

Postprandial plasma lipoprotein changes in human subjects of different ages

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Abstract Plasma lipoprotein changes were monitored for 12 hr after a fat-rich meal (1 g of fat/kg body weight) in 22 subjects (9 males, 13 females, 22–79 yr old). Plasma triglyceride, measured hourly, peaked once in some subjects, but twice or three times in others. The magnitude of postprandial triglyceridemia varied considerably between subjects (range: 650–4082 mg · hr/dl). Males tended to have greater postprandial triglyceridemia than females, and elderly subjects had significantly ($P < 0.05$) greater postprandial triglyceridemia than younger subjects. Total plasma cholesterol, measured every three hr, increased significantly ($6.0 \pm 2.1\%$) in 7 subjects, decreased significantly ($7.1 \pm 1.2\%$) in 10 subjects, and remained unchanged in the remainder. Single spin ultracentrifugation and dextran sulfate precipitation procedures were used to quantitate triglyceride and cholesterol in triglyceride-rich lipoproteins (TRL, $d < 1.006$ g/ml), low density lipoproteins (LDL), and high density lipoproteins (HDL). Plasma TRL and HDL triglyceride increased after the fat meal, while LDL triglyceride decreased at 3 hr but increased at 9 and 12 hr. TRL cholesterol increased postprandially, while LDL and HDL cholesterol decreased. Phospholipid (PL), free (FC) and esterified (EC) cholesterol measurements were carried out on the plasma and lipoprotein fractions of 8 subjects. Plasma PL increased significantly at 3, 6, and 9 hr after the fat-rich meal, due to increases in TRL and HDL. PL. TRL CE increased postprandially, but a greater decrease in LDL and HDL CE caused plasma CE to be decreased. Plasma FC increased, predominantly due to an increase in TRL FC. Plasma concentrations of apolipoprotein A-I and apolipoprotein B both decreased after the fat-rich meal. The magnitude of postprandial triglyceridemia was inversely correlated with HDL cholesterol levels ($r = -0.502$, $P < 0.05$) and positively correlated with age ($r = -0.449$, $P < 0.05$), fasting levels of plasma triglyceride ($r = 0.636$, $P < 0.01$), plasma apoB ($r = 0.510$, $P < 0.05$), TRL triglyceride ($r = 0.564$, $P < 0.01$), TRL cholesterol ($r = 0.480$, $P < 0.05$) and LDL triglyceride ($r = 0.566$, $P < 0.01$). Change in postprandial cholesterolemia was inversely correlated with fasting levels of HDL cholesterol ($r = -0.451$, $P < 0.05$) and plasma apoA-I ($r = -0.436$, $P < 0.05$). Our data are consistent with the following concepts: a) the magnitude of postprandial triglyceridemia is dependent on age and gender; b) many subjects have more than one postprandial triglyceride peak; and c) increases in TRL triglyceride are associated with decreases in LDL and HDL cholesterol, as well as alterations in LDL and HDL triglyceride.—Cohn, J. S., J. R. McNamara, S. D. Cohn, J. M. Ordovas, and E. J. Schaefer. Postprandial plasma lipoprotein changes in human subjects of different ages. *J. Lipid Res.* 1988. 29: 469–479.

Supplementary key words postprandial triglyceridemia • triglyceride-rich lipoproteins • VLDL • LDL • HDL • apoA-I • apoB

Human individuals, by eating regular meals, are predominantly in a postprandial state throughout the day. Most studies of lipoprotein metabolism, however, have been carried out in the fasting state, because this is thought to be a more reproducible and better defined baseline for metabolic studies. Since the absorption and transport of dietary fat is mediated by plasma lipoproteins (1, 2) and since intestinally derived lipoproteins have been implicated in the development of atherogenesis (3), investigations into lipoprotein metabolism and kinetics need to be conducted in the fed state. Such experiments depend upon a thorough understanding of the lipoprotein changes that occur following a fat-rich meal.

Postprandial lipoprotein changes have been characterized by several investigators. Initial characterization studies were carried out by Havel (4) and Havel, Kane, and Kashyap (5) using the sequential ultracentrifugation to measure changes in three lipoprotein fractions. Subsequently, Redgrave and Carlson (6) reported the chemical composition of very low density lipoprotein (VLDL) subfractions and low density lipoproteins (LDL) after a fatty meal. More recently, Patsch et al. (7) have reported that levels of high density lipoprotein subfraction 2 (HDL₂) and magnitude of postprandial lipemia are inversely related. Other reports have documented the postprandial changes of HDL itself (8, 9) and changes in particular plasma apolipoproteins (10–12).

The aim of the present study was to further characterize the postprandial lipid and apolipoprotein changes in

Abbreviations: VLDL, very low density lipoprotein; LDL, low density lipoprotein; HDL, high density lipoprotein; IDL, intermediate density lipoprotein; CETP, cholesteryl ester transfer protein; TRL, triglyceride-rich lipoprotein; PL, phospholipid; EC, esterified cholesterol.

total plasma and lipoprotein fractions in a group of subjects of varying age and gender. In order to obtain reliable quantitative data, single spin ultracentrifugation and dextran sulfate precipitation methods were used to separate lipoprotein fractions, a procedure based on Lipid Research Clinic methodology (13). This procedure minimizes the loss of lipoprotein constituents, which occurs when lipoproteins are separated by extensive ultracentrifugation, and allows the plasma concentration of lipoprotein components from total plasma to be measured.

METHODS

Human subjects

Twenty two healthy subjects (9 males, 13 females) ranging in age from 22 to 79 years were studied. Mean ages and body mass indexes are shown in **Table 1**. Subjects were selected from volunteers recruited in the Boston area. Fasting plasma triglyceride and cholesterol concentrations were below the 95th percentile. Subjects had no history of ulcer disease, bleeding tendency, or of medications known to affect plasma lipids. The experimental protocol was approved by the Human Investigation Review Committee of the New England Medical Center and Tufts University.

Fat feeding protocol

After a 14-hr overnight fast, subjects were given a fat meal, containing 1.0 g of fat/kg body weight and 7.0 mg/kg of cholesterol (given as egg yolk powder). The fat was given as soybean oil in 12 subjects and as soybean oil plus cream (1:1, w/w) in the remaining 10 subjects. Since no difference was observed between subjects fed the two fat mixtures, data were analyzed together for all 22 subjects. The amount of fat given was designed to be $\frac{1}{2}$ – $\frac{2}{3}$ of that which an aver-

age American ingests per day. The meal was prepared as a formula milkshake with added flavoring. Polycose and egg white protein were added to the formula so that the meal contained 33.3% fat, 33.3% protein, and 33.3% carbohydrate (by weight) or 53% fat, 23.5% protein, 23.5% carbohydrate (by energy). Blood samples (20 ml) were obtained via a small forearm indwelling catheter prior to the test meal and at 3, 6, 9, and 12 hr after the meal. Two-ml blood samples were collected at 1, 2, 4, 5, 7, 8, 10, and 11 hr. Water, but no food, was allowed during the study period.

Lipid analysis

Blood was collected in tubes containing EDTA to give a final concentration of 0.1% EDTA. Plasma was separated by centrifugation (2,500 rpm) for 20 min at 4°C. Triglyceride, total cholesterol, free cholesterol, and phospholipid measurements were obtained with an Abbott Diagnostics ABA-200 bichromatic analyzer using enzymatic reagents and adapted Lipid Research Clinics methodology (13), as previously described (14). Our total cholesterol, triglyceride, and HDL cholesterol assays have been standardized by participation in the Centers for Disease Control–National Heart, Lung and Blood Institute Standardization program. Cholesteryl ester concentrations were calculated as the difference between total cholesterol and free cholesterol concentrations. HDL lipids were quantitated by analyzing the supernate obtained following precipitation of a plasma aliquot with dextran sulfate-Mg²⁺ as described by Warnick, Benderson, and Albers (15). Chylomicrons and VLDL (triglyceride-rich lipoproteins (TRL)), were separated from 5 ml of plasma by a single ultracentrifugal spin (39,000 rpm, 18 hr, 4°C) at density 1.006 g/ml in a Beckman 50.3 Ti rotor. The infranate fraction was analyzed for lipids, and the TRL (d < 1.006 g/ml) fraction was measured by sub-

TABLE 1. Postprandial triglyceridemia in subjects grouped according to age and gender^a

Group	Age	Body Mass Index	Fasting Plasma Cholesterol	Fasting Plasma Triglyceride	Peak Plasma Triglyceride Concentration	Twelve Hour Plasma TG Concentration	Maximum Rise in Plasma Triglyceride	Change in Postprandial Triglyceridemia
	<i>yr</i>	<i>kg/m²</i>			<i>mg/dl</i>			<i>mg · hr/dl</i>
Younger females (5) ^b	32 ± 3	21.8 ± 2.1	161 ± 9	66 ± 11	163 ± 29	55 ± 11	98 ± 18	499 ± 129
Younger males (4)	26 ± 1	25.1 ± 2.9	166 ± 16	103 ± 35	274 ± 74	94 ± 33	171 ± 46	789 ± 199
Older females (8)	64 ± 3	23.7 ± 0.6	211 ± 13	104 ± 10	288 ± 35	88 ± 16	184 ± 27	893 ± 157
Older males (5)	67 ± 2	24.8 ± 2.1	190 ± 11	135 ± 26	357 ± 50	153 ± 50	221 ± 38	1264 ± 228
Female subjects ^c	52 ± 5	23.0 ± 0.9	192 ± 11	89 ± 9	240 ± 30	75 ± 12	151 ± 22	742 ± 124
Male subjects	49 ± 7	24.9 ± 1.6	179 ± 10	121 ± 21 (<i>P</i> = 0.098)	320 ± 36 (<i>P</i> = 0.076)	127 ± 31 (<i>P</i> = 0.095)	199 ± 29	1053 ± 167 (<i>P</i> = 0.096)
Younger subjects ^c	29 ± 2	23.3 ± 1.7	163 ± 8	82 ± 17	212 ± 39	72 ± 16	130 ± 25	628 ± 118
Older subjects	66 ± 2 (<i>P</i> = 0.001)	24.1 ± 0.9	203 ± 9 (<i>P</i> = 0.015)	116 ± 12 (<i>P</i> = 0.090)	314 ± 30 (<i>P</i> = 0.043)	113 ± 22	199 ± 27 (<i>P</i> = 0.060)	1036 ± 140 (<i>P</i> = 0.036)

Values are means ± SEM.

^aSubjects were divided into four groups as shown in the left-hand column.

^bNumbers in parentheses represent the number of subjects in each group.

^cThe data were analyzed statistically by analysis of variance. Statistical differences between female and male subjects and between younger and older subjects are shown by *P* values in parentheses, where *P* < 0.1.

tracting infranate values from plasma values. LDL was quantitated by subtracting HDL values from infranate values. This single spin ultracentrifugation and dextran sulfate precipitation method for separating lipoproteins minimizes the loss of lipoprotein constituents, which commonly occurs when lipoproteins are separated by extensive ultracentrifugation. The procedure is therefore advantageous for the quantitative recovery and determination of lipoprotein components of total plasma, but has the disadvantage of allowing only three lipoprotein fractions to be separated. The so-called "LDL fraction" isolated by this method is actually composed of IDL plus LDL density fractions ($1.006 < d < 1.063$ g/ml) as defined by ultracentrifugation.

Apolipoprotein quantitation

Plasma apolipoprotein A-I (apoA-I) and apolipoprotein B (apoB) were measured by a noncompetitive enzyme-linked immunosorbent assay (ELISA) (16). Polystyrene microtiter plates (Nunc Immunoplate 1, Nunc, Denmark) were coated with affinity-purified polyclonal antibodies to human apoA-I or apoB. Duplicate plasma samples were diluted 1:3,000 for the apoB assay or 1:60,000 for the apoA-I assay with phosphate-buffered saline and were then added to designated wells in the microtiter plates, along with standards and controls. After overnight incubation, immunopurified apoB or apoA-I antibody conjugated to alkaline phosphatase was added. Color development was achieved with the addition of a substrate (0.1% *p*-nitrophenyl phosphate in 0.1 M glycine buffer). After 20 min, the plates were read at 410 nm on a microtiter plate reader (Dynatech MR600, Dynatech Inc., Vienna, VA), interfaced with an IBM XT microcomputer, programmed with Immunosoft (Dynatech).

Quantitation of postprandial changes in plasma lipids, lipoproteins, and apolipoproteins

Postprandial lipidemia, lipoproteinemia, or apolipoproteinemia was quantitated from plasma response curves measured hourly (in the case of plasma triglyceride) or tri-hourly (in the case of plasma cholesterol, plasma apolipoproteins, and lipoprotein lipids). Two area measurements (with units in mg · hr/dl) were made for each curve: 1) the area between the curve and baseline (zero concentration), called total postprandial lipidemia, lipoproteinemia, or apolipoproteinemia; and 2) the area between the curve and a line drawn through the fasting plasma concentration (zero hour concentration), called change in lipidemia, lipoproteinemia, or apolipoproteinemia. The first measurement was always positive, and represented the total amount of that component in the plasma for the total 12-hr postprandial period. The second measurement was either positive or negative, depending on whether the concentration of the particular plasma component increased or decreased after fat feeding. In some circumstances, the plasma response was biphasic resulting in the plasma concentration being

greater than the fasting concentration for a certain period of time and less than the fasting concentration during a different period of time. In these cases, total postprandial change was calculated as the sum of the positive and negative areas. For some analyses, postprandial change was not summed, and positive and negative components were analyzed independently.

Statistics

Data were tabulated and stored in a VAX-11/780 computer (Digital Equipment Co., Maynard, MA), using the scientific software package RS/1 (BBN Research Systems, Cambridge, MA). Statistical analysis was carried out with Statistical Analysis System software (SAS Institute Inc., Cary, NC). Paired and unpaired *t*-tests were used to compare the significance of mean differences. Pearson correlation coefficients (*r*) were computed to identify significant correlations between lipid parameters. Two-way analysis of variance was used to determine the relative effects of age and gender on postprandial lipemia. Stepwise multiple linear regression analysis was also carried out, utilizing forward selection, backward elimination, and maximum R-square improvement procedures.

RESULTS

Plasma triglyceride concentrations were measured at hourly intervals for 12 hr after the fat meal. Mean data for the 22 subjects are shown in **Fig. 1**. Within 1 hr, the mean plasma triglyceride concentration had risen significantly. It peaked at 4 hr and remained significantly elevated for 9 hr after the fat meal. The magnitude of postprandial triglyceridemia was quantitated in two ways (see Methods). Total postprandial triglyceridemia indicated the total mass of triglyceride in the plasma for the 12 hr following the fat meal. The change in postprandial triglyceridemia indicated the extent of plasma triglyceride increase after the fat meal. Total postprandial triglyceridemia and change in postprandial triglyceridemia both varied considerably among subjects (total: 2071 ± 210 (mean \pm SEM), range: 650–4082 mg · hr/dl; change: 868 ± 103 (mean \pm SEM), range: 239–2006 mg · hr/dl). The mean data (**Fig. 1**) do not reflect the quantitative or qualitative differences observed between individual subjects. This heterogeneity in plasma triglyceride response to the fat meal is exemplified in **Fig. 2**, in which results are presented individually for 12 arbitrarily selected subjects. Panels A, C, and E depict the plasma triglyceride response of 6 females and panels B, D, and F depict the response of 6 males. The top panels show examples of subjects with a single plasma triglyceride peak; the middle panels show subjects with two triglyceride peaks; the bottom panels show subjects with three triglyceride peaks. Of the total 22 subjects studied, 5 had one triglyceride peak (3 females, 2 males, mean age = 50 ± 11 yr); 11

had two triglyceride peaks (7 females, 4 males, mean age = 54 ± 6 yr); 6 had three peaks (3 females, 3 males, mean age = 46 ± 9 yr). Thus, in this group of subjects, a biphasic plasma triglyceride response was more common than a monophasic or triphasic response. Furthermore, the type of plasma triglyceride response (i.e., number of peaks) was not associated with age or gender. No correlation was found between fasting plasma lipid or lipoprotein levels and the number of peaks. The number of postprandial peaks was not related to the magnitude of change in postprandial triglyceridemia (one peak: 794 ± 152 ; two peaks: 905 ± 161 ; three peaks: 866 ± 230 mg · hr/dl) nor to total triglyceridemia.

In order to determine whether subjects had a characteristic, and hence reproducible, pattern of postprandial triglyceridemia, arbitrarily selected subjects ($n = 5$) were fed the same fatty meal on a second occasion. Subjects with one postprandial triglyceride peak tended to respond with one peak, and subjects with two triglyceride peaks almost always responded with two. Some exceptions were observed however, suggesting that an individual's response to the fat-rich meal was sometimes, but not always, reproducible. Similar results have been observed by Kashyap et al. (11).

In order to assess the effect of age and sex on postprandial lipoprotein changes, the 22 subjects were divided into four groups: young females, old females, young males, and old males. The mean age and mean body mass index of the four groups are shown in Table 1. Four measures of postprandial triglyceridemia are also shown: 1) peak plasma

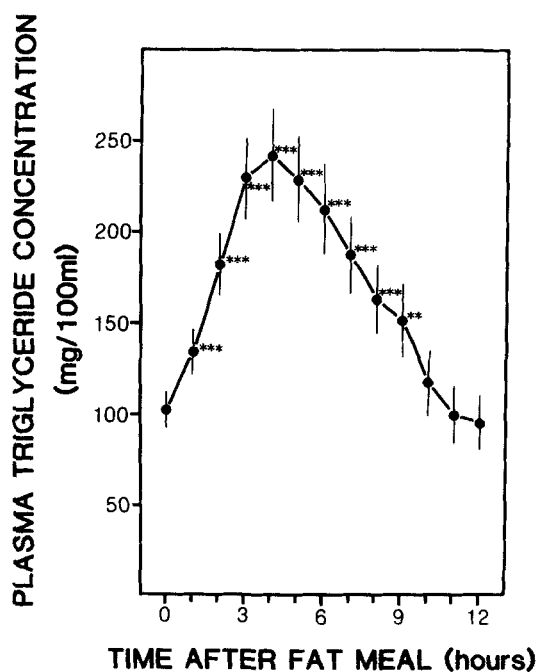


Fig. 1. Change in plasma triglyceride concentration after the fat-rich meal. Results are expressed as mean \pm SEM for 22 subjects. Significantly different from zero time by paired *t*-test: ** $P < 0.01$; *** $P < 0.001$.

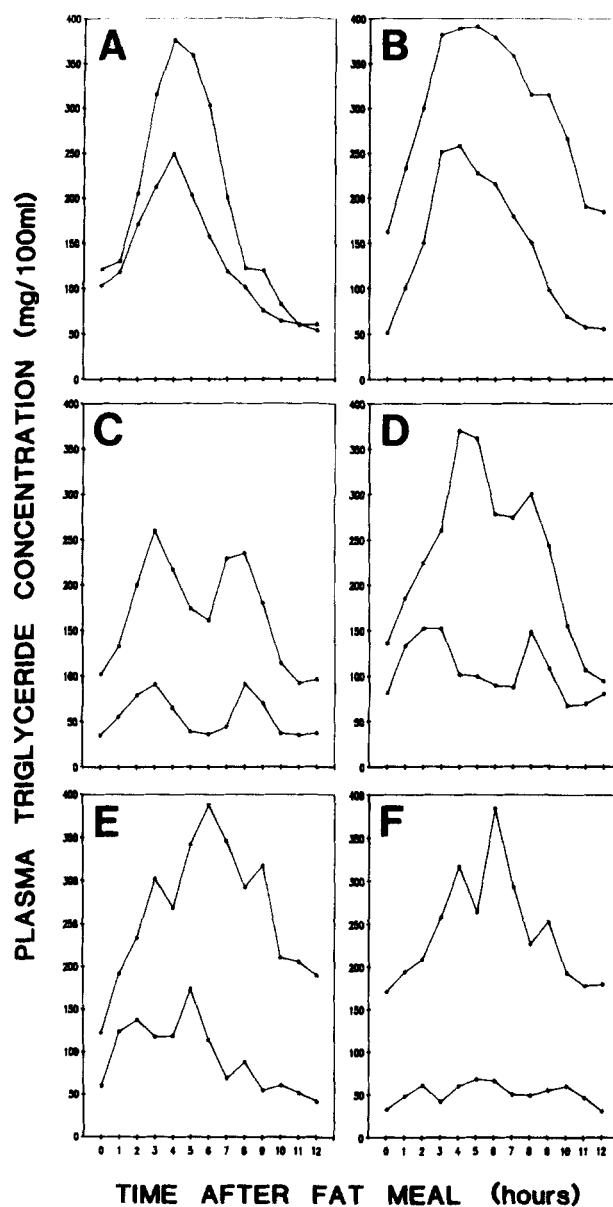


Fig. 2. Individual differences in plasma triglyceride response to the fat-rich meal. The left-hand panels (A, C, and E) show the plasma triglyceride response of six females; the right-hand panels (B, D, and F) show the response of six males. Subjects with one postprandial plasma triglyceride peak are shown in panels A and B; subjects with two triglyceride peaks are shown in panels C and D; subjects with three triglyceride peaks are shown in panels E and F.

triglyceride concentration; 2) 12-hr plasma triglyceride concentration; 3) maximum rise in plasma triglyceride concentration (difference between the zero hour triglyceride concentration and the maximum postprandial plasma triglyceride concentration); and 4) change in plasma triglyceridemia (as measured by area). Statistical analysis was carried out by comparing the mean data for males versus females, and the mean data for young versus elderly subjects (Table 1). Significance of differences are shown by

P values where *P* < 0.1. Although not all parameters were statistically different at the *P* < 0.05 level, males tended to have greater postprandial triglyceridemia than females, and older subjects had greater postprandial triglyceridemia than younger subjects.

The mean plasma cholesterol concentration for the group as a whole did not change significantly after the fat meal, as shown in Table 2. The mean data disguise the fact, however, that some subjects had a significant increase in plasma cholesterol, while a similar number had a consistent decrease. Subjects were selectively divided into three groups according to their cholesterolemic response (Table 2). Seven subjects (including both males and females) had a significant rise in plasma cholesterol concentration ($6.0 \pm 2.1\%$ increase), while 10 subjects (also both males and females) had a significant fall ($7.1 \pm 1.2\%$ decrease). Five subjects had no significant change.

The time course of changes in lipoprotein triglyceride and cholesterol following the fat meal is shown in Fig. 3. TRL triglyceride concentrations were significantly elevated at 3 and 6 hr (*P* < 0.001) and 9 hr (*P* < 0.05) after the meal. HDL triglyceride increased significantly at 3 and 6 hr and then decreased. In contrast, LDL triglyceride decreased significantly (*P* < 0.01) at 3 hr and then increased at 9 and 12 hr. The increase in TRL triglyceride was associated with an increase in TRL cholesterol and a reciprocal decrease in LDL cholesterol. The HDL cholesterol concentration was significantly (*P* < 0.01) decreased at 3, 6, and 9 hr after the fat meal.

Complete lipoprotein lipid analysis was carried out on trihourly postprandial plasma samples from 8 arbitrarily selected subjects. Total plasma lipids, apoA-I, and apoB concentrations together with lipoprotein lipid concentrations are shown in Table 3. The postprandial increase in plasma triglyceride was associated with an increase in total plasma phospholipid and free cholesterol. In contrast, the mean concentration of plasma cholesteryl ester, apoB, and apoA-I decreased. A similar mean decrease in plasma apoB and apoA-I concentration was observed in the total group of 22

subjects (of the 22 subjects, 15 had a lower plasma apoB concentration 6 hr after the fat-rich meal and 17 subjects had a lower plasma apoA-I concentration). TRL triglyceride, cholesteryl ester, free cholesterol, and phospholipid all increased and at 6 hr after the fat meal were significantly higher than at zero time. The increase in TRL free cholesterol and cholesteryl ester was associated with a significant decrease in both LDL and HDL free cholesterol and cholesteryl ester. The mean LDL phospholipid concentration did not change significantly and LDL triglyceride was significantly higher at 9 hr (*P* < 0.05). HDL triglyceride was increased at 3 and 6 hr and HDL phospholipid was significantly higher (*P* < 0.01) at 6 and 9 hr postprandially.

Changes in plasma cholesterol concentration after the fat meal were quantitated by area as described for changes in plasma triglyceride concentration. Whereas total cholesterolemia was positive for all subjects, change in cholesterolemia was either positive or negative depending on whether the postprandial cholesterol concentration rose or fell. Change in postprandial cholesterolemia was not correlated with total cholesterolemia (*r* = 0.027). In contrast, plasma triglyceride concentration increased significantly in all subjects after fat feeding and change in postprandial triglyceridemia was therefore proportional to total triglyceridemia (*r* = 0.896, *P* < 0.001). Measurements of triglyceridemia and cholesterolemia are correlated with various parameters in Table 4. Total and change in triglyceridemia were significantly correlated with age and fasting triglyceride levels. Both indices of postprandial triglyceridemia were also significantly correlated with TRL and LDL triglyceride, TRL cholesterol, and plasma apoB levels, and inversely correlated with fasting HDL cholesterol concentrations. Total cholesterolemia (but not change in cholesterolemia) was correlated with age. Fasting LDL cholesterol and plasma apoB levels correlated better than TRL cholesterol levels with total cholesterolemia. There was no significant correlation with fasting HDL cholesterol or plasma apoA-I levels. In contrast, change in cholesterolemia correlated inversely with fasting HDL cholesterol and plasma apoA-I levels, but

TABLE 2. Mean plasma cholesterol concentrations at 3-hr intervals after the fat meal in the group of subjects as a whole, and as groups divided according to their cholesterolemic response^a

Group	0 Hour	3 Hour	6 Hour	9 Hour	12 Hour
All subjects (9 males, 13 females)	187 ± 8	184 ± 8	185 ± 8	185 ± 7	183 ± 7
Group One (3 males, 4 females)	188 ± 14 (100%) ^b	194 ± 14 (103.6 ± 2.0%)	196 ± 14** (104.9 ± 1.3%)	197 ± 13*** (105.8 ± 1.4%)	198 ± 13* (106.0 ± 2.1%)
Group Two (3 males, 2 females)	164 ± 17 (100%)	164 ± 17 (100.1 ± 1.1%)	163 ± 17 (99.6 ± 1.7%)	163 ± 17 (99.5 ± 0.7%)	160 ± 17 (98.0 ± 1.0%)
Group Three (3 males, 7 females)	197 ± 10 (100%)	188 ± 11*** (95.0 ± 0.8%)	189 ± 11*** (95.2 ± 1.1%)	187 ± 10*** (95.0 ± 0.8%)	183 ± 10*** (92.9 ± 1.2%)

^aSubjects were selectively divided into three groups: group one, subjects with a postprandial increase in plasma cholesterol; group two, subjects with relatively little plasma cholesterol change; group three, subjects with a postprandial decrease in plasma cholesterol.

^bPercentages (mean ± SEM) in parentheses represent the plasma cholesterol concentration expressed as a percentage of zero time concentration. Significantly different from zero time concentration by paired *t*-test: *, *P* < 0.05; **, *P* < 0.01; ***, *P* < 0.001.

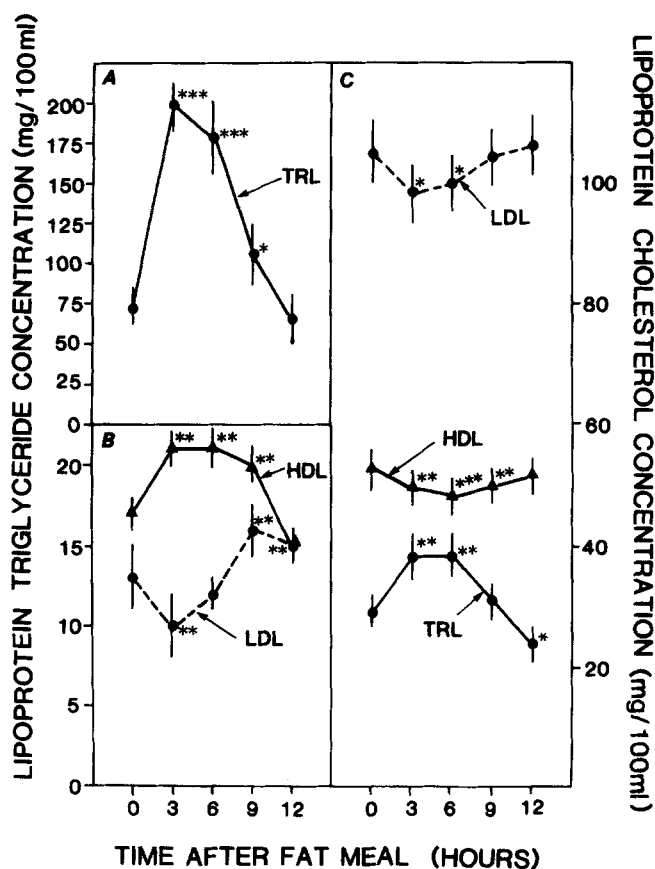


Fig. 3. Timecourse of changes in lipoprotein cholesterol and triglyceride concentrations following the fat-rich meal. Panel A shows changes in TRL triglyceride; panel B shows changes in LDL and HDL triglyceride; panel C shows changes in TRL, LDL, and HDL cholesterol. Results are expressed as means \pm SEM. Significantly different from zero time by paired *t*-test: * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$.

not significantly with any other parameter. Body mass index was not significantly correlated with postprandial cholesterolemia or triglyceridemia, though it was correlated with fasting plasma triglyceride and TRL triglyceride levels ($r = 0.463$, $P < 0.05$ and $r = 0.477$, $P < 0.05$, respectively). Stepwise multilinear regression analysis was undertaken to establish which fasting lipid parameters could best predict the postprandial triglyceride and cholesterol responses. Significant predictors of change in triglyceridemia were firstly, plasma triglyceride concentration ($r = 0.64$, $P < 0.001$) and then LDL triglyceride ($r = 0.41$, $P < 0.05$). The only significant predictor of change in cholesterolemia was HDL cholesterol ($r = 0.45$, $P < 0.05$).

In order to understand the relationship between changes in lipoprotein cholesterol and triglyceride concentrations, lipoprotein concentration changes were quantitated by planimetry from plasma response curves. Simple correlations were then sought between these measurements. Significant correlations are shown diagrammatically in Fig. 4. This analysis showed that subjects with a greater postpran-

dial increase in TRL triglyceride tended to have a greater increase in HDL triglyceride and a greater initial decrease in LDL triglyceride. Those subjects with a greater postprandial increase in TRL triglyceride also tended to have a greater increase in TRL cholesterol, which was significantly correlated with a decrease in LDL cholesterol but not HDL cholesterol. The magnitude of postprandial decrease in HDL cholesterol was positively correlated with the magnitude of postprandial increase in HDL triglyceride. Finally, subjects with a small initial decrease in LDL triglyceride tended to have a greater secondary increase in LDL triglyceride and, conversely, subjects with a greater initial decrease in LDL triglyceride had a less pronounced increase in LDL triglyceride at later time points.

DISCUSSION

In the present study, considerable heterogeneity was observed in the plasma triglyceride response of subjects fed a fat-rich meal. Variability between individuals was observed in both the magnitude and in the pattern of postprandial triglyceridemia. The extent of postprandial triglyceridemia was significantly greater in older compared to younger subjects, and tended to be greater in male compared to female subjects (Table 1). The pattern of postprandial triglyceridemia also varied considerably between subjects, such that plasma triglyceride was found to peak either once, twice, or three times during the 12-hr period following the fat-rich meal.

Most previous studies have suggested that the change in plasma triglyceride concentration after a fatty meal is monophasic—an initial rise followed by a fall (4, 6–10, 17). Multiple peaks in postprandial triglyceride concentration have not been documented for several reasons. Either an insufficient number of subjects have been investigated, plasma has been sampled at too few timepoints to clearly define plasma triglyceride changes, or mean data for a group of subjects have been presented, which has disguised individual differences. Mean data for the present study shown in Fig. 1 clearly demonstrate how individual differences (Fig. 2) can be disguised. Some studies, however, have shown that postprandial plasma triglyceride change can be biphasic. Olefsky, Crapo, and Reaven (18) showed an initial postprandial peak occurring 1 to 3 hr and a secondary peak 4 to 7 hr after feeding a liquid formula meal. Kashyap et al. (11) have also reported a biphasic plasma triglyceride response in three female subjects, but not in three male subjects, fed a fat meal. Furthermore Barr, Kottke, and Mao (12) showed that in five male subjects there was a biphasic response in plasma triglyceride after intraduodenal infusion of medium chain triglyceride oil, but not after infusion of long-chain triglyceride oil. These results together clearly show that the plasma triglyceride concentration after

TABLE 3. Plasma and lipoprotein lipid, plasma apoB and apoA-I concentrations at 3-hr intervals after the fat-rich meal in eight subjects

Fraction	0 Hour	3 Hour	6 Hour	9 Hour	12 Hour
Plasma					
Triglyceride	114 ± 11	252 ± 34***	220 ± 42*	129 ± 33	83 ± 17*
Cholesteryl ester	145 ± 9	137 ± 9**	140 ± 9	140 ± 9	138 ± 9*
Free cholesterol	55 ± 3	59 ± 3*	59 ± 4	56 ± 4	54 ± 4
Phospholipid	219 ± 10	231 ± 11**	241 ± 12***	237 ± 12*	222 ± 12
ApoB	85 ± 4	81 ± 5	80 ± 5	77 ± 5**	73 ± 6*
ApoA-I	172 ± 13	162 ± 13**	161 ± 13**	166 ± 10	164 ± 11
TRL					
Triglyceride	68 ± 12	216 ± 33**	182 ± 39*	89 ± 31	51 ± 16
Cholesteryl ester	16 ± 2	18 ± 2	24 ± 3*	17 ± 2	14 ± 2
Free cholesterol	11 ± 1	17 ± 2**	17 ± 3*	10 ± 3	8 ± 1
Phospholipid	36 ± 2	52 ± 4**	53 ± 7*	36 ± 7	30 ± 3
LDL					
Triglyceride	13 ± 3	12 ± 3	14 ± 2	19 ± 3*	16 ± 3
Cholesteryl ester	87 ± 6	80 ± 5**	79 ± 5**	83 ± 6	82 ± 7
Free cholesterol	31 ± 3	29 ± 2*	29 ± 2	32 ± 2	32 ± 3
Phospholipid	70 ± 5	71 ± 4	68 ± 4	75 ± 6	69 ± 6
HDL					
Triglyceride	20 ± 2	23 ± 2**	24 ± 2*	22 ± 2	16 ± 2*
Cholesteryl ester	42 ± 4	39 ± 4***	38 ± 4***	40 ± 4	42 ± 4
Free cholesterol	13 ± 2	12 ± 2**	12 ± 2**	14 ± 2	14 ± 2
Phospholipid	113 ± 10	108 ± 11	120 ± 11**	126 ± 11**	122 ± 10

Values are means ± SEM (mg/dl).

Significantly different from zero time concentration by paired *t*-test: *, *P* < 0.05; **, *P* < 0.01; ***, *P* < 0.001.

a fat-rich meal can often have more than one postprandial peak.

In discussing the etiology of the multiple postprandial plasma triglyceride peaks, one must consider the various factors that control the plasma triglyceride concentration. These include the rate of output of triglyceride from the intestine, the rate of secretion of triglyceride from the liver, the activity of lipoprotein lipase (the enzyme which catalyzes the hydrolysis of triglyceride in the circulation), and

the rate of uptake of triglyceride-containing lipoproteins by receptor and non-receptor-mediated processes. The effect of meal feeding on these processes in humans has not been well defined. Further studies need to be carried out to determine which of the above-mentioned factors are responsible for the postprandial peaks in plasma triglyceride. Analyses are being carried out in our laboratory to define whether the triglyceride within different peaks is of intestinal origin or of hepatic origin. Ongoing experiments (data

TABLE 4. Correlation between postprandial lipemia and age, body mass index, fasting lipid,^a and apolipoprotein concentrations

	Total Triglyceridemia ^b	Change in Triglyceridemia ^b	Total Cholesterolemia ^b	Change in Cholesterolemia ^b
Age	0.463*	0.449*	0.667***	0.285
Body mass index	0.368	0.224	0.244	0.018
Plasma triglyceride	0.894***	0.636**	0.360	0.289
TRL triglyceride	0.844***	0.564**	0.267	0.352
LDL triglyceride	0.448*	0.566**	0.372	-0.134
HDL triglyceride	0.224	0.115	0.432*	0.207
Plasma cholesterol	0.289	0.290	0.977***	-0.186
TRL cholesterol	0.559**	0.480*	0.439*	0.168
LDL cholesterol	0.340	0.343	0.890***	-0.123
HDL cholesterol	-0.593**	-0.502*	0.280	-0.451*
Plasma apoB	0.550**	0.510*	0.805***	0.119
Plasma apoA-I	-0.323	-0.300	0.321	-0.436*

Values represent Pearson correlation coefficients.

^aFasting samples were taken at zero time after a 14-hr overnight fast.

^bIndices of postprandial lipemia were measured as areas from time-response curves (see Methods). Total triglyceridemia and cholesterolemia measure the total triglyceride or cholesterol in plasma for the 12-hr postprandial period. Change in triglyceridemia and cholesterolemia measure the extent to which triglyceride or cholesterol increased or decreased during the 12-hr postprandial period.

Significantly correlated: *, *P* < 0.05; **, *P* < 0.01; ***, *P* < 0.001.

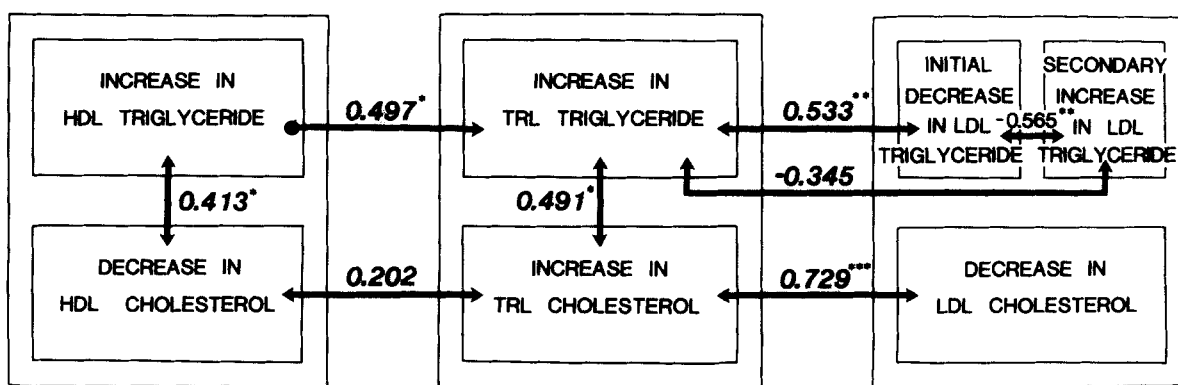


Fig. 4. Relationship between postprandial changes in lipoprotein triglyceride and cholesterol concentrations, as measured by Pearson correlation coefficients. Postprandial lipoprotein changes were quantitated by measuring the area above or below plasma response-time curves (see Methods). Significant correlations are designated by asterisks: * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$.

not shown) suggest that subjects with two postprandial triglyceride peaks have increased concentrations of retinyl ester and apoB-48 in both peaks of plasma triglyceride. Since these components represent the presence of intestinally derived lipoproteins, it appears that peaks of plasma triglyceride at later time-points are not solely due to the output of triglyceride-rich lipoproteins from the liver.

In agreement with published data (7, 11, 17), we have found that postprandial triglyceridemia was positively correlated with fasting levels of plasma triglyceride and plasma apoB, and was inversely correlated with fasting levels of HDL cholesterol (Table 4). We have extended these observations by showing that postprandial triglyceridemia was also significantly correlated with age, TRL triglyceride, TRL cholesterol, and LDL triglyceride. No significant correlation was found between change in triglyceridemia and body mass index (Table 4). Recently completed studies in our laboratory have shown that, in both males and females, LDL size, as measured on nondenaturing polyacrylamide gradient gels, is very strongly and inversely correlated with fasting plasma triglyceride levels and positively correlated with fasting HDL cholesterol levels (19). Therefore, both postprandial triglyceridemia and LDL size are strongly correlated with fasting plasma triglyceride levels. This implies that LDL size and the magnitude of postprandial triglyceridemia are also strongly related. It can thus be inferred that individuals with pronounced postprandial triglyceridemia must have small-sized LDL particles and individuals with less pronounced postprandial triglyceridemia have larger sized LDL. This concept is consistent with the data of Genest et al. (20) who showed that hyperapobetalipoproteinemic subjects (individuals with decreased LDL particle size) had more pronounced postprandial triglyceridemia than normal subjects.

As reported by others (4, 6, 9), fat feeding was associated with an increase in both TRL triglyceride and HDL tri-

glyceride. The increase in TRL triglyceride was positively correlated with the increase in HDL triglyceride concentration (Fig. 4). Presumably, the rise in HDL triglyceride was mediated by the cholesteryl ester transfer protein (CETP) (21), which caused the net transfer of cholesteryl esters from HDL to triglyceride-containing lipoproteins and the reverse transfer of triglyceride from TRL to HDL (22). The rise in TRL triglyceride was presumably due to the secretion of triglyceride-rich chylomicrons from the intestine. A small proportion of postprandial triglyceridemia might also have been due to hepatic secretion of triglyceride in VLDL, but it is not known whether hepatic secretion of VLDL is increased, unchanged, or decreased after fat feeding in humans. Studies, in which carbohydrate alone has been fed to human subjects, have shown that plasma triglyceride falls postprandially (23, 24), due in part to a reduced secretion of hepatic VLDL. When a mixed meal is fed, however, a considerable flux of dietary lipid reaches the liver and is probably resecreted in VLDL, thus contributing to postprandial lipemia. Increased output of triglyceride by the liver in the fed state is supported by studies with perfused rat livers, which have shown that livers isolated from fed rats secrete more triglyceride (25) and apoB (26) than livers from fasted rats.

The changes observed in LDL triglyceride in the present study have not been previously documented. Two studies have measured LDL concentration after fat feeding but little change was observed in this lipoprotein fraction (4, 6). We have found that LDL triglyceride was decreased significantly 3 hr after the fat meal, but rose at later time points, such that it was significantly increased 9 and 12 hr after the meal (Fig. 3). It is possible to hypothesize that the initial decrease in plasma LDL triglyceride concentration was predominantly due to CETP-mediated transfer of triglyceride to other lipoproteins. One would predict transfer of triglyceride to have mainly occurred from LDL to HDL,

however HDL triglyceride increase and initial LDL triglyceride decrease were not found to be significantly correlated ($r = 0.354$, $P = 0.11$). In contrast, there was a significant correlation between the decrease in LDL triglyceride and the increase in TRL triglyceride ($r = 0.533$, $P < 0.01$, Fig. 4), suggesting that a closer relationship exists between TRL and LDL triglyceride changes than between LDL and HDL triglyceride changes. One possible explanation is that the postprandial influx and subsequent catabolism of chylomicrons in the circulation inhibits the formation of LDL from hepatic VLDL. This is feasible considering that lipoprotein lipase and apoC-II, which are required for VLDL triglyceride hydrolysis, are also required for chylomicron triglyceride hydrolysis. Thus, the greater the accumulation of chylomicrons in the plasma of individuals, the greater the inhibition of LDL formation and the greater the decrease in LDL triglyceride concentration. The rise in LDL triglyceride concentration at later time points (9 and 12 hr) could reflect a reversal of this process, such that a decreased presence of chylomicrons in the circulation would allow for increased hydrolysis of VLDL triglyceride and increased formation of LDL. Alternatively, the later rise in LDL triglyceride could reflect a postprandial increase in the secretion of triglyceride-rich VLDL from the liver, as discussed before, leading to an increased formation of LDL.

Individual variability in postprandial plasma triglyceridemia was associated with variable changes in plasma cholesterolemia. Plasma cholesterol increased significantly in some subjects, decreased significantly in others, and was relatively constant in the remainder (Table 2). The concentration of plasma cholesterol after fat feeding has been measured in numerous other studies (4, 6, 8-12); however, changes have either been negligible in magnitude or mean data have disguised the variable changes of individual subjects. We have found that fasting lipid parameters that correlated with change in triglyceridemia did not correlate with change in cholesterolemia. Change in cholesterolemia was, however, inversely correlated with fasting HDL cholesterol and plasma apoA-I concentrations (Table 4). Thus, subjects with a higher fasting HDL level tended to have a postprandial decrease in total plasma cholesterol and, conversely, subjects with a lower fasting HDL level tended to have an increase in plasma cholesterol. As shown in Fig. 3, postprandial change in total plasma cholesterol was due to a significant rise and then fall in TRL cholesterol, and to reciprocal changes in LDL and HDL cholesterol concentrations.

Postprandial changes in lipoprotein cholesterol need to be discussed in relation to the current concepts of cholesterol metabolism following a fat meal (27, 28). During alimentary lipemia, dietary cholesterol after esterification in the intestine is transported to the liver in chylomicrons. At the same time, the net transport of free cholesterol from cell membranes to plasma is increased. This is associated with an increase in the formation of cholesteryl esters in HDL, due to an increase in lecithin:cholesterol acyltrans-

ferase (LCAT) activity (29). CETP is in turn stimulated and a greater mass of cholesteryl ester is transferred from HDL to VLDL and LDL. It is this movement of cholesteryl ester from HDL to less dense lipoproteins which probably accounts, in part, for the decrease in HDL cholesterol observed in the present study. As shown in Table 3, the decrease in HDL cholesterol was predominantly due to a decrease in cholesteryl ester. Furthermore, the extent of cholesterol decrease in LDL (though not HDL) was significantly correlated with cholesterol increase in the TRL fraction (Fig. 4).

In a recent review of postprandial lipoprotein metabolism (30), it was pointed out that different studies have reported different results for postprandial changes in total HDL cholesteryl ester. HDL cholesteryl ester has been shown to increase (8), decrease (31), or remain unchanged (5) after fat feeding. In the present study, HDL cholesteryl ester decreased postprandially (Fig. 3 and Table 3). Tall has suggested (30) that net change is probably determined by the magnitude of rise in plasma triglycerides. The present study provides evidence that this is indeed true, since change in HDL cholesterolemia was inversely correlated with change in triglyceridemia ($r = -0.143$, $P < 0.05$).

Changes in cholesterol concentration in the LDL and HDL fractions should not be assessed only in the light of cholesterol esterification and cholesterol exchange mechanisms. Changes in the rate of tissue uptake of LDL and/or HDL also probably affect the postprandial concentration of these lipoproteins. This possibility is supported by the finding that the plasma concentration of both apoB and apoA-I decreased significantly (Table 3), suggesting that the postprandial rate of catabolism of these apolipoproteins exceeded their rate of synthesis. A possible change in the rate of catabolism of apoA-I after fat feeding is supported by the finding that apoA-I fractional catabolic rate is inversely correlated with plasma triglyceride concentration in normal volunteers (32). No significant correlation, however, was observed between triglyceridemia and postprandial change in plasma apoA-I concentration in the present study ($r = -0.161$, $P = 0.47$).

It is generally believed that the majority of plasma LDL catabolism occurs by LDL receptor-mediated uptake in the liver (33). One might speculate, therefore, that a postprandial decrease in apoB concentration due to an increase in apoB catabolism is due to increased hepatic LDL receptor activity. However, studies in the dog by Angelin et al. (34) have shown that hepatic LDL (apoB, E) receptor activity (but not apoE receptor activity) is reduced after 6-8 hr of intravenous infusion of lymph lipoproteins. In contrast, studies in the rat by Quarfordt et al. (35) have shown that in vitro binding of apoE-supplemented triglyceride emulsion to hepatic plasma membranes from fed rats was greater than binding to membranes from fasted rats. Despite this difference, the uptake of triglyceride emulsion by livers of fed and fasted rats was similar when evaluated in nonrecy-

clinging single-pass liver perfusion experiments. It is thus unclear from animal studies whether LDL uptake by the liver in vivo is regulated in the short term. Further studies, using recent techniques to quantitate LDL receptors (36, 37), are required to define the effects of fat feeding on hepatic receptor activity.

The fall in plasma apoA-I concentration in the present study needs to be discussed in relation to the results of previous experiments, which have given rise to the concept that HDL apoA-I increases after fat feeding due to the transfer of apoA-I from chylomicrons. In original studies by Havel (4), HDL₁ (1.063 < d < 1.21 g/ml) protein was measured in 5 subjects fed a fat meal and was found to increase in 3 subjects, but remain constant in 2 others. In a second study (5), HDL₂ (1.063 < d < 1.12 g/ml) protein was shown to increase postprandially, but the protein content of HDL₃ could not be measured due to contamination with albumin and other serum proteins. More recent studies have measured postprandial change in apoA-I using specific immunoassays. Tall et al. (8), using a radioimmunoassay technique, and Groot and Scheek (9), using radial immunodiffusion, have both shown that plasma apoA-I increases after fat feeding. In contrast, Castro and Fielding (27) have shown that in 10 subjects, 5 hr after fat feeding, there was no mean change in plasma apoA-I concentration. Essentially no change in total HDL apoA-I has also been observed by Taskinen and Kuusi (38). These results can be contrasted to the data from the present study in which plasma apoA-I was measured by ELISA assay and was found to decrease in 17 of the 22 subjects after the fat meal. As mentioned before, no significant correlation was observed between magnitude of triglyceridemia and postprandial change in plasma apoA-I concentration. Clearly, the concentration of plasma apoA-I is therefore not entirely dependent on the extent of intestinal apoA-I synthesis during absorption, nor is the concentration of apoA-I in HDL entirely dependent on transfer of apoA-I from chylomicrons during lipolysis (39, 40). The present data suggest that, in certain situations, postprandial clearance of apoA-I can exceed apoA-I synthesis.

In summary, the present study has shown: 1) one, two, or three peaks in postprandial triglyceride concentration are observed in subjects fed a fat-rich meal; 2) the magnitude of postprandial triglyceridemia is affected by age and gender; 3) the postprandial plasma concentration of cholesterol can increase, decrease, or remain essentially unchanged; 4) the magnitude of postprandial triglyceridemia is significantly correlated with age, fasting levels of plasma triglyceride and apoB, TRL triglyceride and cholesterol, and LDL triglyceride; 5) change in postprandial cholesterolemia is inversely correlated with fasting levels of HDL cholesterol and apoA-I; and 6) as intestinal triglyceride-rich lipoproteins enter the circulation and are catabolized, complex changes occur in other lipoproteins. The cholesteryl ester concentration of LDL and HDL decreases, presumably

due to CETP-mediated transfer of cholesteryl ester to the TRL fraction. The phospholipid concentration of HDL increases following an earlier increase in TRL phospholipid concentration, suggesting transfer of phospholipid from TRL to HDL. The triglyceride concentration of LDL decreases initially but increases at later time points (concomitant with an initial decrease in LDL cholesteryl ester and a later decrease in plasma apoB). The triglyceride concentration of HDL increases in parallel with an increase in TRL triglyceride, suggesting a transfer of triglyceride from TRL to HDL; and finally, there can be a small but significant decrease in plasma apoA-I concentration. ■

Supported by the United States Department of Agriculture Research Service contract 53-3K06-5-10. Dr. Cohn received support from the Charles A. Dana Foundation, New York, and the National Heart Foundation of Australia.

Manuscript received 13 April 1987, in revised form 3 August 1987, and in re-revised form 28 September 1987.

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