of this rapidly exchangeable lipid pool.

In patients with liver cirrhosis—either of the posthepatitic type or alcohol-induced—a significant increase is noted in plasma FFA (*34–36*); however, there seems to be no statistically significant difference in levels between patients with mild or severe liver disease (*37*), or between patients with severe cirrhosis with or without hepatic coma (*38*). The mechanism of increased plasma FFA is discussed in numerous studies (*37,38*) but still remains unestablished at present. Increased peripheral lipolysis, decreased oxidation, and hepatic esterification of fatty acids have been suggested as explanations (*34*); but the decreased removal by the diseased liver seems to be the crucial step in this mechanism (*36*). Further, a decreased hepatic output—formation and secretion of lipoproteins—in experimental and human hepatic injury is well documented (*39*). The expected rise in triglycerides secondary to increased FFA levels is especially blunted by decreased triglyceride synthesis and hepatic output (*38,40*). In addition, catabolism of triglycerides could be impaired in patients with cirrhosis (*38*).

Support for some of these theses is given by the present study. If liver disease progresses to liver damage as in cirrhosis, the uptake of FFA by liver cells is extremely reduced and the ETs are significantly prolonged as signs of decreased capacity of the liver to handle exogeneous FFA. The degree of impairment of FFA uptake and elimination by the liver seems to be directly correlated with the severity of liver damage. Therefore, a pronounced reduction of uptake and a prolongation in ETs in patients with liver disease may be an early indicator of the transition of a fatty liver to a more advanced stage of the disease or cirrhosis. This may be especially true in patients with alcoholic fatty liver and ethanol-induced cirrhosis.

Moreover, the present study illuminates the question of whether the degree of uptake of a colloidal tracer by Kupffer cells can be regarded as a reliable indication of the integrity or compromise of the hepatocytes as well, because it is generally assumed that most pathologic processes affect both about equally (*41*). From the present data it becomes evident that colloid scans of the liver and metabolic scanning with FFA are only comparable in patients without liver disease and with normal values for serum lipids. In various states of liver injury the blood clearance and liver uptake of a colloidal tracer do not necessarily reflect the rate of influx of a labeled fatty acid tracer, which presumably depends not only upon the integrity of hepatocellular membranes but also upon the levels of serum lipids, the amount of intracellular fatty acids and their rate of oxidation and incorporation into hepatocellular lipids, and the rate of lipid secretion by the liver. The hepatic elimination times for labeled fatty acids are also dependent on the above and other metabolic factors, and are not likely to correlate in any particular way with abnormalities of sulfur colloid uptake. However, it is notable that the generally longer elimination times for the right lobe than the left lobe in the cirrhotic patients agree with right/left liver lobe differences in sulfur colloid uptake found by others (*42*).

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