Metabolism of chylomicrons of differing triglyceride composition

PAUL J. NESTEL* and ROBERT O. SCOW

Laboratory of Metabolism, National Heart Institute, National Institutes of Health, Bethesda 14, Maryland and Laboratory of Nutrition and Endocrinology, National Institute of Arthritis and Metabolic Diseases, National Institutes of Health, Bethesda 14, Maryland

SUMMARY Lymph chylomicrons of widely different fatty acid composition were obtained from donor animals fed either cream and palmitic acid-9,10-H^3 or corn oil and linoleic acid-1-C^{14}. The rates of removal of these two types of chylomicrons from the circulation of recipient dogs and rats were determined from the relative rates of removal of the two isotopes and in some cases by changes in the fatty acid composition of the plasma chylomicrons.

In intact dogs and rats, the removal of cream chylomicrons was the more rapid. In dogs the H^3/C^{14} ratio in hepatic venous blood was lower than that in femoral venous blood. In livers of rats, there was a greater percentage uptake of radioactivity associated with cream chylomicrons than of that associated with corn oil chylomicrons, but similar amounts were recovered from adipose tissue.

When livers of rats were perfused with the two types of chylomicrons, the rate of removal of cream chylomicrons from the perfusate was greater. On the other hand, cream and corn oil chylomicrons were removed in similar amounts when adipose tissue of rats was perfused.

THE RESULTS OF a previous study suggested that the fatty acid composition of chylomicrons can influence their removal from the circulation (1). It was observed in dogs that chyle chylomicrons obtained after feeding cream to a donor animal were removed at a different rate than those obtained after feeding corn oil. These studies did not establish the consistency of such findings or the mechanism responsible for them.

This paper reports the results obtained in a larger number of dogs. In addition, similar studies with chylomicrons of differing composition were performed in rats. Since liver and adipose tissue are the major sites of chylomicron removal, isolated livers and parametrial fat tissue of rats were perfused with such chylomicrons. The relative rates of removal of the cream and corn oil chylomicrons were determined by measuring the rates of removal from the blood of isotopes associated with the triglyceride fatty acids (TGFA) of the chylomicrons, and in some cases by determining the changes in the fatty acid composition of the TGFA during the removal of the chylomicrons.

MATERIALS AND METHODS

Studies in Dogs. The thoracic ducts of four male dogs were cannulated directly in the neck. They are referred to as donor dogs, A, B, C, and D. When the fistulae were flowing freely, each dog was fed 4 g corn oil with 50 μc linoleic acid-1-C^{14} (Applied Sciences Corp., State College, Pa.) on one day, and 4 g cream fat with 1.0 μc palmitic acid-9,10-H^3 (Nuclear Chicago Corp., Des Plaines, Ill.) on the following day. Gas chromatographic analysis of the methyl esters revealed a single chemical peak for each fatty acid. The administered doses of radioactivity were chosen to provide a H^3/C^{14} ratio of approximately 10 or 20 to 1, this being a suitable ratio for the simultaneous counting of both isotopes. Chyle was collected for 12 hr, stored at 4°, and generally used within 2 days. Immediately prior to use, the chyle was layered under 0.15 M NaCl and centrifuged at 20,000 rpm for 30 min in the 30 rotor of a Spinco Model L ultracentrifuge. The chylomicrons were removed after slicing the tubes just below the creamy layer, and resuspended in NaCl. Corn oil and cream chylomicrons, which had been isolated separately, were then mixed in equal proportions by weight for infusion into recipient dogs.

Seven male dogs weighing 8–15 kg were used as recipients. They were anesthetized with pentobarbital (30

* Fellow of Life Insurance Medical Research Fund of Australia and New Zealand. Permanent address: Department of Medicine, University of Melbourne, Australia.

mg/kg). Plastic catheters were placed into the femoral vein for infusion and into the aorta for sampling. The chylomicrons (300–400 μEq TGFA per kg body weight) were infused in a volume of 25 ml over a period of 30 sec. Dogs 1, 2, 5, and 6 each received corn oil and cream chylomicrons obtained from a single donor dog A, B, C, and D, respectively. Dog 3 received cream chylomicrons from dog A and corn oil chylomicrons from dog B; dog 4 received corn oil chylomicrons from dog A and cream chylomicrons from dog B; dog 7 received cream chylomicrons from dog C and corn oil chylomicrons from dog D. Samples of blood were collected into chilled heparinized tubes 5, 15, 30, and 45 min later.

In two additional dogs, the hepatic vein was also catheterized. The catheter was inserted through the jugular vein, and its position within the hepatic vein was confirmed by manual palpation through an abdominal incision. Following the administration of chylomicrons, samples of blood were drawn in rotation from the aorta, femoral vein, and hepatic vein as indicated in Fig. 2. Blood was spun at 1,500 rpm for 10 min at 4° and the plasma was further centrifuged at a density of 1.006 at 20,000 rpm for 30 min in the 40.3 rotor of the ultracentrifuge. The surface layer of chylomicrons was removed and the lipids were extracted into chloroform–methanol 2:1 (v/v).

Studies in Rats. The *cisterna chyli* of male Sprague-Dawley rats was cannulated under ether anesthesia, and cream and corn oil chylomicrons were prepared as in the dog studies just described.

In the first study, the rate of removal of chylomicrons was determined in four recipient male adult rats. The rats had been fed a stock chow diet and were allowed access to food up to the time of the experiment. After the rats had been anesthetized with ether, small catheters were threaded into the inferior vena cava for sampling blood. A total of 70 μEq TGFA in a volume of 0.5 ml was infused in 2 sec into a femoral vein. Samples of blood were obtained as indicated in Table 2. Chylomicrons were separated from plasma as described above.

Further studies were performed in six male rats to determine the tissue distribution of H^3 and C^{14} radioactivity following infusion of chylomicrons. The rats weighed approximately 250 g each. Two rats were killed at 2.5, 5.5, and 8.5 min following the infusions. Portions of liver and epididymal fat pad were homogenized at once and the lipids extracted into chloroform–methanol. Plasma chylomicrons were separated and extracted as before.

The livers of four male rats weighing about 150 g were perfused by the method described by Mortimore (2). The perfusing medium was prepared by diluting defibrinated blood obtained from nonfasted rats with 0.15 M NaCl to yield a final packed cell volume of 20%. Livers were perfused in situ. The portal vein and inferior vena cava above the diaphragm were cannulated, and oxygenated blood was pumped into the portal vein at 6 ml/min. The inferior vena cava was ligated below the liver. The perfusate was oxygenated with 95% O_2 and 5% CO_2 within a 500-ml spherical flask rotating at 60 rpm. The preparation was kept inside an incubator at 37°. Eighty microequivalents of TGFA as chylomicrons were added to 40 ml perfusing fluid and perfusion was continued for varying periods. Small aliquots of the perfusing fluid were removed at intervals, and the chylomicrons were separated and extracted with chloroform–methanol.

The parametrial fat pads of two female rats were perfused with chylomicrons at a concentration of 2 μEq TGFA/ml by the method described by Robert and Scow (3). The perfusing fluid was defibrinated blood from fasting rats diluted 1:10 with 4% albumin in Tyrode's solution (glucose 50 mg/100 ml). The tissue was perfused through the uterine vessels. The perfusate was not recirculated. Following 30 min of perfusion with chylomicrons, the blood vessels were flushed with perfusing fluid for 10 min. The entire fat pad and the lipids in the perfusate were extracted with chloroform–methanol.

Analytical Methods. Following the extraction of chylomicrons and hepatic lipid, the triglycerides were separated from the other lipids on silicic acid columns (4). The ester bonds were measured as hydroxamates (5), and radioactivity was assayed in a liquid scintillation counter using 0.3% diphenyloxazole in toluene as scintillator solvent. Tritium and C^{14} radioactivity were measured simultaneously as described previously (1). Before being assayed for radioactivity, adipose tissue triglycerides were separated from free fatty acids by extraction of the latter into ethanolic NaOH.

In the first four dog studies, the TGFA of the chylomicrons of the 5- and 45-min samples of plasma were converted to the methyl esters by refluxing with 2% H_2SO_4 in dry methanol for 1 hr at 70°. The methyl esters were then separated on a 15% ethylene glycol succinate polyester–Chromosorb W column in a gas chromatograph at 180°, using an argon ionization detector.

RESULTS

Studies in Dogs. When cream chylomicrons and corn oil chylomicrons were infused together, their rates of removal from the TGFA of the chylomicron fraction of plasma were determined by the disappearance of tritium and C^{14}, respectively (Fig. 1). The half-times of disappearance of radioactivity are shown in Table 1. Dogs 1, 2, 5, and 6 received infusions in which both types of chylomicrons were obtained from the same donor dog; the remaining dogs received infusions in which the two

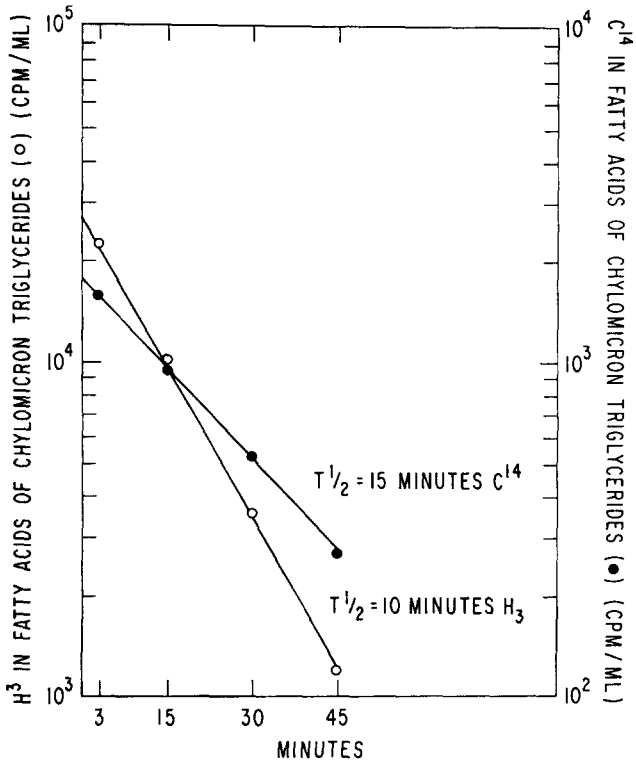

FIG. 1. Rates of disappearance from the blood of triglycerides of cream chylomicrons labeled with H^3 and triglycerides of corn oil chylomicrons labeled with C^{14}; dog 2.

varieties of chylomicrons were provided by different donor dogs. In every experiment, radioactivity associated with the TGFA of cream chylomicrons was removed more rapidly than that associated with corn oil chylomicrons. This was confirmed in the first four experiments by the change in fatty acid composition of the TGFA as analyzed by gas chromatography. The fatty acid composition of the 5-min samples resembled that of the infused chylomicrons, whereas the 45-min samples contained relatively more linoleic acid (the major fatty acid in corn oil) and less stearic and palmitic acids (found to a much greater extent in cream than in corn oil) (Table 2).

TABLE 1 RATE OF REMOVAL FROM THE BLOOD OF RECIPIENT DOGS OF CHYLOMICRONS OBTAINED AFTER FEEDING DONOR DOGS CREAM WITH PALMITIC ACID-9,10-H^3 OR CORN OIL WITH LINOLEIC ACID-1-C^{14}*

Donor Dog	Recipient Dog	Rate of Removal ($T^1/_2$ in minutes) Cream Chylomicrons	Corn Oil Chylomicrons
A	1	17	20
B	2	10	15
A + B	3	17	26
B + A	4	12	15
C	5	11	15
D	6	25	32
C + D	7	18	26

* Calculated from the half-times of removal of H^3 and C^{14} in the triglycerides of plasma chylomicrons.

TABLE 2 PERCENTAGE FATTY ACID COMPOSITION OF TRIGLYCERIDE FATTY ACIDS IN THE CHYLOMICRON FRACTIONS OF PLASMA AT 5 AND 45 MIN IN THE FIRST 4 DOGS

Fatty Acid	Dog 1		Dog 2		Dog 3		Dog 4		Chylomicrons		
	5 min	45 min	5 min	45 min	5 min	45 min	5 min	45 min	Cream	Corn Oil	In-fused
14:0	2	1	3	1	3	1	2	1	5	1	3
16:0	20	14	21	15	22	14	21	15	26	14	20
16:1	1	2	1	1	1	2	1	1	2	1	1
18:0	12	7	10	6	10	7	12	7	16	5	11
18:1	34	35	35	36	36	38	33	34	40	30	35
18:2	31	40	30	40	28	37	31	41	11	49	30

The concentration of triglyceride, phospholipid, and total cholesterol was similar in all batches of chylomicrons. When the chylomicrons were layered below a polyvinylpyrrolidone density gradient (6), only a single band, which floated to the top of the gradient, was obtained with all samples.

The results with the two dogs, in which blood was obtained from the hepatic vein, the femoral vein, and the aorta, are shown in Fig. 2. The removal of the two populations of chylomicrons has been charted as the H^3/C^{14} ratio in the TGFA of the chylomicron fraction of plasma. Any alteration in this ratio indicates a difference in the rate of removal of the two isotopes. It is evident that tritium, the label for the cream chylomicrons, was removed more rapidly and that this was most marked in samples obtained from the hepatic vein. The rates of fall in the H^3/C^{14} ratios were similar in samples from the aorta and femoral vein.

Studies in Rats. The rate of removal of cream chylomicrons and corn oil chylomicrons was compared by

TABLE 3 RATE OF REMOVAL FROM THE BLOOD OF RECIPIENT RATS OF CHYLOMICRONS OBTAINED AFTER FEEDING DONOR RATS CREAM WITH PALMITIC ACID-9,10-H^3 OR CORN OIL WITH LINOLEIC ACID-1-C^{14}

Donor Rat A				Donor Rat B			
Recipient 1		Recipient 2		Recipient 3		Recipient 4	
Time *min*	Ratio* H^3/C^{14}	Time *min*	Ratio H^3/C^{14}	Time *min*	Ratio H^3/C^{14}	Time *min*	Ratio H^3/C^{14}
0	2.86	0	2.86	0	12.6	0	12.6
2	2.21	1	2.68	2	10.7	2	10.2
5	1.96	3	2.19	5	9.9	7	8.7
8	1.69	5	1.75	11	7.6	10	8.0
		8	1.68				
		11	1.59				
($T^1/_2$, 7 min)†		($T^1/_2$, 6.5 min)		($T^1/_2$, 6 min)		($T^1/_2$, 5.5 min)	

* Ratios of H^3 to C^{14} in the triglycerides of plasma chylomicrons.
† Half-times calculated from rate of disappearance of C^{14}.

determining the H^3/C^{14} ratios in the TGFA of plasma chylomicrons in serial samples of blood following the infusion of chylomicrons. The results obtained in four rats are shown in Table 3. Each rat received infusions in which both types of chylomicrons were provided by the same donor rat. In all experiments, radioactivity associated with the cream chylomicrons was removed more rapidly than that of the corn oil chylomicrons.

Chylomicrons were infused in equal amounts into six additional rats, and two rats were killed at 2.5, 5.5, and 8.5 min. The H^3 and C^{14} radioactivity found in TGFA of plasma chylomicrons, liver, and adipose tissue has been expressed as a percentage of the infused radioactivity (Table 4). The H^3/C^{14} ratios determined in the TGFA and phospholipids are shown in Table 5.

There was a progressive fall in the H^3/C^{14} ratios in TGFA of plasma chylomicrons. A greater percentage of infused H^3 than C^{14} was found in hepatic TGFA at all times. Whereas the percentage of H^3 continued to rise in hepatic TGFA, there was little difference between the amounts of C^{14} found at 5.5 and 8.5 min despite the fact that more C^{14} had been removed from the plasma at 8.5 than at 5.5 min. At 2.5 and 5.5 min, there were equivalent percentage increments of H^3 and C^{14} in adipose tissue, and the H^3/C^{14} ratios were similar to that of the infused chylomicrons. There was a disproportionately large increase in the fraction of C^{14} recovered from adipose tissue at 8.5 min, accounting for the low H^3/C^{14} ratio in this sample.

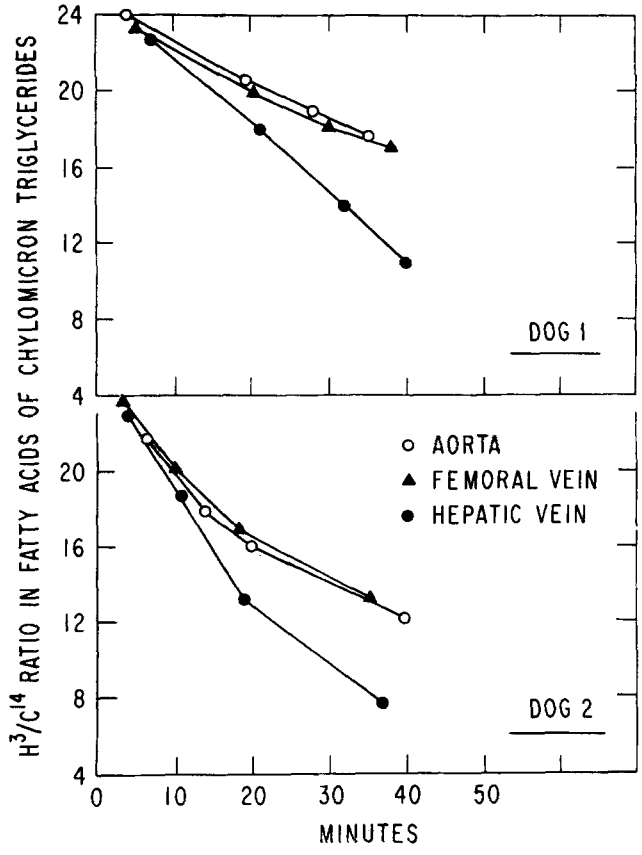

FIG. 2. The H^3/C^{14} ratios in chylomicron triglycerides in blood from the hepatic vein, femoral vein, and aorta; results in two dogs.

TABLE 4 H^3 AND C^{14} RADIOACTIVITY IN TGFA OF PLASMA CHYLOMICRONS, LIVER, AND ADIPOSE TISSUE

Duration of Experiment	Percentage Radioactivity*					
	Plasma† Chylomicron TGFA		Liver TGFA		Adipose‡ TGFA	
	H^3	C^{14}	H^3	C^{14}	H^3	C^{14}
min						
2.5	67	70	26	18	5	5
5.5	27	40	74	36	7	6
8.5	13	25	88	37	8	13

* Expressed as percentages of radioactivity infused with chylomicrons (composition given in Table 2 and described further in the text). Means of two rats killed at each of three time intervals.
† Plasma volume estimated to be 5% body weight.
‡ Adipose tissue estimated to be 15% body weight.

TABLE 5 THE H^3/C^{14} RATIOS IN LIPIDS OF PLASMA, LIVER, AND ADIPOSE TISSUE OF RATS FOLLOWING THE INFUSION OF CHYLOMICRONS

	H^3/C^{14} Ratios* at Times Indicated		
	Rats 1 and 2 2.5 min	Rats 3 and 4 5.5 min	Rats 5 and 6 8.5 min
Infused Chylomicron TGFA†	3.56	3.56	3.56
Plasma Chylomicron TGFA	3.41	2.59	2.01
Liver TGFA	5.00	7.74	9.70
Adipose Tissue TG	3.61	3.78	2.57
Infused Chylomicron PL	2.48	2.48	2.48
Plasma Chylomicron PL	2.46	2.00	1.52
Liver PL	2.88	2.92	4.25

* Ratios are the average of two experiments.
† Composition given in Table 2 and described further in the text.

The changes in the H^3/C^{14} ratio in the phospholipid fatty acids were in the same direction as those in the TGFA.

Chylomicrons that had been obtained from donor rats A and B were perfused through isolated livers of four rats at a concentration of 2 μEq TGFA per ml of perfusing plasma for periods of 50 to 105 min. During this time, 22–44 μEq TGFA were taken up by the liver. The half-times of removal of radioactivity from the TGFA of chylomicrons varied from 40 to 60 min. There was a progressive fall in the H^3/C^{14} ratio of the chylomicrons in the perfusate indicating a more rapid uptake of cream chylomicrons. The percentage falls in the ratios were similar in the four experiments. This was reflected by a rise in the H^3/C^{14} ratio of the hepatic TGFA in the two livers in which this was measured (Table 6).

Rat parametrial adipose tissue was perfused in two experiments with chylomicrons obtained from donor

TABLE 6 THE H^3/C^{14} RATIOS IN TRIGLYCERIDES OF CHYLOMICRONS AND HEPATIC TGFA DURING THE PERFUSION OF LIVERS WITH CHYLOMICRONS*

	Liver 1		Liver 2		Liver 3		Liver 4	
	Time	Ratio	Time	Ratio	Time	Ratio	Time	Ratio
	min		*min*		*min*		*min*	
Chylomicron TG	2	3.40	2	3.54	2	12.5	2	12.6
"	20	3.12	15	3.34	20	11.1	30	10.9
"	45	2.93	30	3.28	40	10.0	60	9.9
"	105	2.46	50	3.06	60	9.0	90	8.0
Liver TG		3.96	—	3.75	—	—	—	—
	($T^1/_2$, 40 min)†		...		($T^1/_2$, 40 min)		($T^1/_2$, 60 min)	

* Composition of infused chylomicrons given in Table 2 and described further in the text.

† Half-times derived from rate of disappearance of C^{14}.

TABLE 7 THE H^3/C^{14} RATIOS IN LIPIDS OF CHYLOMICRONS AND ADIPOSE TISSUE FOLLOWING THE PERFUSION OF RAT PARAMETRIAL FAT WITH CHYLOMICRONS

	Adipose Tissue 1	Adipose Tissue 2
Infused Chylomicron TG	2.93	3.49
Perfusate Chylomicron TG	2.93	3.53
Adipose TG	3.15	3.46
Uptake	1.1%	1.2%

rat A. After 30 min of perfusion, about 1% of the perfused radioactivity, representing 0.4 μEq TGFA, was recovered from the adipose tissue. The H^3/C^{14} ratio in adipose tissue was not significantly different from that in the perfusing chylomicrons (Table 7).

DISCUSSION

The results show that, in the dog and in the rat, chylomicrons obtained after feeding cream to the donor appear to be removed more rapidly from the circulation of the recipient than chylomicrons obtained after feeding corn oil (Tables 1 and 3). This was true, at least in the dog, irrespective of whether both types of chylomicrons were provided by a single or two separate donors.

In general, the rate of removal of the two isotopes from TGFA of plasma chylomicrons has been considered to reflect the rate of removal of the two varieties of chylomicrons. This appears to be justified since similar results were obtained in those experiments in which the rate of removal of chylomicrons was also determined by the change in the fatty acid composition of chylomicron triglycerides in early and late samples of plasma. The fatty acid composition in the late samples resembled more closely the composition of corn oil than that of cream. These changes involved fatty acids other than palmitic acid and linoleic acid. Palmitic, stearic, and myristic acids, fatty acids that were present in the cream chylomicrons in significantly greater amounts than in the corn oil chylomicrons, were all removed from the circulation at a greater rate than linoleic acid. Moreover, Dustin et al. (7) have shown that when linoleate-1-C^{14} and palmitate-9,10-H^3 were incorporated together into lymph chylomicrons, both isotopes were removed at similar rates from the circulation of recipient dogs. This supports the probability that the more rapid removal of labeled palmitate in the present experiments reflected the more rapid removal of cream chylomicrons.

Although cream chylomicrons were removed more rapidly than corn oil chylomicrons in every one of the present experiments, this has not been an invariable finding. Corn oil chylomicrons were found to be removed more rapidly than cream oil chylomicrons in one previously reported experiment (1). Although it is difficult to explain this discrepancy, it does raise the question of changes in the physical state of the chylomicrons that might have been induced by washing and storing.

In the present experiments, both varieties of chylomicrons were treated similarly and simultaneously. Centrifugation was carried out at a relatively low speed and for a short period of time. The chylomicrons were used within 48 hr, stored at 4°, but allowed to disperse at room temperature before infusion.

Since the two major sites of removal of chylomicrons are the liver and adipose tissue, the remaining experiments were concerned more specifically with these tissues. Figure 2 shows the H^3/C^{14} ratios in TGFA of plasma chylomicrons in samples of blood from the hepatic vein, femoral vein, and aorta. The femoral vein drains blood from both muscle and adipose tissue. The hepatic vein drains blood from the portal bed, which includes the liver, adipose tissue, and other viscera. Nevertheless, in this experiment, the femoral vein and hepatic vein were considered to represent extrahepatic and predominantly hepatic venous drainage, respectively. In both dogs, the H^3/C^{14} ratio was lower and fell more rapidly in hepatic venous than in aortic blood, indicating faster removal of cream chylomicrons than corn oil chylomicrons in the liver. On the other hand, the rates of fall in the H^3/C^{14} ratios in femoral venous and aortic blood were similar, indicating equivalent uptake of both types of chylomicrons in extrahepatic tissues. When a large dose of chylomicrons is rapidly injected, the liver appears to be the main site of removal of triglyceride (8) (this is not the case when a constant infusion of a physiological amount of triglyceride is administered [9]); the liver might, therefore, have been the sole organ responsible for the more rapid removal of cream chylomicrons in the intact dog.

In the intact rat, the fall in the H^3/C^{14} ratio in TGFA of plasma chylomicrons was accompanied by a rapid increase in this ratio in hepatic TGFA (Table 5). This

was observed in livers removed as soon as 2.5 min after the injection of chylomicrons. The rapid turnover of linoleic acid within hepatic triglycerides and the rapid discharge of this fatty acid from the liver in the form of triglycerides contained in very low density lipoproteins (1, 10) might have accounted in part for the rising H^3/C^{14} ratio in the liver. However, it is most unlikely that the turnover rate of hepatic TGFA was rapid enough to be solely responsible for these changes and was probably of only minor importance during the initial period of chylomicron removal. The more extensive retransport of linoleate-rich triglyceride became more significant in those animals killed at 8.5 min, as shown by the negligible difference in C^{14} radioactivity in hepatic TGFA of rats killed at 5.5 and 8.5 min.

The H^3/C^{14} ratios in adipose tissue of rats killed 2.5 and 5.5 min following the injection of chylomicrons were only slightly greater than that in the infused chylomicrons. The low H^3/C^{14} ratio in the 8.5-min samples of adipose tissue probably reflects the deposition of linoleate-rich triglyceride transported from the liver. These findings indicate that in the rat, as in the dog, the more extensive removal by the liver of cream chylomicrons is responsible for the more rapid disappearance of cream chylomicrons from the circulation.

The possibility was considered that the falling H^3/C^{14} ratios in the TGFA of plasma chylomicrons were due to significant retransport of linoleate from the liver in very low density lipoproteins. It is evident that such retransport did occur. However, in the dogs, the concentration of triglyceride in the chylomicrons, even in late samples of blood, was 10–20 times as high as that which might have been expected in the very low density lipoproteins. Moreoever, the very short and relatively slow centrifugation used, and the fact that only the surface layer of chylomicrons was removed after slicing the tubes, would have prevented significant contamination of chylomicrons by very low density lipoproteins.

The findings with the perfusions of rat liver and adipose tissue tend to support the observations in the intact animal. In all four liver perfusions there was a progressive fall in the H^3/C^{14} ratios in TGFA of chylomicrons while the ratio in hepatic TGFA was greater than that in the chylomicrons (in the two cases where this was measured) (Table 6). The changes were, however, not nearly as marked as in the intact animals. In the perfusion of rat livers, the livers appeared to remain completely normal throughout the perfusion and continued to extract oxygen at a normal rate. However, a calculation of the uptake of triglyceride by the perfused liver showed this to be considerably less than in the whole animal. The liver of the intact rat removed 35 μEq TGFA in 5.5 min to raise the H^3/C^{14} ratio in hepatic TGFA from 3.56 to 7.74. The perfused liver removed 43.5 μEq TGFA in 105 min to raise the H^3/C^{14} ratio in hepatic TGFA from 3.40 to 3.96.

It seems probable, then, that the more rapid removal of cream chylomicrons from the circulation reflects primarily a more rapid uptake in the liver. The evidence from experiments in which chylomicrons were labeled in several of the lipid moieties (8) or in which the glycerol and fatty acids of the contained triglyceride were separately labeled (11) indicates that chylomicrons are taken up intact by the liver and that the triglycerides do not undergo prior hydrolysis. On the other hand, hydrolysis of triglycerides might precede extrahepatic uptake of TGFA. When chylomicrons in which the cholesterol esters and the TGFA had been separately labeled were infused into hepatectomized dogs (8), only the triglycerides were removed to any significant extent, suggesting that triglycerides were hydrolyzed, presumably by lipoprotein lipase, before being detached from the chylomicron and removed in extrahepatic tissue, since cholesterol esters are not hydrolyzed by lipoprotein lipase. Since lipoprotein lipase has been shown not to discriminate between different triglycerides (12), this would provide a satisfactory explanation for the equivalent rates of removal by adipose tissues of cream and corn oil chylomicrons.

There is no explanation at present for the behavior of the liver in this respect. Since the initial uptake of chylomicrons by the liver appears to be a physical phenomenon, a difference in some of the physical characters of chylomicrons of differing glyceride composition might affect their uptake. It is equally possible that the rate-limiting factor might lie within the liver at a point beyond the uptake of the whole chylomicron.

Manuscript received February 25, 1963; accepted May 10, 1963.

References

1. Nestel, P. J., A. Bezman, and R. J. Havel. *Am. J. Physiol.* **203:** 914, 1962.
2. Mortimore, G. E. *Am. J. Physiol.* **200:** 1315, 1961.
3. Robert, A., and R. O. Scow. *Am. J. Physiol.* **205:** 405, 1963.
4. Havel, R. J., J. M. Felts, and C. M. Van Duyne. *J. Lipid Res.* **3:** 297, 1962.
5. Snyder, F., and N. Stephens. *Biochim. Biophys. Acta* **34:** 244, 1959.
6. Gordis, E. *Proc. Soc. Exptl. Biol. Med.* **110:** 657, 1962.
7. Dustin, J. P., D. S. Fredrickson, P. Laudat, and K. Ono. *Federation Proc.* **20:** 270, 1961.
8. Nestel, P. J., R. J. Havel, and Z. Bezman. *J. Clin. Invest.*, in press.
9. Nestel, P. J., R. J. Havel, and A. Bezman. *J. Clin. Invest.* **41:** 1915, 1962.
10. Nestel, P. J., and D. Steinberg. *J. Lipid Res.* **4:** 461, 1963.
11. Borgström, B., and P. Jordan. *Acta Soc. Med. Upsalien.* **64:** 185, 1959.
12. Korn, E. D. *J. Biol. Chem.* **236:** 1638, 1961.