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Pharmacokinetics of Piperacillin and Gentamicin Following Intravenous Administration to Dogs

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Abstract □ Piperacillin sodium was administered intravenously to dogs, alone or in combination with gentamicin, twice a day (~5 hr apart) for 36–37 days. The pharmacokinetics of neither drug changed in the presence of the other; however, the percentage of the gentamicin dose recovered in the urine decreased significantly when coadministered with piperacillin. The data demonstrate that interaction between the two drugs in urine is feasible.

Keyphrases □ Piperacillin—pharmacokinetics in the dog, effect of concomitant administration of gentamicin □ Gentamicin—pharmacokinetics in the dog, effect of concomitant administration of piperacillin □ Pharmacokinetics—of piperacillin and gentamicin in the dog, effect of concomitant administration

Piperacillin[1], sodium (2*S*, 5*R*, 6*R*)-6-[(*R*)-2-(4-ethyl-2,3-dioxo-1-piperazinecarboxamido)-2-phenylacetamido]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate, is a novel semisynthetic penicillin that possesses broad spectrum antibacterial activity against Gram-negative and Gram-positive pathogenic bacteria, including anaerobes. Results of *in vitro* studies (1) have shown piperacillin to be superior to ampicillin, carbenicillin, and cephalosporins against Gram-negative bacteria, particularly *Klebsiella*, *Proteus*, and *Serratia* species and *Pseudomonas aeruginosa*. In certain cases, a piperacillin and gentamicin combination would be preferred to obtain a synergistic effect. To evaluate the toxicity of these two drugs when administered alone or in combination, a 1-month study was undertaken in dogs. Since aminoglycosides can interact with β-lactam antibiotics (2–4), the study was designed to allow the serum concentrations to be analyzed pharmacokinetically. This paper describes the pharmacokinetics of piperacillin and gentamicin when given alone or in combination.

EXPERIMENTAL

Animal Studies—Six groups of 18–20-month-old beagle dogs[2] (two males and two females in each group) were utilized for the study. The weight range was 9.4–12.3 kg for the males and 7.9–9.6 kg for the females. The dogs were assigned to groups using a table of random numbers. They were housed individually in a room maintained at 21–24°, with a 12-hr on/off light cycle. Food[3] (250–300 g) was offered to each dog daily, ~30 min after the last dose; water was available *ad libitum*.

Drug solutions, made prior to each dose, were administered twice daily (~5 hr apart) over a 5-min period with an infusion pump[4] calibrated using the specific syringes, solutions, and tubing employed. Doses, adjusted to the body weight twice a week, were administered according to the schedule shown in Table I. The concentration of the piperacillin solution in sterile water for injection, expressed as free acid, was 250 mg/ml. The gentamicin solution was made in concentrations of 1 and 2 mg/ml (expressed as base equivalent activity) using sterile isotonic saline. For dogs

[1] Pipracil; American Cyanamid Co.

[2] Marshall Research Animals, North Rose, N.Y.
[3] Respond 2000, Country Foods Div., Agway, Hauppauge, N.Y.
[4] Model 355, Sage Instrument, Cambridge, Mass.

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Table I—Dosing Schedule of Animals Administered Intravenous Piperacillin and Gentamicin Alone or in Combination

Group[a]	Dose, mg/kg BID		Animal	Sex	Samples Collected		Day of Collection		Number of Doses Administered[b]
	Piperacillin	Gentamicin			Serum	Urine	Serum	Urine	
2	500	0	015945	M	X	X	2, 37	5, 6, 34, 35	73
			015966	M	—	X	—	5, 6, 34, 35	71
			015998	F	X	X	2, 37	5, 6, 34, 35	73
			016024	F	—	X	—	5, 6, 34, 35	71
3	0	2	015943	M	X	X	3, 37	5, 6, 34, 35	73
			015956	M	—	X	—	5, 6, 34, 35	71
			015994	F	X	X	3, 37	5, 6, 34, 35	73
			016022	F	—	X	—	5, 6, 34, 35	71
4	0	4	015937	M	X	X	1, 36	5, 6, 34, 35	73
			015952	M	—	X	—	5, 6, 34, 35	71
			016006	F	X	X	1, 36	5, 6, 34, 35	73
			016021	F	—	X	—	5, 6, 34, 35	71
5	500	2	015963	M	X	X	2, 37	5, 6, 34, 35	73
			015965	M	—	X	—	5, 6, 34, 35	71
			016007	F	X	X	2, 37	5, 6, 34, 35	73
			016014	F	—	X	—	5, 6, 34, 35	71
6	500	4	015917	M	X	X	1, 36	5, 6, 34, 35	73
			015953	M	—	X	—	5, 6, 34, 35	71
			016005	F	X	X	1, 36	5, 6, 34, 35	73
			016015	F	—	X	—	5, 6, 34, 35	71

[a] Group 1 is not included as the dogs received no drug and served only as control for the toxicological evaluation. [b] No dose was administered on day 13 and in the evening of day 14 for reasons which were not drug related.

Table II—Mean Serum Concentrations of Piperacillin Following Intravenous Administration Alone or in Combination with Gentamicin [a]

Dose of Piperacillin, mg/kg BID	Dose of Gentamicin, mg/kg BID	Phase	Mean Serum Concentration, μg/ml						
			5 min	10 min	20 min	40 min	60 min	120 min	240 min
500	0	1	2475	1825	1305	715	530	167	13
		2	4200	2188	1380	775	615	154	17
500	2	1	2475	1514	1145	855	510	165	15
		2	2650	1625	1005	780	533	137	18
500	4	1	2700	1763	1325	870	613	179	17
		2	3000	1870	1410	965	825	232	26

[a] $n = 2$ for each group.

that received both drugs, the solutions of piperacillin and gentamicin were prepared independently and mixed in the infusion flow during administration, as illustrated in Fig. 1.

Serum samples were obtained from one dog per sex-group prior to the infusion and at 5 (end of the infusion), 10, 20, 40, 60, 120, and 240 min following the commencement of the infusion during the first (phase I) and last (phase 2) week of dosing. Urine samples (0–24 hr) were collected for 2 consecutive days from all dogs during the first and last weeks of the study.

Antibiotic Assay—Antibiotic concentrations were determined by the disk diffusion method. The assays for piperacillin were performed with *Sarcina lutea* ATCC 9341 (indicator organism) grown on antibiotic medium No. 1[5] to which 0.6% sodium polyanetholesulfonate was added to inhibit gentamicin activity (5). This concentration of sodium polyanetholesulfonate was sufficient to inactivate 50 μg/ml of gentamicin in the solutions containing 2.5–0.16 μg/ml of piperacillin used for the standard curve. The recovery from samples of known piperacillin concentration, alone or combined with gentamicin, was 95–108%; the limit of detection was 0.16 μg/ml.

The assays for gentamicin were performed with *Bacillus subtilis* ATCC 6633 grown on mycin agar[5] to which 1000 kinetic units of pencillinase[6] were added per milliliter of medium to inactivate the piperacillin. This concentration of the enzyme was sufficient to inactivate >440 μg/ml of piperacillin in the solutions containing 2.5–0.16 μg/ml of gentamicin used for the standard curve. Samples were diluted to the range of concentrations in the standard curve. The recovery from samples of known gentamicin concentration, alone or combined with piperacillin, was 96–107%; the limit of detection was 0.16 μg/ml. All samples were assayed twice, and the precision of the assays was ±15%.

Pharmacokinetic Analysis—Pharmacokinetic analysis of the data was performed using the digital computer program AUTOAN (6) in conjunction with the nonlinear regression analysis program NONLIN (7). The serum concentrations were weighted according to the square of their reciprocals. The excretion rate constant (k_u) was computed using:

$$\frac{X_u^\infty}{\text{Dose}} = \frac{k_u}{K_{el}}$$

where X_u^∞ is the amount of unchanged drug excreted in the urine and K_{el} is the overall elimination rate constant of the drug. Renal clearance was estimated by multiplying k_u by the volume of distribution of the central compartment. The other pharmacokinetic parameters were obtained by previously published pharmacokinetic equations (8).

Statistical Methods—The pharmacokinetic model parameters were

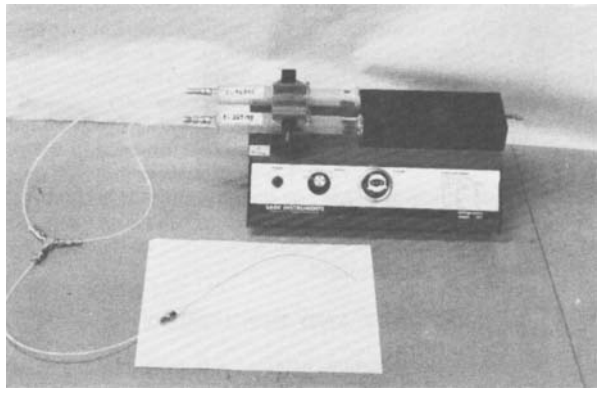

Figure 1—*Apparatus used to combine the piperacillin and gentamicin doses during infusion.*

[5] Difco Laboratories, Detroit, MI 48201.
[6] Baltimore Biological Laboratory, Cockeysville, MD 21050

Table III—Mean Serum Concentration of Gentamicin Following Intravenous Administration Alone or in Combination with Piperacillin [a]

Dose of Piperacillin, mg/kg BID	Dose of Gentamicin, mg/kg BID	Phase	Mean Serum Concentration, μg/ml						
			5 min	10 min	20 min	40 min	60 min	120 min	240 min
0	2	1	9.6	6.0	4.4	2.8	2.2	1.1	0.5
		2	12.4	7.7	6.2	5.1	3.4	1.9	0.8
0	4	1	25.5	18.4	12.9	9.7	7.3	3.5	1.0
		2	29.0	19.6	12.9	8.6	6.8	3.4	1.0
500[b]	2	1	8.1	6.7	5.0	3.5	2.5	1.2	0.4
		2	7.7	6.2	4.6	3.9	3.0	1.6	0.5
500	4	1	17.9	15.3	12.1	8.9	6.9	3.6	1.3
		2	15.4	10.9	8.6	7.5	5.9	3.8	1.3

[a] $n = 2$ unless otherwise noted. [b] $n = 1$; data from dog 016007 (female) was rejected as an outlier.

Table IV—Mean Pharmacokinetic Parameters of Piperacillin and Gentamicin

Drug	Dose, mg/kg BID	Phase	Half-life, min		V_c, ml/kg	Vd, ml/kg	Vd_{ss}, ml/kg	Clearance, ml/min		k_u, min^{-1}
			α	β				Body	Renal	
Piperacillin[a]	500	1	3.9	32.8	154	256	236	50	22	0.016
		2	3.2	35.6	87	263	219	47	21	0.026
Gentamicin[b]	2 or 4	1	5.4	70.1	163	391	347	36	18	0.011
		2	4.1	70.7	123	307	280	30	19	0.015

[a] $n = 2$. [b] $n = 4$.

Table V—Effect of the Piperacillin–Gentamicin Combination on the Pharmacokinetics of Piperacillin [a]

Dose, mg/kg BID		Phase	Half-life, min		V_c, ml/kg	Vd, ml/kg	Vd_{ss}, ml/kg	Clearance, ml/min		k_u, min^{-1}	AUC, μg·min/ml
Piperacillin	Gentamicin		α	β				Body	Renal		
500	0	1	3.9	32.8	154	256	236	50	22	0.016	96,918
	2		1.2	34.8	121	320	302	57	31	0.029	94,134
	4		1.5	34.9	128	314	295	58	32	0.027	105,624
500	0	2	3.2	35.6	87	263	219	47	21	0.026	113,086
	2		2.8	37.1	138	351	312	59	13	0.011	90,823
	4		4.8	37.8	145	254	234	43	13	0.013	124,870

[a] $n = 2$.

Table VI—Effect of the Piperacillin–Gentamicin Combination on the Pharmacokinetics of Gentamicin [a]

Dose, mg/kg BID		Phase	Half-life, min		V_c, ml/kg	Vd, ml/kg	Vd_{ss}, ml/kg	Clearance, ml/min		k_u, min^{-1}	AUC, μg·min/ml
Gentamicin	Piperacillin		α	β				Body	Renal		
2	0	1	5.6	76.5	187	504	440	43	20.9	0.012	425
	500[b]		14.2	76.8	258	486	407	41	1.5	0.0006	468
4	0		5.1	63.7	139	278	255	30	14.3	0.010	1318
	500		10.9	79.9	266	419	378	34	1.5	0.0008	1242
2	0	2	3.1	74.7	126	303	285	27	16.2	0.015	660
	500		4.2	71.4	245	402	387	35	2.3	0.001	523
4	0		5.1	66.7	121	311	274	33	22.1	0.014	1293
	500		2.9	81.4	209	430	413	34	7.4	0.004	1090

[a] $n = 2$ unless otherwise noted. [b] $n = 1$; data from dog 016007 (female) was rejected as an outlier.

subjected to three separate ANOVA to compare the pharmacokinetics of piperacillin with gentamicin, determine the effects of gentamicin on piperacillin pharmacokinetics, and determine the effects of piperacillin on gentamicin pharmacokinetics. The first analysis included animals that received only one drug. The effects tested were drug, phase, and the drug by phase interaction; the dose level of gentamicin was not considered. The second analysis included animals that received 500 mg/kg of piperacillin, alone or in combination with gentamicin at either 2 or 4 mg/kg. The effects tested were dose level of gentamicin, phase, and the interaction between dose level and phase. The final analysis included animals that received gentamicin at either 2 or 4 mg/kg, alone or in combination with 500 mg/kg of piperacillin. The effects tested were dose levels of both drugs, phase, and all interactions. Homogeneity of variance within the male and female dogs was assumed.

RESULTS AND DISCUSSION

The mean serum concentrations attained following administration of 500 mg/kg of piperacillin and 2 or 4 mg/kg of gentamicin (alone or in combination) during phase 1 (day 1, 2, or 3) and phase 2 (day 36 or 37) are shown in Tables II and III. Following administration of 500 mg/kg of piperacillin alone, the mean serum concentration at the end of the infusion in phase 1 was 2475 μg/ml; after 5 min, it declined rapidly and biexponentially. The mean serum concentrations at 10, 20, 40, 60, 120, and 240 min after administration were 1825, 1305, 715, 530, 167, and 12.5 μg/ml, respectively. In phase 2, no detectable levels of piperacillin were present before the start of the infusion. At the end of the infusion, the serum concentration was 4200 μg/ml, a level higher than seen in phase 1. After 5 min, serum concentrations were about the same magnitude as observed in phase 1. Simultaneous administration of gentamicin did not change the serum piperacillin levels to any significant extent.

Following 2 mg/kg of gentamicin alone, the serum concentration at the end of the infusion in phase 1 was 9.6 μg/ml; after 5 min, it declined in a biexponential manner. The respective serum levels at 10, 20, 40, 60, 120, and 240 min were 6.0, 4.4, 2.8, 2.2, 1.1, and 0.5 μg/ml. In phase 2, no detectable levels of gentamicin were present before the start of the infusion. At the end of the infusion, the serum level was 12.4 μg/ml and was higher than that in phase 1. Following the 4-mg/kg dosage regimen, the serum levels in both phases 1 and 2 were about two- to threefold the corresponding serum levels observed following the 2-mg/kg dosage regimen.

The time course of both piperacillin and gentamicin in the dog serum

Table VII—Percentage of Dose Excreted in the Urine Following Intravenous Administration of Piperacillin Alone or in Combination with Gentamicin

Dose, mg/kg BID			Mean[a] Percent of Dose Excreted	
Piperacillin	Gentamicin	Animal	Phase 1	Phase 2
500	0	015945	45.20	39.73
		015998	42.44	49.70
		015966	16.52[b]	1.56[b]
		016024	50.53	30.10
		Mean	46.06	39.84
500	2	015963	57.74	18.61
		016007	51.09	24.45
		015965	60.51	26.55
		016014	55.39	37.13
500	4	015917	51.57	10.21
		016005	59.08	49.88
		015953	49.47	39.03
		016015	58.92	24.54
		Mean[c]	55.47	28.81

[a] Mean of two 0–24-hr collections from 2 consecutive days. [b] Values of 16.52 and 1.56 are considered outliers and were not used in calculating the mean. [c] Mean of 2- and 4-mg/kg dose levels together.

Table VIII—Percentage of Dose Excreted in the Urine Following Intravenous Administration of Gentamicin Alone or in Combination with Piperacillin

Dose, mg/kg BID			Mean[a] Percent of Dose Excreted	
Piperacillin	Gentamicin	Animal	Phase 1	Phase 2
0	2	015943	63.88	60.40
		015994	32.66	59.05
		015956	52.24	68.52
		016022	61.80	43.37
	4	015937	51.01	49.00
		016006	43.83	57.34
		015952	56.89	84.62
		016021	67.83	54.41
		Mean[b]	53.77	59.59
500	2	015963	3.71	5.17
		016007	5.15	8.13
		015965	0.83	17.72
		016014	2.58	12.55
	4	015917	1.11	20.06
		016005	9.25	23.33
		015953	4.88	6.25
		016015	6.67	14.02
		Mean[b]	4.28	13.41

[a] Mean of two 0–24-hr collections from 2 consecutive days. [b] Mean of 2- and 4-mg/kg dose levels together.

could be described by a two-compartment open model. The relevant mean pharmacokinetic parameters estimated based on this model are given in Table IV. Table V shows the effect of gentamicin administration on the pharmacokinetics of piperacillin; Table VI shows the effect of piperacillin administration on the pharmacokinetics of gentamicin.

The pharmacokinetic parameters, except the volume of distribution of the central compartment (V_c), of both of the drugs in phase 2 were not different from those in phase 1. Even though V_c dropped significantly in phase 2, no statistically significant change was observed either in the volume of distribution at steady state (Vd_{ss}) or the overall volume of distribution, Vd. The reason for the lower V_c in the second phase is not known.

Since the two drugs were given in combination, it was considered of interest to compare the pharmacokinetics of piperacillin with that of gentamicin. Based on data from both phases, the half-life of piperacillin was 34 min, the body and renal clearances were 49 and 22 ml/min, respectively, and the volume of distribution at steady state was 228 ml/kg. The corresponding values for gentamicin were 70 min, 33 and 19 ml/min, and 314 ml/kg, respectively. Compared with gentamicin, piperacillin had a shorter half-life and a larger body clearance. There were no statistically significant differences in the volume of distribution nor in the renal clearance of the two drugs.

The percentages of the piperacillin and gentamicin doses excreted in the urine are given in Tables VII and VIII, respectively. The excretion data of dog 015966 were not used in averaging because of the exceptionally low values obtained: these values are considered to be outliers[7]. When piperacillin was administered alone, ~46% of the dose was recovered in 0–24 hr during phase 1 and ~40% in phase 2. The two urinary recoveries were not statistically different ($p > 0.05$). These recoveries remained unaffected when gentamicin was administered concurrently ($p > 0.05$). Following administration of gentamicin alone, ~54% of the dose was excreted in the urine in 0–24 hr in phase 1 and ~60% in phase 2; again, no statistical differences were observed between the two recoveries ($p > 0.05$). Simultaneous administration of piperacillin reduced ($p < 0.05$) the phase recovery by 92% (from 53.8 to 4.3) and the phase 2 recovery by 78% (from 59.6 to 13.4).

Gentamicin did not affect the pharmacokinetics of piperacillin to any large extent, nor were the pharmacokinetics of gentamicin changed significantly when piperacillin was administered simultaneously. The serum levels, area under serum concentration–time curve (AUC), body clearance, and half-life of gentamicin were not affected by the combination. However, the urinary recovery of gentamicin decreased significantly when it was coadministered with piperacillin.

The similarity of the pharmacokinetic parameters of gentamicin administered alone or in combination with piperacillin clearly indicate that the interaction between piperacillin and gentamicin occurred after excretion, *i.e.*, either in the urinary bladder or the collection container. The *in vitro* inactivation of aminoglycoside antibiotics by β-lactam antibiotics has been documented (2–4, 9, 10). It has been proposed (3, 9) that the two interact to form a biologically inactive conjugate linked between the amino group of the aminoglycoside and the β-lactam ring of the penicillin. Piperacillin in high concentrations has been shown to inactivate gentamicin in serum *in vitro*, but less rapidly than carbenicillin (11). It has also been shown that the inactivation of gentamicin proceeds at a much faster rate in saline or distilled water than in serum (9). Since both piperacillin and gentamicin are excreted in the urine rapidly and in high concentrations, the interaction could take place in the urinary system, especially if voiding does not occur for a long time. Inactivation of gentamicin by piperacillin either during infusion or *in vivo* would have resulted in an area under the gentamicin serum concentration–time curve lower than that in dogs given gentamicin alone. Statistically, there was no difference between the AUC values. Thus, the drop seen in the excretion rate constant and the renal clearance is probably an artifact of the computation process since the equation to calculate these parameters utilizes the amount of unchanged drug excreted in the urine. Results very similar to ours were observed by Waitz and coworkers (3) with carbenicillin. They showed that an intravenous administration of carbenicillin had no effect on gentamicin serum levels in dogs, but did result in reduced urinary excretion of gentamicin. Young *et al.* (4) have also investigated the inactivation of gentamicin by carbenicillin. In dogs whose urine flow was obstructed surgically, they were able to demonstrate that an interaction between carbenicillin and gentamicin could take place in the urinary bladder.

An *in vitro* study was conducted to confirm the interaction of the two drugs in urine. Piperacillin and gentamicin, alone and in combination, were incubated in dog urine at 37° at approximately the same concentration levels as were encountered in the urine of dogs receiving piperacillin or gentamicin alone. Aliquots of urine were removed at predetermined intervals and assayed for piperacillin and gentamicin activity

Table IX—Concentrations of Piperacillin and Gentamicin in Dog Urine as a Function of Time Following Incubation at 37° Either Alone or in Combination

Time, hr	Concentration in Urine, μg/ml			
	Piperacillin		Gentamicin	
	Alone	In Combination	Alone	In Combination
0	4270	5120	69.9	60.4
0.5	4350	4790	67.8	47.0
1	4070	4820	65.4	48.8
2	4120	4730	64.9	48.4
4	4110	4670	34.7[a]	40.7
6	4050	4920	64.0	35.2
8	4020	4630	64.2	32.1

[a] An apparent outlier.

[7] Inclusion of data of this animal in the analysis did not affect the results or conclusions.

(Table IX). There was no loss in piperacillin activity whether incubated alone or with gentamicin; however, a 47% loss of the initial activity of gentamicin was noted when it was incubated with piperacillin. The data clearly demonstrate that interaction between the two drugs in urine is feasible.

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Potential Tumor- or Organ-imaging Agents XXIV: Chylomicron Remnants as Carriers for Hepatographic Agents

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Abstract □ This paper describes the possible utility of plasma lipoproteins for the site-specific delivery of diagnostic agents. The class of lipoproteins known as chylomicrons was selected for this preliminary study, since they are known to be rapidly metabolized and taken up by the liver. Cholesteryl iopanoate (II), an iodinated analogue of a normal constituent of the hydrophobic core of chylomicrons, was synthesized from cholesterol and iopanoic acid (I) and subsequently radiolabeled with ioidine-125. Whereas intravenous administration of II in physiological saline resulted in the appearance of ~31% of the dose in the liver at 0.5 hr, prior incorporation of II into chylomicrons resulted in an almost threefold (87%) increase in the liver accumulation of II in the same time period. A more gradual appearance of II in steroid-secreting tissues was consistent with the association of II with high-density lipoproteins following administration.

Keyphrases □ Chylomicron—remnants as carriers for hepatographic agents, potential tumor- or organ-imaging agents □ Tumor-imaging agents—potential, chylomicron remnants as carriers for hepatographic agents □ Organ-imaging agents—potential, chylomicron remnants as carriers for hepatographic agents

The early detection of small metastatic lesions in the liver has been a long-term goal of radiology and nuclear medicine. Among the noninvasive diagnostic approaches, radionuclide scintiscanning, ultrasonography, and computed tomography (CT) have all enjoyed variable success (1). Over the past several years, one of the goals of this laboratory has been to devise approaches for the selective delivery of radiopharmaceuticals or radiopaque agents to the liver on the premise that specific uptake of these agents in either normal or abnormal tissue will significantly improve image resolution of small lesions. While others have employed liposomes as delivery vehicles for radiopharmaceuticals (2) and radiopaque contrast agents (3), the focus of this study is on those naturally occurring macromolecules responsible for the transport of lipophilic substances in the plasma—the lipoproteins.

It has been known for many years that the liver plays a major role in lipoprotein catabolism. This is especially true for the class of lipoproteins known as chylomicrons (4, 5). The chylomicrons are synthesized in the intestinal mucosa during fat absorption and are responsible for the transport of dietary fats to sites of utilization and storage. Structurally they are the largest (800–5000 Å) and the lightest (<0.95 g/ml) of the lipoproteins, and consist of an apolar core of lipid surrounded by a phospholipid monolayer (Fig. 1). The lipophilic core is composed of triglycerides and cholesteryl esters. Free cholesterol and apoproteins are associated with the outer phospholipid membrane.

Once in the circulation, these native chylomicrons are acted on by tissue lipoprotein lipase, the enzyme responsible for hydrolyzing triglycerides and providing free fatty acids for cellular metabolism. The resulting triglyceride-depleted, cholesteryl ester-enriched chylomicrons are referred to as chylomicron remnants. In humans, these smaller remnants (300–800 Å) are rapidly taken up by the liver, and their plasma half-life is in the range of 4–5 min (6).

The uptake of chylomicron remnants by liver cells has been shown to occur by a saturable high-affinity process, suggesting the existence of receptors on the surface of liver cells capable of specificially binding these particles (7, 8). Moreover, the presence of apoprotein E on the surface of the remnants has been shown to be important for the recognition and uptake of these particles (9, 10).

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