Cholesterol absorption and turnover in rhesus monkeys as measured by two methods

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Abstract We compared the absorption of cholesterol in seven rhesus monkeys (four high-responders and three low-responders) as measured by two methods: 1) the dual isotope plasma ratio method of Zilversmit (1972. Proc. Soc. Exp. Biol. Med. 140: 862) and 2) the single isotopic meal feeding technique of Borgström (1969. J. Lipid Res. 10: 331). We also compared the cholesterol pool sizes calculated by kinetic analysis of the plasma cholesterol specific activity decay curves obtained after simultaneous administration of [^{3}H]- and [^{14}C]cholesterol, one given intravenously and the other orally. The ratio of orally to intravenously administered cholesterol radioactivity in plasma did not attain constancy until 6 weeks after isotope administration. Therefore, the percent absorption of cholesterol was calculated by the Zilversmit method 8 weeks after the administration of isotopes. The mean percent absorption of cholesterol by the Borgström method was 66.3 ± 5.1 (S.E.) and by the Zilversmit method was 70.3 ± 7.4. The differences were not statistically significant. However, in two of seven monkeys the percent absorption of cholesterol calculated by the Zilversmit method was higher by 10.4 and 22.6 percentage points than the values obtained by the Borgström method. Cholesterol absorption by either method was higher in the high-responding monkeys than in the low-responding group. The sizes of the rapidly exchangeable pool or the minimum estimate of the total body pool of cholesterol were similar for all monkeys or for either the low-responding or the high-responding animals and were also similar when calculated using the data from either the orally or the intravenously administered radioactive cholesterol. Cholesterol synthesis was significantly higher in the low-responding monkeys (115 mg/day) than in the high-responding (64 mg/day). The present study and our previous studies support the hypothesis that a major factor causing the difference in response of plasma cholesterol to dietary cholesterol between the high- and low-responding rhesus monkeys is a difference in the intestinal absorption of cholesterol.—**Bhattacharyya, A. K., and D. A. Eggen.** Cholesterol absorption and turnover in rhesus monkeys as measured by two methods. *J. Lipid Res.* 1980. **21:** 518–524.

Supplementary key words plasma isotope ratio method · single isotopic meal feeding method · cholesterol synthesis · high- and low-responding rhesus monkeys

In 1972, Zilversmit described the dual isotope plasma ratio method for the measurement of cholesterol absorption in rats (1). Basically, this simple method consists of measuring the ratio of plasma cholesterol radioactivities after it has attained constancy following simultaneous administration of single doses of [^{3}H]- and [^{14}C]cholesterol, one isotope given intravenously and the other orally. The method has been validated in nonhuman primates (2–4) and in man (5). In the present study we compared, in rhesus monkeys, the absorption of cholesterol measured by the dual isotope plasma ratio method of Zilversmit (1, 6) (henceforth called the Zilversmit method) with that measured by the single isotopic meal feeding technique of Borgström (7) (henceforth called the Borgström method).

Bhattacharyya, Connor, and Spector (8) reported that in normal and Type II hypercholesterolemic patients, the size of the rapidly exchangeable pool of cholesterol (M_A) was significantly larger when calculated using the data from the orally administered isotope as compared with the data from the intravenously administered isotope. In the present study, therefore, we also compared the cholesterol pool sizes as determined by kinetic analysis of the plasma cholesterol specific activity decay curves obtained after simultaneous administration of [^{3}H]- and [^{14}C]-cholesterol, one given intravenously and the other intragastrically.

MATERIAL AND METHODS

Selection of animals

Eleven adult, male rhesus monkeys, weighing between 8 and 14 kg, were used in the study. The monkeys were selected previously as high- or low-responders from a group of 36 young adult male monkeys on the basis of the response of plasma cholesterol to an atherogenic diet fed for 12 weeks (9). Of the eleven, six were high-responding and five were low-responding animals. The data from two high- and low-responding monkeys had to be dis-

carded because of problems with radiopurity of [^{3}H]cholesterol. Thus, data presented here are based on studies completed in four high- and three low-responding rhesus monkeys.

Diet

The monkeys were fed a semisynthetic diet designed to be similar in major nutrient classes to that consumed by 20 to 60 year old men (10). This diet provided fat at 38% of calories, proteins at 15% of calories, and cholesterol at 0.15 mg/Kcal (**Table 1**). The animals were fed once daily an amount sufficient to maintain body weight (**Table 2**). On the average, the monkeys consumed about 600 calories a day; thus, the daily cholesterol intake was about 90 mg.

Isotopes

[1,2-^{3}H]Cholesterol (Amersham/Searle, Arlington Heights, IL) and [4-^{14}C]cholesterol (New England Nuclear, Boston, MA) were purified by thin-layer chromatography on silica gel G plates (Applied Science Lab., State College, PA) developed in heptane–ethyl ether 55:45 (v/v). The material that moved with the same R_f as that of pure cholesterol (National Bureau of Standards, Washington, D.C.) was used in the study.

Preparation and administration of cholesterol isotopes

After an overnight fast, each monkey was given single simultaneous doses of [1,2-^{3}H]cholesterol (intravenously) and [4-^{14}C]cholesterol (by gavage). About 45 μCi of [1,2-^{3}H]cholesterol was dissolved in 2 ml of absolute ethanol. The solution was suspended in about 30 ml of 0.9% sodium chloride solution immediately before use. The final solution was injected into the antecubital vein over a 15-sec period. The amount of radioactive cholesterol injected was measured precisely for each animal by analyzing the residual radioactivity in the vials, syringes, and tubing used in the procedure.

Immediately after the infusion, each animal was fed, by gavage, a meal containing about 40 μCi of [4-^{14}C]cholesterol. The isotopic meal was prepared by homogenizing about 20 g of the diet with water to a semi-liquid consistency. The radioactive cholesterol dissolved in a small volume of ethanol was added and mixed thoroughly. An aliquot of the meal was analyzed by liquid scintillation to determine radioactivity in each meal prepared. After the labeled meal was fed, the residual radioactivity in the containers and equipment used in the procedure was determined. That amount was subtracted from the amount of radioactivity in the meal to determine the dose of radioactive cholesterol fed.

TABLE 1. The composition of the diet

Ingredients	g/100 g
Flour	31.8
Sugar	14.7
Egg yolk	1.7
Soy protein	3.8
Casein[a]	6.2
Dry skim milk	7.5
Hegsted salts[a]	3.8
Alphacel	2.8
Vitamin mix[b]	1.0
Applesauce	7.8
Beef tallow	11.0
Soy oil	2.7
Butter (unsalted)	1.3
Cholesterol, crystalline[a]	0.025
Water	3.8
Total fat—38% of calories	
Total cholesterol—0.15 mg/Kcal	

[a] Nutritional Biochemical Corp., Cleveland, OH.
[b] Teklad, Chagrin Falls, OH.

TABLE 2. The body weight and plasma cholesterol during the study period

Group and Animal No.	Body Weight	Plasma Cholesterol
	(kg)	*(mg/dl)*
High-responding		
72	11.3 ± 0.50[a]	166 ± 35[a]
78	10.5 ± 0.20	169 ± 26
79	13.5 ± 0.16	190 ± 25
88	12.0 ± 0.14	395 ± 60
Low-responding		
52	12.0 ± 0.32	183 ± 22
64	8.2 ± 0.23	132 ± 20
74	12.2 ± 0.13	136 ± 21

[a] Values are mean ± S.D. of 15 to 20 determinations during the period of study.

Analytical methods

Fasting venous blood samples were obtained daily for the first 4 days and then at suitable intervals for the next 19 weeks. Plasma was separated by centrifugation at 4°C and stored frozen at −20°C for later determination of plasma total cholesterol concentration and radioactivity. Plasma total cholesterol concentration was measured by the method of Abell et al. (11). The plasma total radioactivity was measured on aliquots of the extracts used for cholesterol determinations. After evaporation of the solvent, the residue was dissolved in 10 ml of scintillation solution (4 g of 2,5,5-diphenyloxazole and 0.1 g of 1,4, bis (2,5-(5-phenyloxazolyl)-benzene per liter of toluene) and the ^{3}H and ^{14}C activities were determined by liquid scintillation spectrometry with external standardization for quench correction. Specific activity of

TABLE 3. The comparison of percent absorption of cholesterol as measured by the Borgström method and the Zilversmit method

Group and Animal No.	Percent Absorption of Cholesterol: Borgström method	Percent Absorption of Cholesterol: Zilversmit method	Difference
High-responding			
72	69.7	92.3 ± 1.8[a]	+22.6
78	82.3	79.2 ± 0.5	−3.1
79	76.3	80.9 ± 0.8	+4.6
88	75.9	86.3 ± 1.0	+10.4
Mean ± S.E.	76.1 ± 2.6[b,d]	84.7 ± 3.0[c,d]	+8.6
Low-responding			
52	48.9	40.9 ± 0.3	−8.0
64	48.4	49.6 ± 0.9	+1.2
74	62.5	63.0 ± 0.5	+0.5
Mean ± S.E.	53.4 ± 4.6[b,e]	51.2 ± 6.4[c,e]	−2.1
All monkeys	66.3 ± 5.1[f]	70.3 ± 7.4[f]	+4.0

[a] Values are mean ± S.D. of six values obtained between weeks 8 through 19 after administration of isotopes.
[b] By Student's t test, the means are significantly different, $P < 0.01$.
[c] By Student's t test, the means are significantly different, $P < 0.005$.
[d,e,f] By paired t test, the means are *not* significantly different.

plasma cholesterol was calculated as the ratio of radioactivity in dpm/ml to mass of cholesterol in mg/ml.

For 7 consecutive days after administration of the isotopes, feces were collected, pooled, and homogenized with water. An aliquot of the homogenized feces was extracted for neutral sterols by the procedure of Miettinen, Ahrens, and Grundy (12). Total ^{14}C-radioactivity in the fecal neutral sterols was determined by liquid scintillation in an aliquot of the extract.

Calculations and analysis of data

The cholesterol absorption (Borgström method) (7) was calculated as the difference between the amount of [^{14}C]cholesterol fed and the amount excreted in the feces during 7 days after the feeding of the isotope.

The percent cholesterol absorption by the Zilversmit method (1, 6) was calculated as follows:

$$\text{Percent Absorption} = \frac{\text{Percentage of the oral dose in an aliquot of plasma}}{\text{Percentage of I.V. dose in the same aliquot of plasma}} \times 100$$

Serum cholesterol specific activity following administration of radiocholesterol was analyzed using the generalized nonlinear least squares technique of Snedecor and Cochran (13) to fit the logarithm of specific activity to the logarithm of the sum of two or three exponentials. Inclusion of the third exponential produced a significant improvement in fit to the data for the intravenously administered tracer in five animals and for the orally administered tracer in one animal. Parameters of the two- or three-pool models of Goodman and Noble (14) and Goodman, Noble, and Dell (15) were then calculated. These include the production rate in the rapidly exchangeable pool, the size of the rapidly exchangeable pool, and the minimum estimate of the size of the total body pool of cholesterol. The parameters of the fitted curve were also used to calculate the mean transit time for cholesterol in the system as described by Perl and Samuel (16). For these calculations, the dose of radioactive cholesterol injected was determined precisely for each animal as described above. When the isotope was given intragastrically, the dose entering the circulation was taken to be the amount of radioactivity absorbed, determined by the Borgström method as described above.

Data were analyzed for statistical significance by the t test of difference between means and by the t test of paired observations (13).

RESULTS

Plasma cholesterol

Among animals the mean plasma cholesterol varied between 132 ± 20 (S.D.) and 395 ± 60 mg/dl (Table 2). Two low-responding monkeys had lower plasma cholesterol than the high-responding monkeys fed the same cholesterol-containing diet (Table 1). One low-responding animal (no. 52) had higher (but not significantly) mean plasma cholesterol than two of the high-responding animals. At the time of selection this animal was considered to be hyperthyroid as judged by behavior, food consumption, and T_4 concentration (four standard deviations above mean of the other eleven animals). At the time of the present study about 7 years later, his T_4 concentration was within the range of the others, but he still appeared to be somewhat hyperactive and thus may still have been relatively hyperthyroid. However, the data from this animal have been included because his plasma cholesterol response to dietary cholesterol, cholesterol turnover, and cholesterol absorption are similar to those of all other low-responding rhesus monkeys. It should also be noted that the diet used in the present study (Table 1) was semisynthetic rather than based on a commercial chow and the cholesterol content was only 15% of that used during the selection of these groups (9).

Cholesterol absorption by the Borgström method compared with that by the Zilversmit method

The mean of six values of percent cholesterol absorption for each animal calculated by the Zilversmit

method (1, 6) (from the ratios of plasma cholesterol radioactivities between weeks 8 and 19 after the administration of the isotopes) is presented in **Table 3,** along with results from the Borgström method. The percent absorption of cholesterol by the Zilversmit method was calculated only during the last 12 weeks of the study because the ratio of plasma cholesterol radioactivities did not become constant until about 5 weeks after administration of the isotopes. This finding is evident from **Fig. 1,** in which the ratio of cholesterol radioactivities in the plasma is shown for the entire period of study. For both high- and low-responding groups, the ratio declined for the first 5 to 6 weeks after administration of the isotopes.

In two of four high-responding monkeys, the percent absorption of cholesterol determined by the Zilversmit method was higher by 22.6 and 10.4 percentage points, respectively, than those obtained by the Borgström method. In the rest of the animals, the difference between the two methods varied from +4.6 to −8.0 percentage points (Table 3).

The mean differences between the Zilversmit and Borgström methods were not statistically significant for all animals or for either the low- or high-responding group. Cholesterol absorption by either method was significantly higher in the high-responding monkeys than in the low-responding monkeys (Table 3).

Comparison of parameters of cholesterol kinetics

In **Table 4,** the mean values for the transit time, various pool sizes, and production rate of cholesterol in the rapidly exchangeable pool are presented. These were calculated from the best fit of the plasma cholesterol specific activity decay curves to either the logarithm of sum of two or three exponentials for each monkey. As seen in Table 4, the parameters of cholesterol kinetics in the high- or low-responding monkeys were essentially the same whether calculated using the data from the orally or the intravenously administered isotope. Indeed, for none of the sizes of body pools of cholesterol was there a significant difference between values derived from orally or intravenously administered radioactive cholesterol. The total exchangeable cholesterol pool in both groups was about 10.5 g. The production rate of cholesterol in the rapidly exchangeable pool averaged about 150 mg/day for all animals; however, it tended to be higher in the low-responding monkeys (164 mg/day) than in the high-responding group (138 mg/day). The distribution of total exchangeable choles-

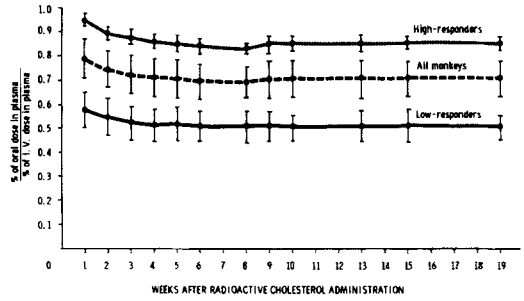

Fig. 1. The ratio of plasma [^{3}H]cholesterol and [^{14}C]cholesterol radioactivities as percent of intravenous and intragastric dose administered during the period of study.

TABLE 4. The parameters of cholesterol kinetics in rhesus monkeys

Kinetic Parameter	Isotopic Cholesterol Given I.V.		Isotopic Cholesterol Given Orally		Weighted Mean[a]	
	High-responders (4)	Low-responders (3)	High-responders (4)	Low-responders (3)	High-responders	Low-responders
Mean transit time, days	79 ± 11	64 ± 9	74 ± 9	60 ± 8	76 ± 10	62 ± 9
Pool sizes[b]						
M_{AP}	1.0 ± 0.2	0.6 ± 0.5	1.0 ± 0.2	0.6 ± 0.5	1.0 ± 0.2	0.6 ± 0.1
M_{AX}	1.7 ± 0.3	1.7 ± 0.3	1.9 ± 0.3	1.9 ± 0.5	1.7 ± 0.3	1.9 ± 0.4
M_A	2.7 ± 0.6	2.3 ± 0.3	2.9 ± 0.3	2.5 ± 0.5	3.0 ± 0.3	2.4 ± 0.3
M_T	11.3 ± 2.1	10.4 ± 1.5	10.1 ± 1.3	10.2 ± 2.0	10.5 ± 1.8	10.2 ± 1.6
Production rate in pool A, PR_A, mg/day	146 ± 15	164 ± 11	137 ± 3	169 ± 23	138 ± 11	164 ± 12

[a] The values of parameters used in calculating these means were the "best estimates" or weighted mean of the two values for each animal, weighing each value by the reciprocal of the variance for that parameter. The latter was obtained by "propagation of errors" using the variance-covariance matrix from the least squares procedure and the residual variance of the observed data about the fitted curve (13).

[b] M_{AP}, total plasma pool = (plasma cholesterol in mg/dl × plasma volume calculated as 36 mg/kg body weight); $M_{AX} = M_A - M_{AP}$, tissue component of cholesterol in rapidly exchangeable pool; M_A, cholesterol mass in rapidly exchangeable pool; M_T, minimum estimate of total exchangeable pool of cholesterol.

All values are mean ± S.E.

Number in parentheses is number of animals in each group.

Note: All differences in mean parameters of cholesterol kinetics between high- and low-responding monkeys are *not* statistically significant whether radioactive cholesterol is administered intravenously or orally.

TABLE 5. Cholesterol synthesis in high- and low-responding rhesus monkeys

Group (No.)	Cholesterol Synthesis, mg/day		
	Isotopic Cholesterol Given I.V.	Isotopic Cholesterol Given Orally	Weighted Mean[a]
High-responding (4)	68 ± 17[b]	63 ± 7	64 ± 13
Low-responding (3)	114 ± 10	119 ± 22	115 ± 12
Levels of significance (P)	<0.05	<0.05	<0.05

[a] For explanation for its derivation, refer to footnote Table 4.
[b] Values are mean ± S.E.

terol among the different body pools was also similar in the two groups. About one-fourth of the total exchangeable cholesterol was present in the rapidly exchangeable pool; about one-third of this rapidly exchangeable pool of cholesterol was present in the plasma compartment.

Cholesterol synthesis

The rate of cholesterol synthesis was estimated by subtracting the mass of cholesterol absorbed per day (estimated amount consumed in the diet × percent absorption as measured by the Borgström method) from the production rate of cholesterol in the rapidly exchangeable pool (PR_A) obtained from the kinetic analysis of the plasma cholesterol specific activity decay curve. The data presented in **Table 5** show that the low-responding monkeys had a significantly higher rate of cholesterol biosynthesis than did the high-responding monkeys when fed the same cholesterol-containing diet.

DISCUSSION

The validation of the Zilversmit method for measuring cholesterol absorption in baboons and vervet monkeys (2), in squirrel, cebus, and rhesus monkeys (3, 4), and in humans (5) has been reported. In the present study, in two of seven monkeys, the percent adsorption of cholesterol measured by the Borgström method (7) was lower (22.6 in monkey #72 and 10.4 percentage points in monkey #88) than the values obtained by the Zilversmit method (1, 6). In the rest of the animals, the percent absorption of cholesterol measured by the two methods compared well. However, the absorption of cholesterol determined by the Zilversmit method had to be calculated between 8 and 19 weeks after the administration of the isotopes (Table 3). At earlier times, the ratio of cholesterol radioactivities in the plasma did not attain constancy which is a requirement in the Zilversmit method (1, 6). Such constancy was only attained about 6 weeks after the administration of the isotopes (Fig. 1). These results disagree with those reported in rats (1, 6), in baboons and vervet monkeys (2), and in squirrel, cebus and rhesus monkeys (3, 4). In rats, Zilversmit found that the ratio of cholesterol radioactivities in the plasma attained constancy by 24 to 96 hours (1, 6). In baboons and vervet monkeys, Kritchevsky et al. (2) reported a constant ratio by 4 days. A constant plasma isotope ratio by 7 days in squirrel, cebus and rhesus was also reported (3, 4).

The reason(s) for the disagreement between our study and those of others mentioned above is not clear. However, certain differences should be noted between our study and those of the others. First, the method of preparation of the isotopic meal for oral administration was different. We prepared the isotopic meal by mixing radioactive cholesterol dissolved in ethanol with a portion of the regular diet of the animals. Zilversmit in his original study (1) dissolved radioactive cholesterol in 200 μmoles of triolein and sonicated it in 0.8 ml of 6.8% skim milk powder in water. In a later study, he added 25 mg of bile salts to the emulsion (6) without noticing any difference in results in rats between the two methods of preparation of the isotopic meal (6). Kritchevsky, Winter, and Davidson (2) fed the animals isotopic cholesterol dissolved in propylene glycol, whereas Corey and Hayes (3) and Tanaka and Portman (4) prepared the isotopic meal by dissolving radioactive cholesterol in 50 μl of ethanol dispersed in 2 ml saline.

A second difference between our study and those of others was in correction for possible degradative losses. In the studies of Kritchevsky et al. (2), Corey and Hayes (3) and Tanaka and Portman (4), the percent absorption of cholesterol calculated by the Zilversmit method agreed well with the values obtained by the fecal method only when the latter values were corrected upwards on the basis of fecal sitosterol recoveries. The sitosterol-loss correction factor ranged from 15.5 to as high as 86.7% (2–4). In other words, in all these studies, the plasma isotope ratio was higher than the uncorrected values for cholesterol absorption determined by the fecal method. In our study, we did not correct the percent absorption values measured by the Borgström method for possible sterol degradation in the gut. However, we think that these values are valid because in a later study, we have found no evidence of significant loss of sitosterol in the gut in these seven monkeys fed the same diet. In this later study, the percent recovery of [4-^{14}C]β-sitosterol in the high- and low-responding animals was found to be 104.0 ± 7.2 (S.D.) and 102.9 ± 5.8, respectively, (range 95–109%).[1]

[1] Bhattacharyya, A. K., and D. A. Eggen. Unpublished results.

A third difference is that we have used highly selected groups of rhesus monkeys. It is not known whether these animals will handle intravenously administered ethanol-saline suspension of radioactive cholesterol differently than other animals in the normal distribution of plasma cholesterol. In rats, radioactive cholesterol dispersed in ethanol-saline given intravenously is phagocytized by the Kupffer cells of the liver and released within 24 hours into the blood stream as free cholesterol (17). Further studies are, therefore, needed to examine the applicability of the simple and elegant plasma isotope ratio method of Zilversmit for the measurement of cholesterol absorption in different species before the method can be used widely. It is worth noting that the method has been reported to be unsuitable for rabbits (5).

In both normal humans and type II hypercholesterolemic patients, a significant difference was found in the cholesterol mass of the rapidly exchangeable pool (M_A) when calculated from the oral and intravenously administered doses of radioactive cholesterol (8). The difference was suggested to reflect, in part, a difference in the isotopic equilibration of plasma cholesterol with mucosal cholesterol. In monkeys, however, we did not observe such a difference in the rapidly exchangeable pool (M_A) when calculated from the intragastrically and intravenously administered doses of radioactive cholesterol (Table 4). In fact, for none of the sizes of the body pools of cholesterol were significant differences observed between values calculated from intravenously or intragastrically administered isotopes.

Our study confirmed the earlier finding that high-responding rhesus monkeys absorb significantly higher amounts of cholesterol than do the low-responding rhesus monkeys (9). Further, there was no significant difference in cholesterol turnover between the two groups, whether turnover parameters were determined from intravenously or from orally administered radiolabeled cholesterol (Table 4). Also, the distribution of total exchangeable cholesterol in the different pools was similar in high-responding and low-responding groups. These results agree with those obtained previously in these monkeys when they were fed either an atherogenic or a basal low-cholesterol, low-fat diet (9). The earlier study also showed that the fecal excretion of neutral sterols and bile acids was similar in the two groups when they were fed the basal commercial monkey diet (9). Furthermore, in the present study the high-responding monkeys had a lower rate of cholesterol biosynthesis than did the low-responding monkeys (Table 5). This would be expected because increased absorption of cholesterol in the high-responding groups would lead to a greater degree of feedback inhibition of cholesterol biosynthesis in the liver (18). These results also agree with our studies in those monkeys (19) in which we measured the relative rates of cholesterol biosynthesis using the "desmosterol suppression" technique of Bricker, Weis, and Siperstein (20). Thus, the difference in intestinal absorption of cholesterol remains the only difference observed between the high- and low-responding rhesus monkeys that might explain, in part, the differential response in plasma cholesterol concentration with cholesterol feeding (9, 19, 21). Jones et al. (22) have reported that hyperresponding squirrel monkeys had greater absorption of cholesterol than hyporesponding monkeys. In contrast to our observations in rhesus (9), Lofland et al. (23) also found that the hyperresponding squirrel monkeys excreted greater amounts of bile acids in the feces than did the hyporesponders. Recently, Parks et al. (24) also showed that those cholesterol-fed African green monkeys with higher serum cholesterol response derived a higher fraction of cholesterol from the diet than those with lower response. These authors, however, argued that gross alterations in cholesterol absorption, synthesis or excretion can not explain *fully* the large variability of serum cholesterol response to dietary cholesterol in nonhuman primates. We agree but also think that the difference in cholesterol absorption that we have found consistently in the high- and low-responding rhesus monkeys on a variety of diets does explain, in part, the differential response of plasma cholesterol to dietary cholesterol.

Rhesus monkeys have been used extensively as an animal model for atherosclerosis research because of their close phylogenetic relationship to man and also because of their susceptibility to cholesterol-induced atherosclerosis (25, 26). The cholesterol metabolism in man and in rhesus monkeys should, therefore, be examined to determine similarities or dissimilarities. There are dissimilarities in the various parameters of cholesterol kinetics between man and rhesus monkeys studied by the same method. The sizes of the various pools of cholesterol expressed per kg body weight were lower in monkeys than in human subjects (8, 14–16). Particularly, the size of the rapidly exchangeable pool (M_A) was significantly lower in monkeys than in normal man. This difference in the mass of cholesterol in the rapidly exchangeable pool between man and rhesus monkey is due to the difference in mass of cholesterol in the tissue component of the rapidly exchangeable pool, because the plasma cholesterol pool in both man and monkeys is similar (8). Also, in the monkeys, the production rate of cholesterol in the rapidly exchangeable pool expressed

per kg body weight was only about half that of humans (8, 14, 15). Furthermore, feeding cholesterol to the monkeys has been shown to expand the total body cholesterol (9, 27, 28). Similar information for man is not available. Thus, cholesterol turnover of rhesus monkeys differs from that of man. These differences should be carefully considered when extrapolating studies in nonhuman primates to the role of dietary factors in atherosclerosis or cholesterol in man.

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