HEPATIC PHAGOCYTIC, METABOLIC, AND BLOOD-FLOW EVALUATION BY DYNAMIC SCINTIGRAPHY

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The diagnostic value of tracer and scintigraphic techniques with reference to the evaluation of liver structure and function (*1–4*) has been demonstrated. In this regard, hepatic configuration, size, vascularity, and the presence of focal hepatic disease can be deduced from such information (*5,6*). Dynamic studies for the most part have been confined to the acquisition and turnover of ^{131}I-labeled rose bengal by the hepatic parenchymal cells and its biliary excretion (*7–10*). The use of scintigraphic techniques for the acquisition of dynamic data relative to hepatic reticuloendothelial (RE) physiology has not been significantly investigated.

The present study was designed to use the scintigraphic method to obtain both quantitative information concerning liver functional activity as well as hepatic visualization on a continuous and dynamic basis. The test colloid was a radioiodinated lipid emulsion (*11–13*) which is removed from the vascular compartment exclusively by the reticuloendothelial system (*14,15*). This particulate preparation is relatively homogeneous, stable in blood, nontoxic, and rapidly metabolized by the Kupffer cells of the liver following phagocytic engulfment (*16*). These characteristics allowed for the dynamic delineation of hepatic configuration in terms of imaging while the test particles were being stored in the liver as well as the dynamic assessment of hepatic RE metabolic activity as the labeled substrate was metabolized and released from the liver. In addition, specific attention was focused on determining the fractional clearance rate (k) of "tracer" doses of the labeled colloid in an attempt to simultaneously quantify hepatic sinusoidal blood flow (*17,18*).

MATERIALS AND METHODS

Animals. Adult, nonfasted, nonconditioned mongrel dogs weighing between 16 and 25 kg were used in all experiments. Prior to experimental evaluation, all dogs were anesthetized with sodium pentobarbital administered intravenously at a dose of 30 mg/kg. Following anesthetization, the femoral vein was cannulated for colloid infusion and the femoral artery was cannulated to facilate rapid serial arterial blood sampling.

Test colloid. The test colloid used was a radioiodinated lipid emulsion previously referred to as the "RE test lipid emulsion" (*11–13,19*). This emulsion was prepared as an anhydrous base by high-speed blending of ^{131}I-triolein (Mallinckrodt Nuclear, St. Louis, Mo.), glycerol, and lecithin in a ratio of 10:10:1 by weight, respectively. Dilution of the ^{131}I-triolein was accomplished with peanut oil in order to prepare a lipid base with a specific activity of 20 μCi/mg. The anhydrous lipid base was suspended in sterile 5% dextrose and water and incubated at 37°C for 15 min prior to intravenous injection. Prepared in this manner, the emulsion manifested excellent stability and an average particle size of approximately 1 micron as determined microscopically. Previous studies on the experimental evaluation of RE function in animals (*11,13,18*) and humans (*12*) have adequately documented the nontoxic nature of this preparation and its exclusive removal from the blood by the reticuloendothelial system, especially the hepatic Kupffer cells. In the present study, doses of 10, 50, 100, and 200 mg/kg were used in a minimum of three animals at each dose in an attempt to delineate the "critical dose" which could be used to evaluate liver blood flow (*17,18*).

Liver blood flow. Hepatic sinusoidal blood flow was determined in accordance with the method described by Dobson and Jones (*17*). In this technique, the fractional clearance rate (k) associated with the removal of a minimal colloid dose was used

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as an index of liver sinusoidal blood flow. The dose determined acceptable was 10 mg/kg since this was below the critical colloid dose (CCD) and associated with a relatively exclusive hepatic localization and a maximum rate of colloid clearance in normal dogs. The fractional clearance rate (k) was calculated from the expression:

$$k\ (\text{fractional clearance rate}) = \frac{0.693}{t/2},$$

in which 0.693 is the natural logarithm of 2, t/2 is the half-time in minutes for the disappearance of the particles from the blood, and the constant k represents the fraction of the blood volume cleared of colloid per minute. Minimum hepatic sinusoidal blood flow (MBF) was then determined by the expression:

$$\text{Minimum Blood Flow (MBF)} = k \times V_B,$$

in which V_B is the calculated blood volume of the experimental animal (*18*). The blood volume (V_B) was determined by estimation on the basis of body weight. For estimation of V_B, the value of 83.2 ml blood/kg body weight as determined previously in dogs was used (*16*). Hepatic sinusoidal blood flow was calculated in terms of ml/min and ml/min/kg body weight.

Scintigraphic equipment. The disappearance from the blood and the simultaneous uptake of the radioiodinated lipid emulsion in the liver was assessed dynamically with a Picker Dynacamera system equipped with a 13-in. NaI(Tl) crystal. In this procedure the lower chest and upper abdominal area were continuously viewed for 1 hr following emulsion injection without geometric alteration between the detector and the animal in order to insure adequate continuous monitoring of heart blood and hepatic localized radioactivity. Care was taken to avoid monitoring areas of interest over major blood vessels in the liver. Information generated relative to disappearance of the colloid from the heart blood pool and its uptake by the liver was recorded on video tapes as a 100 × 100 information point matrix. Count levels as digital information for the two areas of interest (heart blood pool and liver tissue pool) were determined for 100 consecutive time intervals during the 60-min postinjection period. For all experiments, ^{131}I activity was evaluated by video-tape playback and evaluation at both 4- and 24-sec intervals. In order to verify the accuracy of the scintigraphic method in delineating events associated with the clearance of radioiodinated particulate lipid, serial 1-ml samples of systemic arterial blood were obtained at 2-min intervals and assessed for ^{131}I

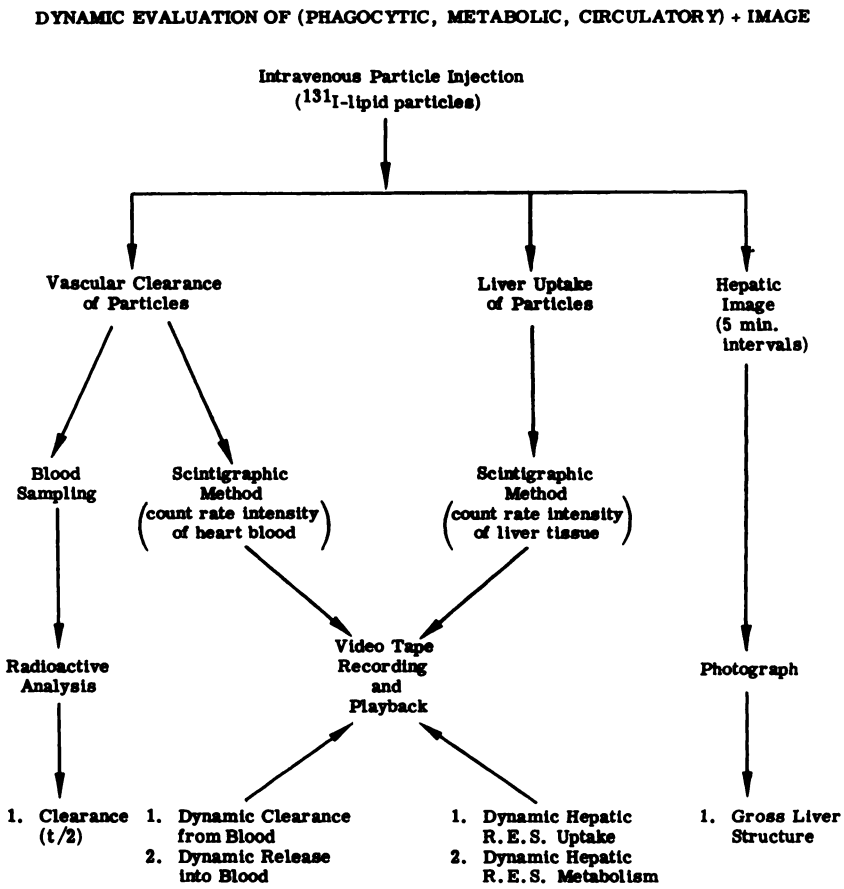

FIG. 1. Experimental design used to comparatively evaluate scintigraphic and arterial blood sampling techniques relative to determination of blood clearance kinetics. Evaluation of video-tape recording was done at both 4- and 24-sec alternate intervals.

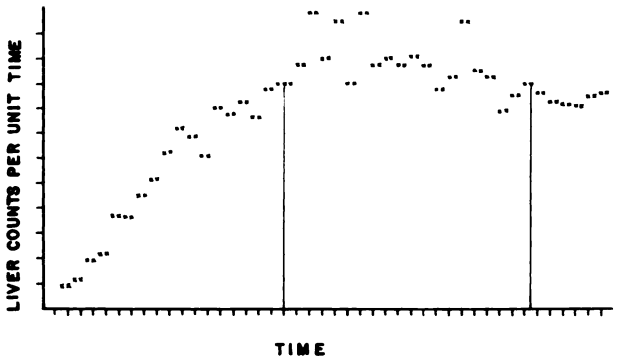

FIG. 2. Dynamic hepatic colloid localization following 200-mg/kg dose of ^{131}I-lipid emulsion. Each point represents liver radioactivity at 24-sec intervals as detected by continuous hepatic scanning.

activity with a deep well counting system. The disappearance curve generated on the basis of this discrete sampling approach was compared to that generated with the scintigraphic method.

Morphological evaluation. The selective removal of the lipid emulsion by RE cells was verified by light and electron microscopic evaluation of the liver, lungs, and spleen and will be the subject of a future publication.

Overall experimental design. Figure 1 shows an overview of the general experimental protocol employed in the dynamic evaluation of liver function and visualization. As can be seen, following injection of the ^{131}I-lipid particles, several parameters were assessed. These were vascular clearance rate, rate of hepatic uptake, and release of radioactivity, as well as liver structure. The vascular clearance rate was determined by both conventional blood sampling and radioassay as well as by scintigraphic methods. The rate of hepatic localization of the particles was determined by scintigraphic methods, and hepatic image was photographed from the oscilloscope screen by 5-min exposures for successive 5-min intervals postinjection. In this study the data generated by scintigraphic techniques will be emphasized.

RESULTS

Figure 2 contains a dynamic representation of the radioactivity in the liver of a 200-mg/kg dose determined by counting-rate intensity determinations at alternate 24-sec intervals following colloid injection. With this dose, the t/2 for the initial blood disappearance curve was usually 2.5–3.5 min with a maximum hepatic specific activity at 15–20 min postinjection. During the 20–60-min experimental period, there was a slight but continuous decrease in hepatic ^{131}I activity. The hepatic image as delineated with the 200-mg/kg dose of the labeled emulsion at 15–20 min postinjection is shown in Fig. 3. As can be seen, a well-defined hepatic image was obtainable.

In an attempt to relate the dynamics associated with the phagocytic clearance and subsequent metabolic turnover of the labeled lipid particles with the test load administered, lower test doses were used and evaluated with reference to their rate of clearance, rate of hepatic uptake, and rate of metabolic degradation. In this regard, the clearance, hepatic localization, and subsequent hepatic degradation of both a 100- and 50-mg/kg dose is shown in Figs. 4 and 5, respectively. Comparison of clearance curves generated by arterial blood samples and by scintigraphic evaluation of heart blood activity showed no significant difference in relationship to the rate and

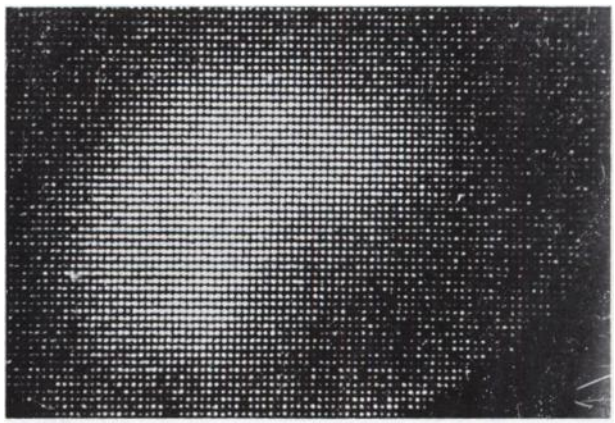

FIG. 3. Hepatic scintigraphic image obtained on Polaroid film from Dynacamera oscilloscope. Film was exposed for 5-min intervals between 15 and 20 min after intravenous injection of radioiodinated lipid emulsion at dose of 200 mg/kg. Fifteen to twenty-min postinjection interval corresponds temporally to maximum hepatic specific activity in terms of localization of particulate lipid.

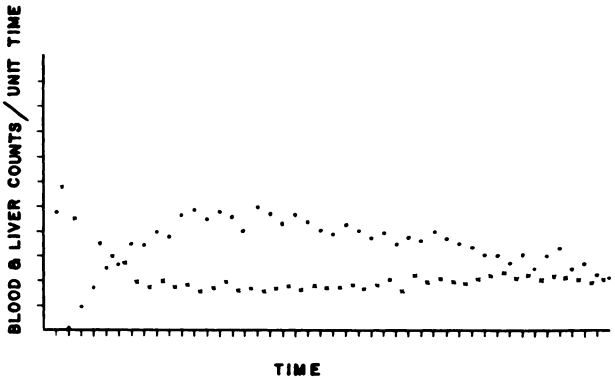

FIG. 4. Dynamic vascular clearance (descending curve) and hepatic localization (ascending curve) of 100-mg/kg intravenous dose of ^{131}I-lipid emulsion. Each point represents blood or liver radioactivity at alternate 24-sec intervals as detected by continuous scanning of cardiac blood pool or hepatic tissue. Disappearance curve obtained by periodic blood sampling and radioassay was not significantly different ($p > 0.05$) than that obtained by scintigraphy.

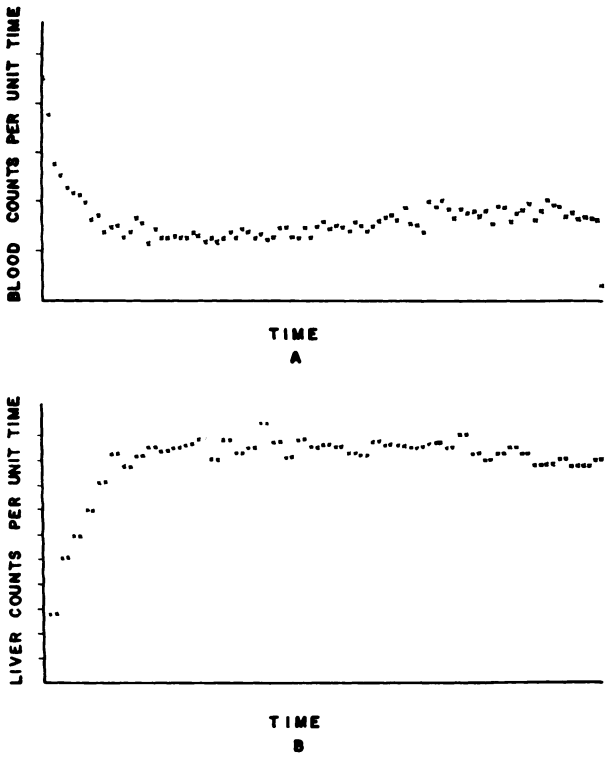

FIG. 5. Dynamic vascular clearance and hepatic localization of intravenously injected 50-mg/kg dose of ^{131}I-lipid emulsion. Each point represents heart blood or hepatic tissue radioactivity at alternate 24-sec intervals. A shows blood clearance, and B, hepatic localization.

pattern of clearance. Although the dynamic handling of the particles altered with the dose injected, excellent hepatic imaging was possible with all doses. While quantification of the clearance curve was possible with data accumulation at 24-sec intervals, a more specific delineation of the exponential nature of the initial clearance curve was obtained by analysis of heart blood activity at 4-sec intervals (Fig. 6). The plot presented is linear when displayed on a semilogarithmic scale.

Since in theory the progressive decrease in administered dose should eventually be reflected in a maximum and constant clearance rate, progressively smaller doses were injected to determine this critical colloid dose level. Figure 7 shows the dynamics associated with the clearance of a 10-mg/kg dose which was below the critical colloid dose. At this dose level the liver is almost the exclusive site of particle localization, and a maximum clearance rate was observed. The continuous evaluation of the hepatic activity revealed a rapid turnover of the labeled compound in the liver and release of activity into the blood (Fig. 7). The rapid vascular clearance, selective hepatic localization, and subsequent rapid hepatic turnover of the emulsion administered at a dose level of 10 mg/kg was confirmed by the serial images of the liver made at 5-min intervals after colloid injection (Fig. 8). In this regard, there is an excellent correlation between the dynamic image intensity changes apparent and the specific quantitative counting rate intensity levels observed by specific area analysis.

Since a major impetus for this study was the desire to use scintigraphic methods in the simultaneous dynamic evaluation of organ structure and function, and since previous studies have adequately revealed the validity of employing the fractional clearance rate (k) as an index of hepatic blood flow (*17,18*), hepatic sinusoidal blood flow was determined from the t/2 associated with the clearance of the 10-mg/kg dose and compared to that calculated on the basis of discrete arterial blood sampling. Table 1 gives

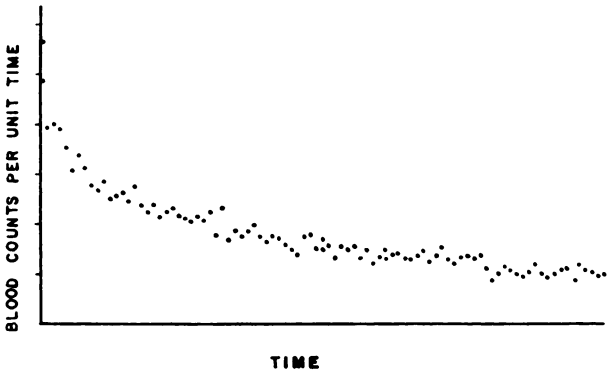

FIG. 6. Specific delineation of exponential nature of vascular clearance curve as obtained by continuous scintigraphic analysis of heart blood radioactivity at 4-sec intervals after intravenous injection of radioiodinated lipid emulsion at dose of 100 mg/kg. Total duration of continuous monitoring was 6.66 min as reflected in 100 count level determinations (·) spaced at 4-sec intervals.

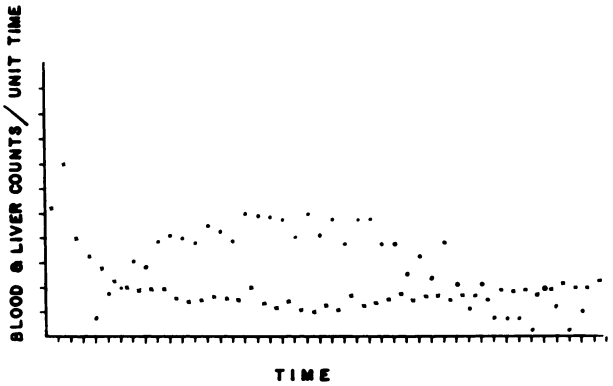

FIG. 7. Representative example of blood clearance, hepatic localization, hepatic metabolism and release, and subsequent blood accumulation of radioactivity. Alternate dual area analysis of both heart blood pool and liver tissue were done at alternate 24-sec intervals. Emulsion was injected intravenously at dose of 10 mg/kg. Total experimental period of continuous scanning was 60 min.

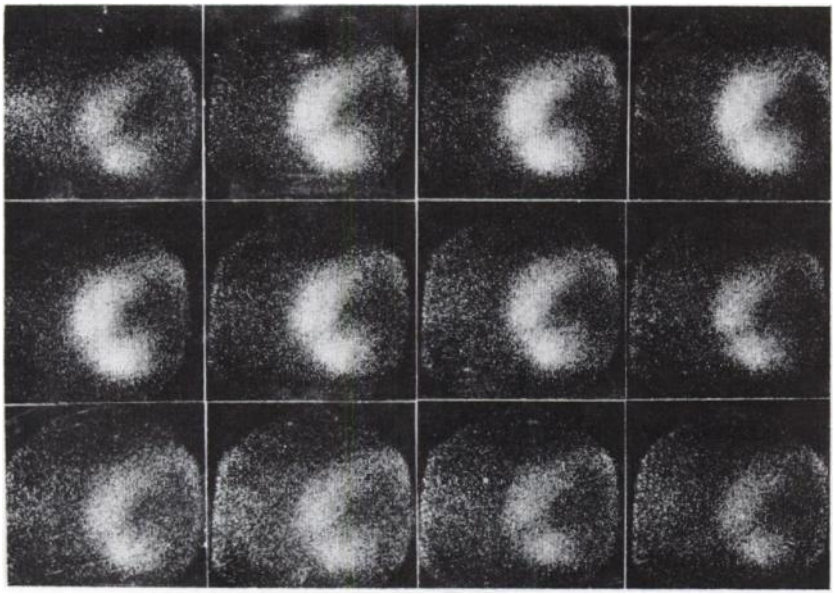

FIG. 8. Serial hepatic images obtained by film exposure for 5-min intervals following intravenous injection of ^{131}I-lipid emulsion at dose of 10 mg/kg. Sequence is in horizontal rows beginning at top left to bottom right. Intensity of liver image increases with phagocytic accumulation phase and decreases following metabolic degradation and release phase. In each picture, right side of dog is downward and head is to left of each frame. Twelve images at 5-min intervals correspond to 60-min experimental duration as shown in Fig. 7.

TABLE 1. MINIMUM HEPATIC SINUSOIDAL BLOOD FLOW AS DETERMINED BY SCINTIGRAPHIC EVALUATION OF CLEARANCE KINETICS*

Dog	Weight (kg)	Liver blood flow† ml/min	ml/min/kg	ml/min/gm‡
1	24.2	581.47	24.44	0.81
2	24.6	546.26	22.21	0.75

* The ^{131}I-lipid emulsion was injected at a dose of 10 mg/kg.

† Disappearance curve obtained by timed sampling of arterial blood coupled with radioassay was similar to that obtained by continuous scintigraphy viewing the heart blood pool. In this regard in 12 experimental determinations with ^{198}Au clearance in dogs using a critical colloid dose of 50 μg/kg body weight, the average liver blood flow was 543.94 ± 8.3 ml/min and 0.97 ± 0.02 ml/min/gm.

‡ Blood flow of a ml/min/gm of liver tissue was calculated from an estimate of the liver size. The value used was 29.8 gm liver/kg body weight as determined by previous studies. Flows presented represent minimum values in contrast to maximum values which would include the percentage of intrahepatic nonsinusoidal shunt flow.

the hepatic sinusoidal blood flow on a ml/min and ml/min/kg basis in two dogs of comparable size as measured with the fractional clearance rate generated by scintigraphic counting-rate intensity determinations.

Morphologic examination of the liver, lung, and spleen following injection of the emulsion demonstrated an exclusive localization of the particles in the RE cells (*19*). With reference to the liver, no transfer of the fat particles to the parenchymal cells was detected during the entire 60-min experimental interval.

DISCUSSION

The rapid and selective clearance of foreign particulate and colloidal matter from the blood by cells of the reticuloendothelial system (RES) has been repeatedly demonstrated (*14,15*). In the present study, the selective clearance of the "RE test lipid emulsion" by RE cells is in agreement with previous studies in animals (*11,13*) and in humans (*12*) on its selective phagocytic clearance. Unlike many colloidal preparations, e.g., colloidal gold, which have been used for hepatic scanning (*3,4*), the data demonstrate that this lipid emulsion can be rapidly metabolized by RE cells especially the Kupffer cells of the liver. This feature of selective localization, coupled with the ability to be rapidly metabolized, emphasize its potential value in liver scanning since so-called "inert colloids" are stored in RE cells and can lead to circulatory, metabolic, and hematologic injury (*13,20*).

As can be seen by the present findings, excellent hepatic imaging can be accomplished with this ^{131}I-lipid emulsion. Furthermore, it can be seen that while the clearance rate is inversely related to the dose injected, a well-defined liver image was obtainable at all test doses as long as the emulsion had a high enough specific activity. The inverse relationship between clearance rate and colloid dose agrees with previous findings on the kinetics for RE clearance of other particulate materials such as technetium sulfur colloid, colloidal carbon, and denatured human serum albumin (*14,15*). As indicated by these findings, the dynamics associated with hepatic colloid localization and vascular clearance can be simultaneously studied in the intact animal with the use of scintigraphic methods. Furthermore, by using a metabolizable particle in conjunction with continuous blood and tissue evaluation, it was possible to generate information to dynamically assess both functions without any distortion of the hepatic image.

In the present study there is an apparent rapid

hepatic localization and metabolism of the injected lipid particles. These findings coupled with previous studies (*16,18*) indicated quite clearly that the Kupffer cells of the liver are the major site of particle localization and metabolism. Recent findings attempting to delineate the relative involvement of hepatic macrophage and parenchymal cells in lipid metabolism have suggested that the clearance and metabolism of chylomicron triglyceride is a function exclusively related to the parenchymal cells (*21*). However, the selective localization of these lipid particles in Kupffer cells as well as the ability for Kupffer cells to metabolize this triglyceride and release free ^{131}I and labeled lipid into the blood (*16*) suggests an important role for the Kupffer cell in lipid metabolism. Macrophages can ingest lipid under both in vitro and in vivo conditions (*22–26*), and the incorporation of triglyceride into phagocytic vacuoles followed by its degradation has been observed (*22*). This metabolic activity is probably related to the enzymatic profile of macrophages since both esterase and lipase activity have been demonstrated in RE cells (*27–29*). Macrophage uptake and metabolism of lipids, coupled with the storage of lipid in RE cells during reticuloendotheliosis (*30*) and atherosclerosis (*24*), suggest an important role for the RES in lipid metabolism. The ability to dynamically assess both the uptake and turnover of lipids in RE cells with scintigraphic techniques may be a useful method to quantitate the activity of this system in normal and abnormal states.

The reproducible and readily detectable decrease in liver radioactivity with a subsequent rise in blood radioactivity (*19*) reflects the intrahepatic RE degradation of the lipid particles with the release of both free ^{131}I and lipid-bound ^{131}I activity into the plasma. This concept is supported by recent findings by Cornell and Saba (*16*) concerning the release of radioactivity into the blood following RES removal of this particulate lipid in dogs. In this regard, free ^{131}I represents the major fraction of the release material and ^{131}I-labeled lipid, possibly lipoprotein, represents the minor portion (*16*). This finding, coupled with the present data demonstrating a rapid turnover of the lipid and release of radioactivity into the blood, suggest that RE cells of the liver may be capable of synthesizing and releasing lipoproteins. Experimental production of hyperlipoproteinemia in rabbits following injection of particulate lipids cleared by the RES supports this concept (*31*).

While gross hepatic configurational alterations delineated by scintigraphy are used in determining vascular alterations in the liver, the ability to simultaneously quantify hepatic blood flow in addition to viewing organ structure suggests additional diagnostic value of the scintigraphic technique in terms of hepatic investigation. That is, one can readily obtain excellent hepatic visualization and relate such structural data to quantitative data on variations in hepatic sinusoidal blood flow and liver metabolic activity in the same experimental subject.

Thus it appears possible on the basis of the present findings to quantitatively evaluate various parameters of liver function on a dynamic basis by scintigraphic methodology. It is envisioned that this approach will have useful application for the clinical evaluation of liver function in health and disease.

SUMMARY AND CONCLUSIONS

The present findings clearly demonstrate the value of scintigraphic techniques to assess the rapid clearance and turnover of a metabolizable lipid emulsion by the RES, especially the Kupffer cells of the liver. In this regard, the dynamics associated with the blood clearance, hepatic storage, and hepatic degradation of the labeled lipid can be rapidly and simultaneously quantified by this technique. In addition to dynamic functional evaluation, specific aspects of the hepatic image can be related to quantitative data on hepatic blood flow. The employment of scintigraphic technique permits the quantitative determination of the various functions discussed with minimum time, effort, and technical manipulation of the subject when compared with classical physiologic techniques. The importance of the RES as a host-defense system coupled with the central role of the liver in a variety of disease processes suggests that this rapid, nontoxic, and nonstressful method of simultaneously assessing hepatic clearance, metabolic, and circulatory parameters will have significant diagnostic value.

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