Cholesteryl ester transfer protein (CETP) plays a key role in the reverse cholesterol transport system by mediating the transfer of cholesteryl ester (CE) from high-density lipoprotein (HDL) to low-density lipoprotein (LDL). CETP may contribute to the atherogenicity of LDL in subjects with familial hypercholesterolemia (FH). To identify the major CE acceptors among LDL subspecies, we investigated the qualitative and quantitative features of CE transfer and exchange to LDL on incubation of plasma under physiological conditions. LDL subspecies were fractionated by density-gradient ultracentrifugation. Both mass transfer and exchange of HDL CE to and with very-low-density lipoprotein plus intermediate-density lipoprotein and LDL were linear for the first 6 hours of incubation. Thereafter mass transfer ceased, but exchange continued at a comparable rate. The rate of CE mass transfer to apolipoprotein B-containing lipoproteins was significantly enhanced in heterozygous FH subjects compared with normolipidemic individuals (91.6±28.2 versus 52.9±19.6 μg CE/h per milliliter plasma, FH versus normal subjects, P<.02). In FH subjects the predominant LDL subspecies (LDL 3 and 4, d=1.029 to 1.050 g/mL) accounted for 59.7±9.2% of the total CE transferred to LDL from HDL. By contrast, expression of CETP activity is correlated with increased plasma concentrations of CETP.

In plasma, LDL is distributed as a continuum of particles over the density range between d=1.019 and d=1.063 g/mL. In this density interval, multiple LDL subspecies possessing different physical, chemical, hydrodynamic, immunological, and structural properties have been described in the plasma of normolipidemic and hypercholesterolemic subjects. We determined both exchange and net mass transfer of CE from HDL to LDL partitions by a methodology involving the simultaneous determination of CE radioactivity and mass in both normolipidemic and hypercholesterolemic subjects. We investigated possible relations between CE transfer and the establishment of the LDL profile in human plasma. Moreover, we identified which LDL subspecies may represent the preferential CE acceptors in FH patients with familial hypercholesterolemia (FH) compared with those in normolipidemic subjects. Elevated CE transfer to preferred LDL subspecies may represent a determinant factor in promoting the atherogenic LDL profile generally observed in FH patients.

Methods

Subjects and Blood Samples

Approval by the Human Subjects Review Committee of the hospital and informed consent from all participants was obtained. Six heterozygous FH subjects (4 men and 2 women)
with a total plasma cholesterol of >300 mg/dL were selected and were taken off all lipid-modifying drugs for 6 weeks before blood sampling. Two of the male subjects were aged 19 and 24 years with a body mass index (BMI) of 21.6 and 21.4, respectively. The remaining 4 patients were between 53 and 65 years of age with BMIs between 21.4 and 26.2. The mean BMI for all heterozygous FH subjects was 23.0±2.2. Five normolipidemic subjects (4 men and 1 woman) displayed cholesterol levels of <250 mg/dL and ranged in age from 26 to 30 years old. Their mean BMI was 21.9±1.4. Blood samples (up to 40 mL) were obtained by venipuncture after an overnight fast and placed in EDTA-containing tubes (final concentration, 1 mg/mL). Plasma was separated by low-speed centrifugation at 4°C. EDTA (0.1 g/L), NaN₃ (0.01%), and gentamicin (0.05%) were then added to the plasma, which was maintained at 4°C. All subjects in this study had low levels of lipoprotein(a) (<12 mg/dL) and were nonsmokers.

### Measurement of Exchange and Net Mass Transfer of CE

CE exchange and net mass transfer were determined in whole plasma from each normolipidemic and hypercholesterolemic subject.²⁰ Briefly, radiolabeled HDL was obtained from the d>1.063 g/mL fraction of 1 mL plasma isolated by ultracentrifugation at 541 000g × min/min at 10°C by using a Beckman TL100 centrifuge as follows. The d>1.063 g/mL fraction was incubated for a total of 18 hours at 37°C in the presence of 4 μL [l,2,6,7-3H]cholesterol (specific activity, 71 Ci/mmol). This quantity corresponds to 20.8 ng of free cholesterol and represents less than 0.02% of total HDL-free cholesterol in the sample. HDL containing the esterified radiolabeled CE was then isolated from the d>1.063 g/mL fraction by adjusting the density to 1.21 g/mL by adding dry solid potassium bromide and centrifuging at 541 000g × min/min at 10°C. The radiolabeled HDL was diazylated against phosphate-buffered saline buffer. A typical radiolabeled HDL preparation had a specific radioactivity of approximately 5000 cpm/mmol CE and contained more than 95% total radioactive free cholesterol added as labeled CE. Moreover, the chemical composition of the radiolabeled HDL was not significantly different from the unlabeled HDL present in the individual patient’s plasma (data not shown). Several 1-mL aliquots of each subject’s plasma containing radiolabeled HDL (equivalent to 1% of the total HDL CE mass present in 1 mL of the subject’s plasma) were incubated at 37°C for up to 18 hours in the presence of 15 μmol/L iododeoxyuridine, which completely inhibits endogenous lecithin:cholesterol acyltransferase (LCAT) activity.

For each incubation time, lipoproteins present within the plasma aliquots were fractionated by density-gradient ultracentrifugation as described by Chapman et al.²⁵ To ensure complete removal of the VLDL fraction from the gradient, the first two gradient fractions were pooled and represent a density interval of d=1.006-1.019 g/mL. This fraction is referred to as VLDL+IDL. The radioactive content and lipid composition of each individual or pooled density fraction were determined. The recovery of total cholesterol from the gradient was 98% and 90% to 95% for the other lipids. Radioactivity was quantified by liquid scintillation spectrometry using a Pharmacia Rack Beta 309. Recovery of radioactivity within the gradient fractions exceeded 97% in all experiments. Exchange of CE between HDL and apoB-containing lipoproteins was calculated as the difference between the net mass transfer of CE determined by enzyme assay and the transfer of CE calculated from the specific radioactivity of the radiolabeled HDL after its addition to plasma.²⁰

### Lipid and Protein Analyses

Lipids in plasma or in isolated lipoprotein fractions were quantified enzymatically by using Bio-Merieux kits (model 69280) for total cholesterol, free cholesterol, triglyceride (TG), and phospholipid levels.²¹ CE mass was calculated as 1.67×(free cholesterol mass). Protein was measured by the method of Lowry et al.²² using bovine serum albumin as the standard. Lipoprotein mass corresponded to the sum of the mass of the individual components (free cholesterol, CE, TG, phospholipids, and protein) for each lipoprotein subfraction.

### Measurement of LCAT Activity

LCAT activity was measured by nonradioactive endogenous cholesterol esterification methods in which the decrease in plasma free cholesterol content with time upon incubation at 37°C was determined.

### Statistical Analysis

Nonparametric analysis was performed to evaluate the significance of differences between sample groups according to the method of Mann and Whitney by using the STATVIEW program for Apple Macintosh. Data in Table 4 and in Fig 1 were transformed into natural logarithms before nonparametric analysis.

### Results

#### Plasma Lipoprotein Profile and Chemical Composition

Plasma lipid and apolipoprotein levels in both normolipidemic and FH subjects are shown in Table 1. No significant difference was observed in plasma VLDL+IDL and LDL levels between each group of subjects. By contrast, the mean total LDL cholesterol concentration was twofold higher in FH patients compared with normolipidemic subjects (240.4±68.3 and 129.2±44.1 mg/dL, respectively; P<.0005). Moreover, despite the observation that plasma HDL concentrations were similar in each group, the relative proportion of HDL was significantly decreased in FH patients compared with normolipidemic subjects (28.5±5.2% and 42.8±7.8% respectively; P=.0006). Under these conditions, each group had distinct mass ratios of LDL/HDL; 1.2 in normolipidemic and 2.3 in FH subjects. The mass distribution profiles of LDL subfrac-

<table>
<thead>
<tr>
<th>TABLE 1. Plasma Lipid and Apolipoprotein Levels</th>
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<tbody>
<tr>
<td>NL, mg/dL</td>
</tr>
<tr>
<td>Total cholesterol</td>
</tr>
<tr>
<td>Free cholesterol</td>
</tr>
<tr>
<td>Cholesterol esters</td>
</tr>
<tr>
<td>Triglycerides</td>
</tr>
<tr>
<td>Phospholipids</td>
</tr>
<tr>
<td>VLDL+IDL cholesterol</td>
</tr>
<tr>
<td>LDL cholesterol</td>
</tr>
<tr>
<td>HDL cholesterol</td>
</tr>
<tr>
<td>ApoB</td>
</tr>
<tr>
<td>ApoA-I</td>
</tr>
</tbody>
</table>

NL indicates normolipidemic subjects (n=5); FH, heterozygous familial hypercholesterolemic patients (n=6); VLDL, very-low-density lipoprotein; IDL, intermediate-density lipoprotein; LDL, low-density lipoprotein; HDL, high-density lipoprotein; and Apo, apolipoprotein. Values are mean±SD. VLDL+IDL cholesterol, LDL cholesterol, and HDL cholesterol were determined by analysis of VLDL+IDL (d<1.019 g/mL), LDL (d=1.019-1.063 g/mL), and HDL (d=1.063-1.145 g/mL), respectively, following isolation by density-gradient ultracentrifugation (see "Methods"). *P<.005, tP<.05, vs normolipidemic subjects.
tions observed in both groups were quite distinct (Table 2). The most abundant LDL subfractions in normolipidemic subjects were LDL-2 and LDL-3 ($d=1.023$ to $1.039$ g/mL), which corresponded to $64\pm4\%$ of the total LDL mass. By contrast, the LDL profile in FH patients displayed significant increases in the masses of the LDL-3, LDL-4 ($d=1.039$ to $1.050$ g/mL), and LDL-5 ($d=1.050$ to $1.063$ g/mL) subfractions ($P<.005$).

Moreover, the LDL-3 and LDL-4 subfractions from FH patients contained a slightly elevated proportion of CE ($40.0\pm3.2\%$ and $39.2\pm2.8\%$, respectively) compared with their normolipidemic counterparts ($37.3\pm2.7\%$, $P<.05$ and $35.2\pm3.3\%$, $P<.005$, respectively; data not shown). These results were consistent with those of earlier studies.17,21,23

### Measurement of CE Exchange and Mass Transfer in Whole Plasma

CE exchange was evaluated in each subject by measuring the rate of radiolabeled CE transfer from HDL to apoB-containing lipoproteins during incubation of whole plasma at 37°C for up to 18 hours. The Figure shows a progressive increase of radiolabeled CE content in the apoB-containing lipoproteins (VLDL, IDL+LDL) as a function of the period of incubation in both normolipidemic and heterozygous FH subjects. CE radioactivity increased linearly during the first 4 through 6 hours of the incubation and in normal subjects paralleled the increase in CE mass. Thus, in these individuals, calculation of mass transfer based on the specific radioactivity of HDL CE reflects, with a fair degree of accuracy, the actual mass transfer for the first 6 hours of incubation. In the heterozygous FH subjects, in contrast, the mass transfer calculated from the HDL CE specific radioactivity was somewhat greater than the chemically determined mass transfer over the first 6 hours of incubation (Figure). This indicates the presence of a significant exchange component in addition to net mass transfer over this period.

After 6 hours of incubation, net mass transfer of CE to the apoB-containing lipoproteins in both subject groups ceased; however, radioactive CE continued to increase in the VLDL, IDL+LDL fraction, indicating a continuing exchange of lipid between the lipoprotein particles. For normolipidemic and mildly hypertriglyceridemic subjects, the latter phase of incubation (from 6 hours through 18 hours) reflected only CE exchange between the donor and acceptor particles. The observed linear increment in both net mass transfer and radioactivity over the first 6 hours of incubation permitted calculation of both the rate of CE mass transfer from HDL to the apoB-containing lipoproteins (VLDL, IDL+LDL) and the rate of CE exchange between these particles (Table 3). The increase in CE mass calculated from the specific radioactivity of the HDL CE reflects both mass transfer and exchange. The difference between these values and that determined by enzymatic analysis represents the

### Table 2. Concentrations of Plasma LDL Subfractions

<table>
<thead>
<tr>
<th>LDL Subfractions</th>
<th>Density, g/mL</th>
<th>NL, mg/dL</th>
<th>FH, mg/dL</th>
<th>NL, %</th>
<th>FH, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL-1</td>
<td>1.019-1.023</td>
<td>44±16</td>
<td>44±25</td>
<td>13±5</td>
<td>6±5</td>
</tr>
<tr>
<td>LDL-2</td>
<td>1.023-1.029</td>
<td>114±34</td>
<td>100±68</td>
<td>32±8</td>
<td>13±8</td>
</tr>
<tr>
<td>LDL-3</td>
<td>1.029-1.039</td>
<td>112±33</td>
<td>315±114*</td>
<td>32±8</td>
<td>41±6*</td>
</tr>
<tr>
<td>LDL-4</td>
<td>1.039-1.050</td>
<td>52±18</td>
<td>227±97†</td>
<td>15±5</td>
<td>30±10†</td>
</tr>
<tr>
<td>LDL-5</td>
<td>1.050-1.063</td>
<td>27±6</td>
<td>64±23*</td>
<td>8±1</td>
<td>9±3</td>
</tr>
</tbody>
</table>

NL indicates low-density lipoprotein; NL, normolipidemic subjects (n=5); and FH, heterozygous familial hypercholesterolemia (n=6). LDL subfractions were isolated by density-gradient ultracentrifugation. The mass of each chemical component in individual fractions was determined by chemical analysis as described in “Methods,” and the total mass of each fraction was then calculated as the sum of the mass of each component. Data are mean±SD. *P<.05, †P<.002 vs normolipidemic subjects.
Net Mass Transfer of CE From HDL to LDL Subfractions

The CE mass content of each LDL subfraction was determined as a function of the period of incubation after fractionation of the plasmas by density-gradient ultracentrifugation. The total increase in CE mass determined in each LDL subfraction in both normolipidemic and FH subjects is shown in Table 4. On a quantitative basis, no significant difference of CE mass increase in the light LDL subfractions, LDL-1 (d = 1.019 to 1.023 g/mL) and LDL-2 (d = 1.023 to 1.029 g/mL), was observed between normolipidemic and FH subjects. Net mass transfer of CE in the denser LDL subfractions, LDL-3 (d = 1.029 to 1.039 g/mL), LDL-4 (d = 1.039 to 1.050 g/mL), and LDL-5 (d = 1.050 to 1.063 g/mL), of FH patients was significantly greater than in their normolipidemic counterparts (P < .02). In both subject groups, the predominant LDL subfractions of intermediate density, LDL-2, LDL-3, and LDL-4, accounted for 75.1% to 78.4% of the total CE transferred from HDL to LDL. However, in FH patients 61.5% of the CE was transferred to the LDL-3 and LDL-4 subfractions. The quantitative features of CE transfer from HDL to LDL subspecies appear to be determined principally by the concentration of acceptor particles (r = .75, P < .0001).

Preferential CE Acceptors Among LDL Subspecies

Expression of CE mass transfer relative to the mass of each lipoprotein acceptor qualitatively evaluates the ability of each LDL subfraction to accept CE from HDL (Table 5). Under these conditions, in normolipidemic subjects LDL-1 represented the preferential CE acceptor compared with the other LDL subfractions (LDL-1, 99.4 ± 44.3 versus LDL fractions 2 through 5, 52.7 to 69.2

TABLE 3. Rates of CE Exchange and Transfer Between HDL and Apolipoprotein B-Containing Lipoproteins

<table>
<thead>
<tr>
<th>VLDL, IDL+LDL</th>
<th>LDL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mass transfer</td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>53±20</td>
</tr>
<tr>
<td>Heterozygous FH</td>
<td>92±26*</td>
</tr>
<tr>
<td>Transfer+exchange</td>
<td>65±25</td>
</tr>
<tr>
<td>Normal</td>
<td>64±39</td>
</tr>
<tr>
<td>Heterozygous FH</td>
<td></td>
</tr>
</tbody>
</table>

CE indicates cholesteryl ester; HDL, high-density lipoprotein; VLDL, very-low-density lipoprotein; IDL, intermediate-density lipoprotein; LDL, low-density lipoprotein; and FH, familial hypercholesterolemia. Rates of exchange and transfer were estimated over the first 6 hours of incubation using the gradients of the slopes of the trends obtained when data for each subject were plotted as shown in the Figure. Each value represents mean±SD for five subjects. The interassay coefficients of variation for the transfer assay were <5%. Values are micrograms CE per hour per milliliter plasma.

*P < .05, †P < .02 vs normal subjects after logarithmic transformation of data.
LDL indicates low-density lipoprotein; CE, cholesteryl ester; HDL, high-density lipoprotein; NL, normolipidemic subjects (n=5); and FH, heterozygous familial hypercholesterolemic patients (n=6). Transfer of CE from HDL to LDL subspecies was quantified during the first 6 hours of incubation of plasma at 37°C (see “Methods”). The activity of individual LDL subspecies as acceptors of CE is expressed as micrograms CE transferred relative to the mass in milligrams of each LDL subspecies.

*P<.05, tP<.005 vs LDL-2 through LDL-5 in NL subjects and vs LDL-3 through LDL-5 in FH patients.

μg CE/mg LDL mass, P<.05). In FH subjects, both the LDL-1 and LDL-2 fractions were active CE acceptors compared with the LDL subfractions of higher density (LDL fractions 3 through 5, 47.1±64.1 versus 136.5±40.8 μg CE/mg LDL mass, P<.0005, and LDL-2, 94.8±66.8 μg CE/mg LDL mass, P<.05). Comparison of each LDL subfraction in both groups for their ability to accept CE from HDL showed that the LDL-1 fraction in normolipidemic subjects and the LDL-2 in FH patients displayed a similar affinity for CE. The ability of LDL subspecies to accept CE from HDL was positively correlated with their relative TG content (r=.5, P<.0001, n=50).

**Discussion**

We determined the quantitative and qualitative features of CE exchange and transfer from HDL to the apoB-containing lipoproteins in both normolipidemic and heterozygous FH subjects by using a new methodology.20 We also identified and compared the major CE acceptors among the LDL subspecies in these individuals. Most significantly, LDL-1 in normolipidemic subjects and LDL-1 and LDL-2 in FH patients represented the preferential CE acceptors on a qualitative basis. In addition, a significant positive correlation was observed between net mass transfer of CE from HDL to LDL subspecies and the mass of each lipoprotein subfraction in both subject groups. Furthermore, the capacity of LDL subspecies to accept CE from HDL was correlated with the relative TG content of the lipoprotein acceptors. Finally, plasma CE mass transfer and exchange was significantly increased in FH patients compared with normolipidemic subjects.10,11,24

CE transfer was determined by measuring the increase of CE mass in each LDL subfraction isolated by density-gradient ultracentrifugation after plasma incubation at 37°C. Total net mass transfer of CE from HDL to LDL particles was twofold higher in FH patients than in normolipidemic subjects (453.5±119.5 versus 203.9±94.5 μg CE transferred, respectively). LDLS of intermediate density (LDL-2 through LDL-4) were quantitatively the major CE acceptors in both subject groups. LDL-3 and LDL-4 from FH patients accepted up to 59.7% of total CE transferred from HDL to LDL. The normolipidemic group exhibited an LDL/HDL ratio significantly lower than the FH group (1.4±0.4 versus 2.4±0.7, respectively, P<.0005). However, no differences were observed in the VLDL/HDL ratios in these two subject groups (0.15±0.07 versus 0.14±0.05 in normolipidemic subjects and FH patients, respectively). In mildly hypertriglyceridemic subjects with elevated VLDL/HDL ratios, the net mass transfer of CE from HDL to VLDL is twofold higher than normolipidemic subjects.20 In this case, the ability of VLDL to accept CE from HDL was the same in both groups of subjects when expressed on a per particle basis. These results suggested that the relative proportions of donor and acceptor particles present in plasma are significant determining factors of CE transfer activity.

Unesterified cholesterol has a potent role in regulating lipid transfer mediated by CETP.28 Dullaart et al25 studied the effect of the composition of different apoB-containing lipoproteins on their ability to accept CE from HDL and showed that the unesterified cholesterol/phospholipid molar ratio affects the CE transfer rate to VLDL. These studies indicate a role of the surface of VLDL particles in the CE transfer process. Our chemical compositional analyses of native LDL subfractions showed that LDL-3 and LDL-4 from heterozygous FH patients displayed a slight elevation of their CE content compared with LDL subfractions from normolipidemic subjects. However, no significant difference in the unesterified cholesterol/phospholipid ratio was noted between LDL fractions isolated from either group of individuals in this study. In contrast, a correlation did exist between the relative TG content of the LDL subfractions and their qualitative ability to accept HDL CE. Thus, we conclude that the quantitative difference in CE mass transferred to each LDL subfraction is most probably strongly related to its relative concentrations, whereas qualitative differences in the acceptor capacity between these particles is related to their relative TG contents.

McPherson et al11 show that CETP activity is positively correlated with plasma CETP mass, but there is no direct evidence indicating that plasma CETP concentration is the major determinant of CETP activity in vivo. Several other plasma factors could influence CE transfer activity. Among them, the structure and composition of both donor and acceptor lipoproteins appear to play an important role.25-27 LCAT and lipoprotein lipase increase CETP activity by increasing the binding of CETP to lipoprotein particles.28 Moreover, nonesterified fatty acids modulate the CE transfer activity of CETP.20 Recent studies have demonstrated the role of CETP activity on the size redistribution of LDL and HDL profiles in normolipidemic subjects.31 These data suggest that lipid exchange between HDL and the apoB-containing lipoproteins mediated by CETP could actively modulate the establishment of the LDL profile.

Marzetta et al22 examined the transfer of HDL-derived CE to apoB-containing lipoprotein subfractions in normolipidemic subjects. Our data for normolipidemic individuals are similar to theirs in that the lighter LDL subfractions appear to be the preferential acceptors of HDL CE. Marzetta et al, who used a similar approach, calculated CE mass transfer on the basis of radioactivity, and there appeared to be no direct chemical determination of mass transfer. Thus, net mass transfer and exchange were not simultaneously deter-
mined in their study. In addition, we reported data for five LDL subfractions in both normolipidemic and heterozygous FH subjects compared with Marzetta et al, who divided the LDL fraction from normolipidemic subjects into light (LDL-1, d = 1.026 to 1.039 g/mL) and heavy (LDL-2, d = 1.037 to 1.054 g/mL) subfractions. These fractions are equivalent to our LDL-2 and LDL-3 (d = 1.023 to 1.039 g/mL) and LDL-4 (d = 1.039 to 1.050 g/mL), respectively, and do not include the lightest (LDL-1, d = 1.019 to 1.023 g/mL) and heaviest (LDL-5, d = 1.050 to 1.063 g/mL) fractions. Furthermore, we also presented data indicating which lipoprotein subspecies are superior CE acceptors on a per unit mass basis. When expressed in this fashion, our LDL-1 in normolipidemic subjects and both our LDL-1 and LDL-2 in FH subjects are qualitatively the best acceptors of HDL CE. Our report confirms the findings of Marzetta et al.\textsuperscript{2} and extends their study to FH subjects for whom both net CE mass transfer and exchange were simultaneously measured in vitro over an extended time period.

In FH subjects the normal LDL profile was modified such that there was an increase in the concentrations and relative proportions of the denser LDL-3 through 5 subfractions. LDL-3 and LDL-4 contained elevated proportions of CE compared with normolipidemic subjects (data not shown). Furthermore, 73% of the total mass of CE from HDL was transferred to these dense LDL subfractions in FH subjects, as opposed to 54% in normal subjects. These results suggest that CETP, which is elevated in hypercholesterolemic subjects, plays an important role in the establishment of the LDL profile and may contribute to the formation of the denser LDL subfractions. Dense LDL subcategories display a low binding affinity for the LDL receptor in normolipidemic subjects,\textsuperscript{3,4} suggesting that their removal from the circulation may be delayed. Indeed, it is relevant that such subcategories are present at elevated concentrations in FH (Table 2). Furthermore, dense, small LDL subcategories are associated with elevated CETP activity by an antibody against human plasma lipid transfer protein-I.\textsuperscript{6}

\textbf{Acknowledgments}

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\textbf{References}


Preferential cholesteryl ester acceptors among the LDL subspecies of subjects with familial hypercholesterolemia.

M Guérin, P J Dolphin and M J Chapman