Neutral lipid mass transfer among lipoproteins in plasma from normolipidemic subjects is not an equimolar heteroexchange

Xiao Q. Liu and John D. Bagdade[1]

Section of Endocrinology and Metabolism, Rush-Presbyterian-St. Luke's Medical Center, Rush Medical College, 1653 West Congress Parkway, Chicago, IL 60612

Abstract To further characterize the cholesteryl ester transfer protein (CETP)-mediated distribution of neutral lipids that occurs among lipoproteins in plasma, the net mass transfer of core lipids between donor and acceptor lipoproteins in intact plasma was measured in ten healthy normolipidemic subjects. The rate of loss of cholesteryl ester (CE) from high density lipoprotein-3 (HDL_3) (19.5 ± 8.8 nmol/ml per h) was linear and increased significantly ($P < 0.01$) during the 6-h incubation. Approximately 50% of the CE transferred from HDL_3 (118.7 ± 54.3 nmol/ml) went to very low density lipoprotein (VLDL); the remainder was distributed to low density lipoprotein (LDL) (~30%) and HDL_2 (~20%). The rate of loss of triglyceride (TG) from VLDL (14.5 ± 6.6 nmol/ml per h) to the HDL subfractions and LDL also was linear and increased significantly with time ($P < 0.01$). About 50% of the TG mass lost from VLDL (85.2 ± 38.4 nmol/ml) was transferred to LDL and the remainder was recovered in HDL_2 (~ 10%) and HDL_3 (~40%). As the number of nmoles of CE lost from HDL_3 was almost three times greater than the nmoles of TG it acquired, these findings indicate that the exchange of core lipids in plasma that result from the interaction between CETP-VLDL-HDL_3 is not equimolar. Even in the absence of VLDL, HDL_3 continued to donate CE to LDL and HDL_2 to almost the same degree as in intact plasma (plasma minus VLDL: 17.5 ± 5.9 nmol/ml per h vs. intact plasma: 20.2 ± 7.5 nmol/ml per h) without accepting any TG. Our findings demonstrate that independent pathways exist for the transfer of CE and TG among the plasma lipoproteins and, contrary to what is generally believed, a heteroexchange of TG for CE during cholesteryl ester transfer is not obligatory.—**Liu, X. Q., and J. D. Bagdade.** Neutral lipid mass transfer among lipoproteins in plasma from normolipidemic subjects is not an equimolar heteroexchange. *J. Lipid Res.* 1995. **36:** 2574-2579.

Supplementary key words cholesteryl ester transfer • triglyceride • cholesterol • lipoprotein core lipid composition

The protein-mediated transfer of cholesteryl ester and triglyceride between lipoprotein classes has received considerable attention since Nichols and Smith (1) first showed that in reconstituted plasma a reciprocal transfer of cholesteryl ester and triglyceride mass occurred between plasma HDL and VLDL when these lipoproteins were incubated. Using a similar experimental system, Chajek and Fielding (2) subsequently found that this transfer was equimolar and mediated by a neutral lipid transfer protein that has been designated cholesteryl ester transfer protein (CETP) (3). This observation, however, was not confirmed by other workers (4–6). On the basis of these earlier observations, a number of different in vitro test systems using labeled HDL, reconstituted lipoprotein fractions, and CETP have been developed to indirectly estimate the protein-mediated net transfer of CE and TG between lipoproteins in vivo (7). As assays of this type do not use native lipoproteins, they are far removed from in vivo conditions and may provide misleading information. To circumvent these problems, in the present report we have measured the magnitude and rates of the net mass transfer of lipoprotein core lipids among the major lipoprotein classes that occurs during incubation of freshly drawn intact human plasma.

METHODS

Study population

Ten healthy normolipidemic subjects (five male, five female, age 35.3 ± 12.9; range 25–62 years; TG 79.6 ± 36.1 mg/dl; cholesterol 152.0 ± 18.9; HDL-cholesterol 48.2 ± 9.2) were studied. None smoked cigarettes or was taking medications that affected lipid transport. The study protocol was approved by the Institutional Human Investigation Committee. Informed consent was obtained and the project was carried out according to

Abbreviations: VLDL, very low density lipoprotein; LDL, low density lipoprotein; HDL, high density lipoprotein; TG, triglyceride; CE, cholesteryl ester; CETP, cholesteryl ester transfer protein; CET, cholesteryl ester transfer; LCAT, lecithin:cholesterol acyltransferase.

[1]To whom correspondence should be addressed.

the principles of the Declaration of Helsinki. Venous blood samples were obtained after a 12-hr overnight fast in Na-EDTA-containing tubes and plasma was separated promptly at 4°C by low speed centrifugation.

Cholesteryl ester transfer

Plasma from each subject was incubated in a metabolic shaker at 37°C in the presence of 1.5 mM dithio-bis-dinitrobenzoic acid (DTNB) to inhibit plasma lecithin:cholesterol acyltransferase (LCAT) (8). DTNB at this concentration has not been found to significantly inhibit the net mass transfer of CE in experiments with the LCAT inhibitors DTNB, E-600, and iodoacetate performed in our laboratory (unpublished results; Liu, X-Q., Ritter, M. C., Bagdade, J. D.). Plasma from each subject was divided into four (2 ml) aliquots and added to tubes containing DTNB, mixed by vortexing, then placed at 4°C for 1 h before initiating the 37°C incubation. The tube containing the zero-time sample was kept at 4°C throughout the 6-h incubation. After incubation, 1 ml (0.15 M) NaCl with 1 mM EDTA, pH 7.4, was added to each tube and then placed in a prechilled ultracentrifuge (4°C). VLDL was then isolated by ultracentrifugation according to the method of Mann et al. (9) at a density of 1.006 g/ml. LDL, HDL_2, and HDL_3 were then separated in the infranant by differential precipitation with dextran sulfate (10). The mass of cholesteryl ester and triglyceride transferred among the major lipoprotein classes was measured in aliquots of plasma that were removed at zero time and after 2, 4, and 6 h, except CE transfer in LDL which was derived indirectly by subtracting the increments of CE measured in HDL_2 and VLDL from the total CE lost from HDL_3. Triglyceride and total and free cholesterol were measured in plasma and in the lipoprotein fractions with enzymatic kit methods (Boehringer Mannheim, Houston, TX). HDL_3 lipids were extracted by the Bligh and Dyer (11) procedure prior to their measurement. Cholesteryl ester was calculated from the difference between total and free cholesterol. The coefficient of variation for CE was 5.3 ± 4.2% and for TG 6.6 ± 5.1% (mean ± SD). The mass of CE transferred at each time interval was determined by subtracting the value from zero-time CE in HDL_3. Transfer rates were obtained by linear regression analysis.

Statistical methods

Measurements obtained before and after each incubation time point were compared by the paired *t*-test.

RESULTS

Redistribution of CE and TG among lipoprotein fractions

The content of cholesteryl ester decreased significantly ($P < 0.01$) and linearly ($P = 0.007$) in HDL_3 at a rate of 19.5 ± 8.8 nmol/ml per h (**Table 1**) and by 6 h 14% of the mass present at zero time was transferred to acceptor lipoproteins. Approximately 50% of the total CE mass lost from HDL_3 appeared in VLDL; the remainder was distributed to LDL (~ 30%) and HDL_2 (~20%).

Conversely, VLDL triglyceride decreased linearly ($P = 0.048$) at a rate of 14.5 ± 6.6 nmol/ml per h during incubation and by 6 h about 30% of the TG present in VLDL at zero time had been transferred to the HDL subfractions and LDL. Of the total TG mass lost from VLDL, HDL_3 and HDL_2 together accepted about 50%; the remaining TG went to LDL (**Table 2**).

Changes in lipoprotein core lipids during CET

The proportion of TG and CE in each lipoprotein fraction changed during CET. In HDL_3, HDL_2, and LDL the TG/CE ratios increased progressively and significantly ($P < 0.01$); in VLDL the core lipid ratio decreased in a reciprocal manner ($P < 0.01$) (**Table 3**) during the 6-h incubation. The rates at which this ratio increased in HDL_2 and HDL_3 were very similar (0.013/h and 0.012/h, respectively). Owing to the large mass of CE present in LDL, the rise in the LDL TG/CE ratio was somewhat slower (0.005/h). In VLDL this ratio decreased more rapidly (0.630/h).

The concentration of lipoprotein core lipids (TG + CE) changed significantly in all lipoprotein fractions

TABLE 1. CET activity in normolipidemic subjects during 6 h incubation

	CE Mass Net Changes			
	Baseline	2 h	4 h	6 h
	nmol/ml plasma			
HDL_3	847.3 ± 102.6	-44.8 ± 24.9[a]	-78.5 ± 29.9[a]	-118.7 ± 54.3[a]
HDL_2	126.8 ± 80.8	+14.6 ± 16.7[a]	+21.4 ± 16.4[a]	+26.5 ± 20.9[a]
LDL	2012.2 ± 472.7	+3.25 ± 32.6	+10.1 ± 28.7	+37.3 ± 62.8
VLDL	58.8 ± 48.3	+27.0 ± 17.4[a]	+44.4 ± 29.7[a]	+57.6 ± 37.6[a]

Values given as mean ± SD.
[a]$P < 0.01$ comparing with baseline values.

TABLE 2. Triglyceride transfer activity in normolipidemic subjects during 6 h incubation

	Net Mass Changes			
	Baseline	2 h	4 h	6 h
	nmol/ml plasma			
VLDL	288.7 ± 207.3	33.7 ± 20.0[a]	-68.6 ± 34.7[a]	-85.2 ± 38.4[a]
LDL	413.4 ± 186.7	+21.3 ± 14.3[a]	+41.5 ± 23.6[a]	+52.1 ± 29.2[a]
HDL_3	84.2 ± 28.7	+13.9 ± 11.4[a]	+27.9 ± 17.0[a]	+42.6 ± 21.8[a]
HDL_2	17.8 ± 14.3	+6.0 ± 4.2[a]	+10.5 ± 6.1[a]	+13.6 ± 7.4[a]

Values given as mean ± SD.
[a]$P < 0.01$ comparing with baseline values.

during CET (**Table 4**) declining in both VLDL and HDL_3 ($P < 0.001$), while a net increase was observed in the core lipid content of HDL_2 and LDL ($P < 0.01$ and $P < 0.05$, respectively). These findings indicate that exchange of core lipids among lipoproteins was not equimolar; VLDL and HDL_3 were net donors and LDL and HDL_2 were net acceptors.

Non-heteroexchange of CE and TG in HDL_3 during transfer

To further delineate the role that VLDL core lipids play in neutral lipid transfer, VLDL (d < 1.006 g/ml) was removed by ultracentrifugation from the plasma of six subjects. CET of the VLDL-free d > 1.006 g/ml fraction and of intact plasma from the same subjects were then determined simultaneously and compared.

The amount of cholesteryl ester transferred from HDL_3 to other lipoproteins in intact and VLDL-deficient plasma was virtually identical; as expected, in the absence of VLDL there was little increase in TG in HDL_3 (**Fig. 1**). In contrast, when VLDL was present a significant increase in HDL_3 TG was observed at all time points.

DISCUSSION

A number of lines of evidence indicate that the activity of the cholesteryl ester transfer protein (CETP), which mediates the transfer and exchanges of cholesteryl ester and triglyceride between lipoproteins in plasma, is proatherogenic. Murine species such as mice and rats and families in Japan who lack CETP activity because of mutations of the CETP gene appear to be relatively resistant to developing atherosclerosis (12). In contrast, those animals such as rabbits and humans with active CETP systems are highly susceptible to dietary-induced atherosclerosis (13, 14). When mice, a species normally atherosclerosis resistant, are made transgenic for simian CETP, they demonstrate increased susceptibility (15). In addition, a direct correlation has been shown between CETP mass, LDL cholesterol levels, and intimal plaque area in monkeys with experimental atherosclerosis (16).

As the directional flux of each lipid during CET is determined by its concentration gradient (17, 18), the net mass transfer of core lipids occurs primarily among lipoproteins with the greatest differences in core lipid composition. Thus, the proportion of core lipids in a particular lipoprotein (i.e., TG/CE molar ratio) predicts whether it functions as a donor or acceptor of CE and TG. In the present study, HDL_3, the site of active CE synthesis by LCAT, had the greatest amount of CE relative to TG and therefore was the principal CE donor to other lipoproteins. Conversely, because VLDL had the most TG relative to CE, it donated TG down its gradient to those lipoproteins with lower TG/CE ratios (i.e., LDL, HDL_2, HDL_3). As the TG/CE molar ratios of

TABLE 3. Lipoprotein core lipid changes during lipid transfers: TG/CE molar ratios

	Incubation Time			
	0 h	2 h	4 h	6 h
HDL_3	0.091 ± 0.036	0.123 ± 0.046[a]	0.148 ± 0.050[a]	0.165 ± 0.058[a]
HDL_2	0.127 ± 0.045	0.159 ± 0.057[a]	0.188 ± 0.068[a]	0.204 ± 0.068[a]
LDL	0.220 ± 0.045	0.230 ± 0.040[a]	0.238 ± 0.048[a]	0.248 ± 0.057[a]
VLDL	5.58 ± 2.90	3.07 ± 1.28[a]	2.12 ± 0.89[a]	1.70 ± 0.75[a]

Values given as mean ± SD.
[a]$P < 0.01$ compared with 0 h.

TABLE 4. Lipoprotein core lipid sum changes after 6 h incubation

	TG + CE	
	Preincubation	After 6 h Incubation
	nmol/ml plasma	
HDL_3	925.1 ± 113.8	838.0 ± 115.8[a]
HDL_2	142.7 ± 92.5	180.3 ± 113.9[b]
LDL	2418.1 ± 609.0	2508.9 ± 656.0[c]
VLDL	344.5 ± 255.9;	308.4 ± 245.5[a]

Values given as mean ± SD.
[a]P < 0.001.
[b]P < 0.01.
[c]P < 0.05.

HDL_2 and LDL were intermediate between those of VLDL and HD_3, they accepted both CE from HDL_3 and TG from VLDL; as a result, under the conditions of our assay, they gained core lipid mass. A less consistent increase in LDL-core lipid than the one we find in the present study has been recently reported by Ko, Ohnishi, and Yokoyama (19). Indeed, we find that a greater percentage of the moles of TG lost from VLDL was recovered in LDL (52.9%) than in HDL_3 (40.6%), whereas 32% of the CE lost from HDL_3 was recovered in LDL and about half in VLDL (49.1%). If the exchange between HDL_3 and VLDL were equimolar, the same number of nanomoles of TG and CE would be expected to be recovered in HDL_3 and VLDL, respectively.

The fact that the TG/CE ratios of HDL_2 and to a lesser degree LDL increased compared to baseline values indicated that as their core lipid content increased there was a tendency to accrue more TG than CE. Because HDL_3 lost more moles of CE than it acquired in TG, its TG/CE ratio also increased. Conversely, the disproportionate directional changes in VLDL TG and CE resulted in a decline in the TG/CE ratio.

Models for the transfer and exchange of core lipids between lipoproteins have been based largely on a variety of reconstituted in vitro systems (7) using radiolabeled donor lipoproteins. With these assays, a radiolabeled CE donor lipoprotein is incubated with an excess of an acceptor in the presence of the CETP-containing d > 1.21 g/ml fraction from an unknown plasma. In one such system containing equimolar amounts of HDL, VLDL, and CETP, Marcel et al. (20) found a greater net mass transfer rate of CE from HDL to VLDL (80 nmol/ml per h) than the one we found in intact plasma. This difference probably reflects the absence of LDL in their assay system which our data show can both accept CE from HDL_3 and donate CE to HDL_2. In reconstituted assay systems, changes in the net mass and ratios of lipoprotein core lipids have been ignored and transfer rates have been represented as exchange rates between the donor and acceptor lipoproteins. While the transfer rates we find may not reflect true transfer rates because CE and TG are being redistributed simultaneously among the lipoproteins in plasma, nevertheless the serial changes we describe in the core lipids of each lipoprotein class during CET in intact human plasma provide a more detailed picture of the extent of their engagement in CET than has been provided in earlier studies.

One new finding in our study that would not be detected with isotopic CET assays is that VLDL and HDL_3 are both net donors of TG and CE, respectively, to other lipoproteins and, as a result, there is a net increase in core lipids in LDL and HDL_2. Another new observation is that the HDL_3 subfraction is responsible for most of the change in HDL net mass. In earlier studies with radiolabeled HDL, Chajek and Fielding (2) reported that the transfer of lipoprotein CE and TG during CET was reciprocal and equimolar. Moreover, no net transfer of total core lipid was apparent in this or in other studies when labeled HDL was incubated with either an artificial triglyceride-phospholipid emulsion (21), LDL, or VLDL (22).

In concert with our data obtained in intact plasma, Barter and Hopkins (4) also found earlier with a mass transfer assay that when VLDL, the entire HDL fraction, and CETP were isolated and then combined, the loss of CE and gain in TG by HDL was not equimolar. As in the present study, more recently Channon et al. (6) have reported that a greater molar loss of CE from HDL than gain in TG from VLDL + LDL occurred during CET in intact human serum.

Our experiments with VLDL-depleted plasma show that CE can be transferred without the reciprocal move-

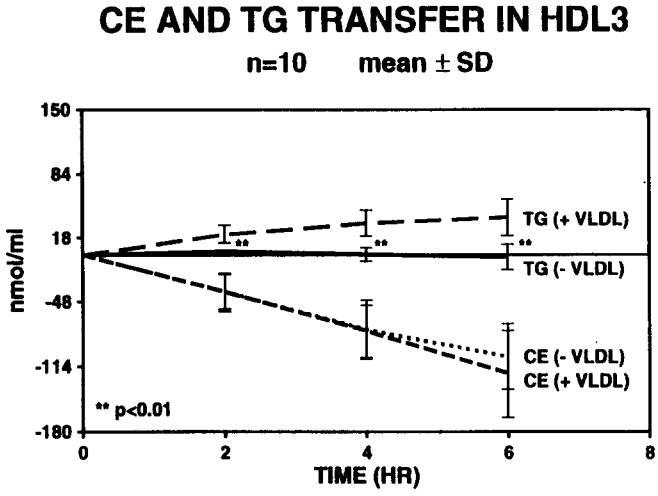

Fig. 1. Changes in the mass transfer of CE and TG in HDL_3 incubated in the presence and absence of VLDL.

ment of TG. This observation is at odds with a recent study that reported that TG and CE mass transfer in whole plasma was coupled based on evidence obtained with monoclonal antibodies that selectively inhibited the putative sites on CETP for TG and CE transfer (19). van Tol, Scheek, and Groener (5) however, in a different experimental system, found as we have in the present study that TG and CE can be transferred independently.

Eisenberg (23) pointed out several years ago that VLDL was a preferential TG donor and a CE acceptor during CET net mass transfer in whole plasma from normolipidemic subjects. It was not surprising, therefore, when Mann and coworkers (9) subsequently reported that the net mass transfer of CE was increased in hypertriglyceridemic patients in whom the number of VLDL particles was increased. Guerin, Dolphin, and Chapman (24) have shown that in hypercholesterolemic subjects the TG-rich lipoproteins continue to be the predominant CE acceptor even though their pool size relative to the cholesterol ester-rich lipoproteins is diminished. While Marzetta, Meyers, and Albers (25) have shown that CE transferred preferentially from HDL to lipoproteins in the buoyant LDL density range in the presence of VLDL, these results are not strictly comparable to those in the present study since the redistribution of radiolabeled CE and not CE net mass was measured. Our studies with VLDL-depleted plasma demonstrate that when VLDL is completely unavailable as a substrate for CETP, LDL becomes the principal CE acceptor and does so without exchanging TG from VLDL. Moreover, under these conditions HDL_3 transfers CE without acquiring TG. Our data, therefore, support the belief that in intact plasma, the transfer of CE and TG between VLDL and HDL_3 is primarily an equilibration process that reflects the marked differences in their core lipid composition. That this process is not equimolar indicates that it may not necessarily be a reciprocal exchange as has been suggested (2). Many questions remain regarding the mechanism of lipid transfer. On the one hand, the fact that each lipoprotein TG/CE molar ratio is selectively altered during CET suggests that each core lipid equilibrates among lipoproteins in plasma independently and our experiments showing that CE transfer taken place in the absence of VLDL support this possibility. In vivo, however, the likelihood that CET takes place in the absence of VLDL is small and for this reason it is still possible that the distribution that we measure includes synchronous heteroexchanges between the HDL subfractions and apoB-containing lipoproteins that affect these ratios.

This work was supported by grants from the National Institutes of Health (National Heart, Lung, and Blood Institute RO1 DK 43227). The authors are grateful to Dianne Noibi for expert manuscript preparation.

Manuscript received 31 May 1995 and in revised form 14 September 1995.

REFERENCES

1. Nichols, V., and L. Smith. 1965. Effect of very low density lipoprotein on lipid transfer in incubated serum. *J. Lipid Res.* **6:** 206–210.
2. Chajek, T., and C. J. Fielding. 1978. Isolation and characterization of a human serum cholesteryl ester transfer protein. *Proc. Natl. Acad. Sci. USA.* **75:** 3445–3449.
3. Tall, A. R. 1993. Plasma cholesteryl ester transfer protein. *J. Lipid Res.* **34:** 1255–1274.
4. Barter, P. J., and G. J. Hopkins. 1983. Relative rates of incorporation of esterified cholesterol into human very low density lipoproteins and low density lipoproteins. *Biochim. Biophys. Acta.* **751:** 33–40.
5. van Tol, A., L. M. Scheek, and J. E. M. Groener. 1991. Net mass transfer of cholesteryl ester from low density lipoproteins to high density lipoproteins in plasma from normolipidemic subjects. *Arterioscler. Thromb.* **11:** 51–63.
6. Channon, K. M., R. J. Clegg, D. Bhatnagar, M. Ishola, S. Aryol, and P. N. Durrington. 1990. Investigation of lipid transfer in human serum leading to the development of an isotopic method for the determination of endogenous cholesterol esterification and transfer. *Atherosclerosis.* **80:** 217–226.
7. Quig, D. W., and D. B. Zilversmit. 1990. Plasma lipid transfer activities. *Annu. Rev. Nutr.* **10:** 169–193.
8. Stokke, K. T., and K. R. Norum. 1971. Determination of lecithin:cholesterol acyltransfer in human blood plasma. *J. Clin. Lab. Invest.* **27:** 21–27.
9. Mann, C. J., F. T. Yen, A. M. Grant, and B. E. Bihain. 1991. Mechanism of plasma cholesteryl ester transfer in hypertriglyceridemia. *J. Clin. Invest.* **88:** 2059–2066.
10. Warnick, G. R., J. Benderson, and J. J. Albers. 1983. Dextran sulfate-Mg^{2+} precipitation procedure for quantitation of high-density lipoprotein cholesterol. *In* Selected Methods of Clinical Chemistry. Vol. 10. G. R. Cooper, editor. American Association for Clinical Chemistry, Washington DC. 91–99.
11. Bligh, E. C., and W. J. Dyer. 1959. A rapid method of total lipid extraction and purification. *J. Biochem. Physiol.* **37:** 911–917.
12. Hirano, K., S. Yamashita, T. Funahashi, N. Sakai, M. Menju, M. Ishigami, H. Hiraoka, K. Kameda-Takemura, K. Tokunaga, T. Hoshino, et al. 1993. Frequency of intron 14 splicing defect of cholesteryl ester transfer protein gene in the Japanese general population–relation between the mutation and hyperalphalipoproteinemia. *Atherosclerosis.* **100:** 85–90.
13. Hopkins, G. J., and P. J. Barter. 1980. Transfer of esterified cholesterol and triglyceride between high density and very low density lipoproteins. In vitro study of rabbits and humans. *Metabolism.* **29:** 546–550.
14. Quig, D. W., and D. B. Zilversmit. 1988. Plasma lipid transfer activity in rabbits: effects of dietary hyperlipidemias. *Atherosclerosis.* **70:** 263–271.
15. Marotti, K. R., C. K. Castle, T. H. Boyle, A. H. Lin, R. W. Murray, and G. W. Melchior. 1993. Severe atherosclerosis in transgenic mice expressing simian cholesteryl ester transfer protein. *Nature.* **364:** 73–75.
16. Quinet, E., A. Tall, R. Ramakrishnan, and L. Rudel. 1991. Plasma lipid transfer protein as a determinant of the atherogenicity of monkey plasma lipoproteins. *J. Clin. Invest.* **87:** 1559–1566.
17. Dullaart, R. P. F., J. E. M. Groener, and D. W. Erkelens. 1987. Effect of the composition of very low density lipoproteins on the rate of cholesteryl ester transfer from high density lipoproteins in man, studied in vitro. *Eur. J. Clin. Invest.* **17:** 241–248.
18. Fielding, C. J. 1993. Reverse cholesterol transport: lecithin:cholesterol acyltransferase and cholesteryl ester transfer

in insulin-dependent and non-insulin-dependent diabetes mellitus. *In* Diabetes and Atherosclerosis—Molecular Basis and Clinical Aspects. B. Draznin and R. H. Eckel, editors. Elsevier New York, Amsterdam, London, Tokyo. 103–117.

19. Ko, K. W. S., T. Ohnishi, and S. Yokoyama. 1994. Triglyceride transfer is required for net cholesteryl ester transfer between lipoproteins in plasma by lipid transfer protein. *J. Biol. Chem.* **269:** 28206–28213.
20. Marcel, Y. L., C. Vezina, B. Teng, and A. Sniderman. 1980. Transfer of cholesteryl ester between human high density lipoproteins and triglyceride-rich lipoproteins controlled by a plasma protein factor. *Atherosclerosis.* **35:** 127–133.
21. Weinberg, R. B., and A. M. Scanu. 1982. In vitro reciprocal exchange of apoproteins and nonpolar lipids between human high density lipoproteins and an artificial triglyceride-phospholipid emulsion (Intralipid). *Atherosclerosis.* **44:** 141–152.
22. Deckelbaum, R. J., S. Eisenberg, Y. Oschry, E. Butbul, Z. Sharon, and T. Olivecrona. 1982. Reversible modification of human plasma low density lipoproteins toward triglyceride-rich precursors. *J. Biol. Chem.* **257:** 6509–6517.
23. Eisenberg, S. 1985. Preferential enrichment of large-sized very low density lipoprotein populations with transferred cholesteryl esters. *J. Lipid Res.* **26:** 487–494.
24. Guerin, M., P. J. Dolphin, and M. J. Chapman. 1994. Identification of preferential cholesteryl ester (CE) acceptors among LDL subspecies in familial hypercholesterolemia (FH). *Arterioscler. Thromb.* **14:** 679–685.
25. Marzetta, C. A., T. J. Meyers, and J. J. Albers. 1993. Lipid transfer protein-mediated distribution of HDL-derived cholesteryl ester among plasma apoB-containing lipoprotein subpopulations. *Arterioscler. Thromb.* **13:** 834–841.