Feedback regulation of cholesterol biosynthesis in rhesus monkeys with variable hypercholesterolemic response to dietary cholesterol[1]

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Abstract To test the hypothesis that high-responding rhesus monkeys should have a greater degree of feedback inhibition of hepatic cholesterol biosynthesis than the low-responding monkeys because the former group absorbs a higher percentage of cholesterol than the latter group, we determined the relative rates of cholesterol biosynthesis by measuring plasma desmosterol levels while feeding triparanol along with diets high and low in cholesterol and with or without 2% plant sterols. The build-up of plasma desmosterol was more rapid in low-responders than in high-responders on all diets; the difference was significant only on diets low in plant sterols. In both groups, adding plant sterols to either diet increased the initial slope of plasma desmosterol build-up (significant only for high cholesterol diet). The mean percent cholesterol absorption in high-responders was significantly higher than in low-responders on high and low cholesterol diets with low levels of plant sterols. On adding 2% plant sterols to both diets, the percent cholesterol absorption decreased significantly and became essentially the same in both groups. Triparanol feeding decreased plasma cholesterol significantly in both groups on both diets; the decrease in the low-responders was smaller than in high-responders. Addition of plant sterols to either diet also reduced plasma cholesterol in both groups, but the decrease was significant only in the high-responders on high cholesterol diet. The study demonstrates that high-responders have a greater degree of feedback inhibition of cholesterol biosynthesis than low-responders probably because of higher absorption of cholesterol. The results also indicate that both endogenous and exogenous cholesterol are effective mediators of the feedback inhibition mechanism.—**Bhattacharyya, A. K., and D. A. Eggen.** Feedback regulation of cholesterol biosynthesis in rhesus monkeys with variable hypercholesterolemic response to dietary cholesterol. *J. Lipid Res.* 1981. **22:** 16–23.

Supplementary key words plasma desmosterol · cholesterol absorption · plant sterols · high- and low-responding rhesus monkeys

We have previously reported that rhesus monkeys that responded with the greatest increase in serum cholesterol concentrations when fed a high-cholesterol diet (high-responders) absorbed a significantly higher percentage of intestinal luminal cholesterol than the monkeys that responded with only a small increase in serum cholesterol concentration (low-responders) (2). The difference in the intestinal absorption of cholesterol has been the only difference observed in respect to cholesterol metabolism between the high- and low-responding rhesus monkeys that might explain the differential response in plasma cholesterol concentration with cholesterol feeding (2–4).

Because absorbed dietary cholesterol in the form of lipoproteins of intestinal origin mediates the feedback inhibition of hepatic cholesterol biosynthesis (5), we hypothesized that the greater absorption of cholesterol in the high-responding monkeys should produce a greater degree of feedback inhibition of hepatic cholesterol biosynthesis than in the low-responding rhesus monkeys when fed a high-cholesterol diet. We tested this hypothesis using the "desmosterol suppression" technique (6) to determine relative rates of cholesterol biosynthesis in high- and low-responding monkeys. We measured plasma desmosterol levels while feeding triparanol, a drug that blocks cholesterol synthesis at the point of conversion of desmosterol to cholesterol (7, 8), concurrently with diets first with high- and then with low-cholesterol content. On each diet we also determined the relative rates of cholesterol biosynthesis in both groups of monkeys after interfering with cholesterol absorption by adding 2% plant sterols to the diets.

Abbreviation: PS, plant sterols.

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MATERIALS AND METHODS

Selection of animals

Eleven adult, male rhesus monkeys (six high-responders and five low-responders), weighing between 8 and 14 kg, were used in the study. The monkeys used were selected and studied 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 (2).

Diets

The diets were semi-synthetic high-cholesterol or low-cholesterol diets providing fat at 38% of calories and proteins at 15% of calories. The cholesterol content of the high-cholesterol diet was 0.15 mg/Kcal, whereas that of the low-cholesterol diet was 0.02 mg/Kcal. The composition of the high-cholesterol diet has been described (4). The low-cholesterol diet was identical to the high-cholesterol diet except for the deletion of egg yolk powder and crystalline cholesterol. A mixture of plant sterols (PS) containing β-sitosterol, campesterol, and stigmasterol, 60:35:5 (United States Biochemicals, Cleveland, OH), was added to the diet at 2% level (5 g/Kcal) and triparanol was added at 0.05% as dictated by the experimental protocol described below.

The animals were fed once daily an amount of diet sufficient to maintain body weight. On the average, the monkeys consumed about 150 g diet or 600 calories a day; thus the daily cholesterol intake was about 90 mg per day on the high-cholesterol diet and about 12 mg per day on the low-cholesterol diet. Plant sterol intake was about 3 g per day during the high plant sterol periods and about 0.01 g per day during other periods.

Experimental protocol

The monkeys were fed the semi-synthetic high cholesterol diet for about a year before the present series of experiments was begun. Without disturbing the animals' long-established metabolic steady state, we measured plasma cholesterol levels twice, 1 week apart, and cholesterol absorption as described below. The animals were then fed triparanol (0.05% in the diet) for 28 days. During this period, blood was obtained twice weekly for sterol determinations as described below. After the withdrawal of the drug, the animals were maintained on the high-cholesterol diet and blood was obtained once a week for the next 3 weeks.

In the second phase of the study, 7 months later, 2% plant sterols were added to the diet for a total of 14 weeks. Plasma cholesterol was determined weekly and cholesterol absorption was measured during the 6th week of plant sterol feeding. Triparanol was then added to the diet for 28 days and blood was obtained twice weekly for sterol determinations. After the withdrawal of the drug, the animals continued on the high plant sterol diet for 4 weeks after which plant sterols were also withdrawn from the diet and the animals were maintained on the low plant sterol, high-cholesterol diet for 3 more weeks.

The animals were then switched to the low-cholesterol diet and 7 months later the procedures of the first and second phase were repeated as described above.

Analytical methods

All blood samples were obtained from monkeys that had been fasted overnight; the blood was collected in tubes containing EDTA (1 mg/ml). The plasma was separated by centrifugation at 4°C and was stored frozen at −20°C for later analysis. Plasma cholesterol and desmosterol concentrations were measured in an aliquot of the plasma by gas–liquid chromatography (GLC) after saponification and extraction of the sterols by the method of Abell et al. (9). The hexane extract was evaporated to dryness, 5α-cholestane was added as internal standard, and sterols were converted to silyl derivatives by adding trimethylsilyl reagent (Applied Science Labs., State College, PA) at room temperature for 30 min. A small aliquot of the solution was injected directly into a gas chromatograph equipped with a hydrogen flame ionization detector and an automatic digital integrator. The glass column was a 183 cm U-tube, 4 mm I.D., filled with 3% SE-30 on 100–120 mesh Gas Chrom Q (Applied Science Labs.). Temperatures of column, detector, and flash heater were 210°, 225° and 250°C, respectively. The carrier gas was helium at 30 ml/min; the inlet pressure was 40 psi. Under these conditions, the retention times for cholesterol and desmosterol were 28 and 30 min, respectively.

Cholesterol absorption was measured by the single isotopic meal-feeding method of Borgstrom (10). Briefly, the monkeys were fed by gavage a meal containing 4 μCi of [1,2-^{3}H]cholesterol and 2 μCi of [4-^{14}C]β-sitosterol (New England Nuclear, Boston, MA; both isotopes were purified by thin-layer chromatography as described previously) (4). The isotopic meal was prepared by homogenizing 20 g of the diet with water to a semi-liquid consistency. The radioactive sterols dissolved in a small volume of ethanol were added and mixed thoroughly. Radioactivity in

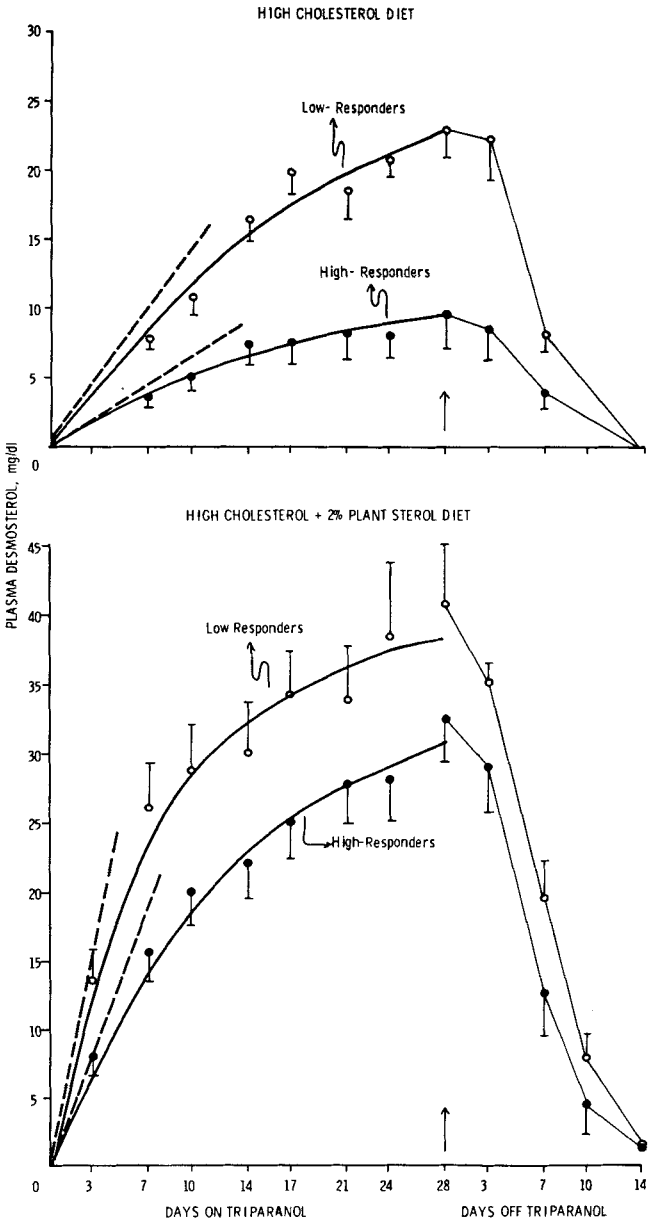

Fig. 1. Mean plasma desmosterol concentrations (±S.E.M.) in six high- and five low-responding rhesus monkeys fed triparanol with high cholesterol, low plant sterol diet (upper panel) and high cholesterol, high plant sterol diet (lower panel). At time indicated by arrows, the drug was withdrawn. The heavy solid lines represent the accumulation of desmosterol in plasma and were obtained by fitting the data by least squares to a model describing the relationship between concentration with time (see Methods). The dashed lines, which are the initial slope of the derived plasma desmosterol concentration curve, provide an estimate of the initial rate of desmosterol synthesis.

an aliquot of the meal was determined by liquid scintillation counting. After feeding the labeled meal, the residual radioactivity in the container and equipment used in the procedure was determined. That amount was subtracted from the radioactivity in the meal to determine the doses of radioactive cholesterol and β-sitosterol fed. Feces collected daily for 7 days after the feeding of the radiolabeled meal were stored frozen until pooled and homogenized with water. An aliquot of the homogenized feces was extracted for neutral sterols by the method of Miettinen, Ahrens, and Grundy (11). Total ^{14}C- and ^{3}H-activity in an aliquot of the extract were determined by liquid scintillation spectrometry with external standardization for quench correction. The cholesterol absorption was calculated as the difference between the amount of [^{3}H]cholesterol fed and the amount excreted in the 7-day feces pool and expressed as percent of the dose fed. The latter value was corrected for possible degradation in the intestine on the basis of the recovery of [^{14}C]β-sitosterol in the feces, which ranged between 95 and 109%.

Calculation of the relative rate of sterol synthesis

When the conversion of desmosterol to cholesterol was blocked by feeding triparanol, the plasma desmosterol concentration increased first rapidly and then slowly while approaching an apparent plateau (**Figs. 1 and 2**). This plateau, or the value at any point during the build up, depends not only on the rate of synthesis of the sterol but also on its excretion or catabolism by routes other than conversion to cholesterol. The slope of the increase immediately after the cessation of the very rapid conversion to cholesterol reflects more directly the rate of synthesis at the time the triparanol was first administered. We have therefore used this initial slope as an indicator of the *relative* rate of sterol synthesis among animals.

To calculate the best estimate of this slope for each animal under each diet condition, we fitted the observed data to the expression $C{=}C_\infty (1 - e^{-t/\tau})$ describing the relationship of concentration (C) with time (t) in a single pool system in which input (synthesis) remains constant while the rate of loss from the system is suddenly decreased to a very small fraction of its initial value (see curve, Figs. 1 and 2). For this we used the non-linear least squares procedure (NLIN) of the SAS system (SAS Institute, Raleigh, NC) to calculate C_∞, the concentration that would be attained at steady state and τ, a constant with dimensions of time. By differentiation, the slope at $t = 0$ is found to be equal to C_∞/τ.

RESULTS

Relative rates of cholesterol synthesis

The time courses of the mean plasma desmosterol concentrations for each group and each diet are shown

in Figs. 1 and 2, together with the curve for least squares fit to the model described above and the initial slope calculated from this model. **Table 1** gives data on the initial rate of change of plasma desmosterol concentration for individual animals and means of these values by group and diet.

On feeding cholesterol (high-cholesterol, low-PS diet), the high-responders had a significantly lower rate of accumulation of desmosterol in the plasma than the low-responders (0.65 versus 1.4 mg/dl plasma per day, $P < 0.01$). Similarly, on the low-cholesterol, low-PS diet, the high-responders had a significantly lower rate of accumulation of desmosterol in plasma than the low-responders (2.2 versus 3.3 mg/dl plasma per day, $P < 0.05$). Addition of plant sterols to either the high- or the low-cholesterol diet significantly increased the initial rate of accumulation of desmosterol in the plasma in the high-responders. Adding plant sterols to either diet also increased the mean initial slope for low-responders (Table 1); however, this increase was significant only for the high-cholesterol diet. Thus, the build-up of plasma desmosterol was more rapid in the

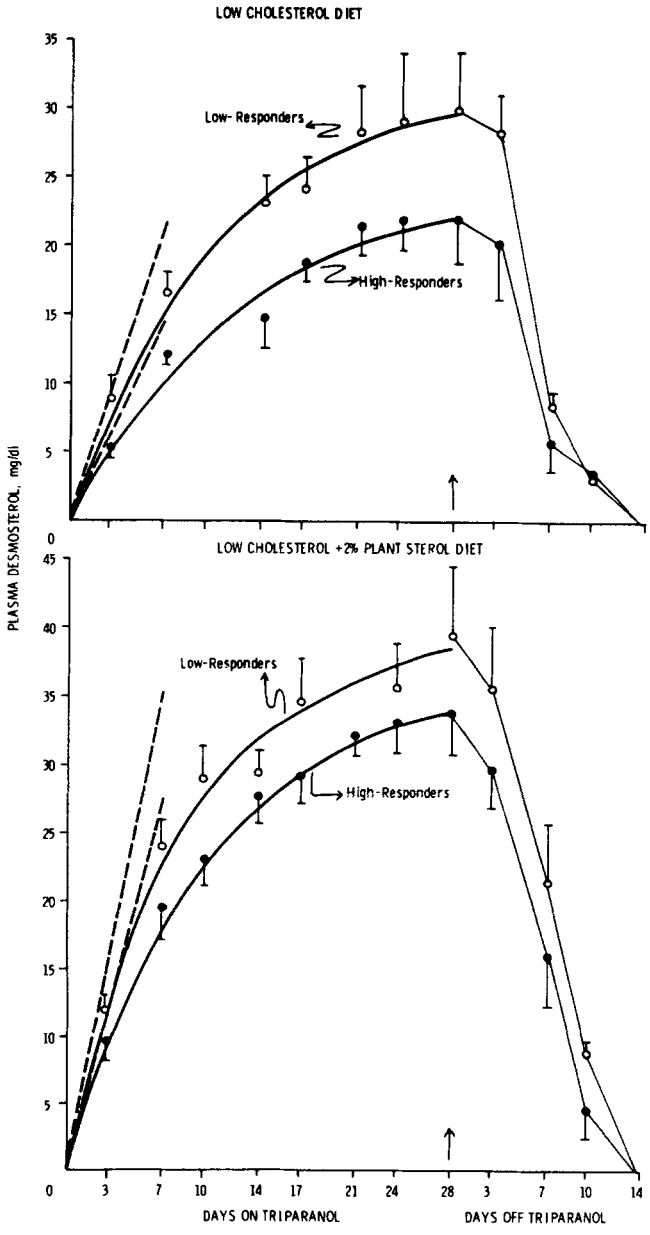

Fig. 2. Mean plasma desmosterol concentrations (±S.E.M.) in six high- and five low-responding rhesus monkeys fed triparanol with low cholesterol, low plant sterol diet (upper panel) and low cholesterol, high plant sterol diet (lower panel). For further explanations, please refer to the legend for Fig. 1.

TABLE 1. Initial rate of increase of plasma desmosterol concentration following administration of triparanol to high- and low-responding rhesus monkeys while fed low or high cholesterol diets with or without 2% plant sterols

Group and Animal No.	Diets: High Cholesterol Low PS[a]	High Cholesterol High PS	Low Cholesterol Low PS	Low Cholesterol High PS
	mg/dl plasma/day			
High-responders				
1	0.65	4.2	4.3	7.3
2	0.56	3.8	2.1	4.4
3	0.72	1.9	1.4	2.4
4	0.95	1.3	1.9	3.9
5	0.39	2.8	1.9	3.4
6	—[b]	4.2	1.6	4.0
Mean ± S.E.M.	0.65 ± 0.09	3.0 ± 0.5	2.2 ± 0.4	4.1 ± 0.7
Low-responders				
7	1.1	—	3.5	—
8	1.8	9.3	3.8	4.9
9	1.0	4.1	3.3	3.5
10	1.5	5.4	3.0	7.0
11	—	4.0	2.8	4.5
Mean ± S.E.M.	1.4 ± 0.2	5.7 ± 1.2	3.3 ± 0.2	5.0 ± 0.7

Statistical Significance—*P* Values

Between high- and low-responders[c]	*Low PS diet*	*High PS diet*
On high cholesterol diet	<0.01	NS[d]
On low cholesterol diet	<0.05	NS
Between diets[e]	*High-responders*	*Low-responders*
High cholesterol vs. low cholesterol	<0.05	<0.005
High cholesterol vs. high cholesterol + 2% PS	<0.05	<0.05
High cholesterol + 2% PS vs. low cholesterol + 2% PS	NS	NS
Low cholesterol vs. low cholesterol + 2% PS	<0.005	NS

[a] PS, plant sterols.
[b] Data not obtained due to technical difficulties.
[c] By *t*-test of difference between means.
[d] NS, not significant.
[e] By *t*-test of paired observations.

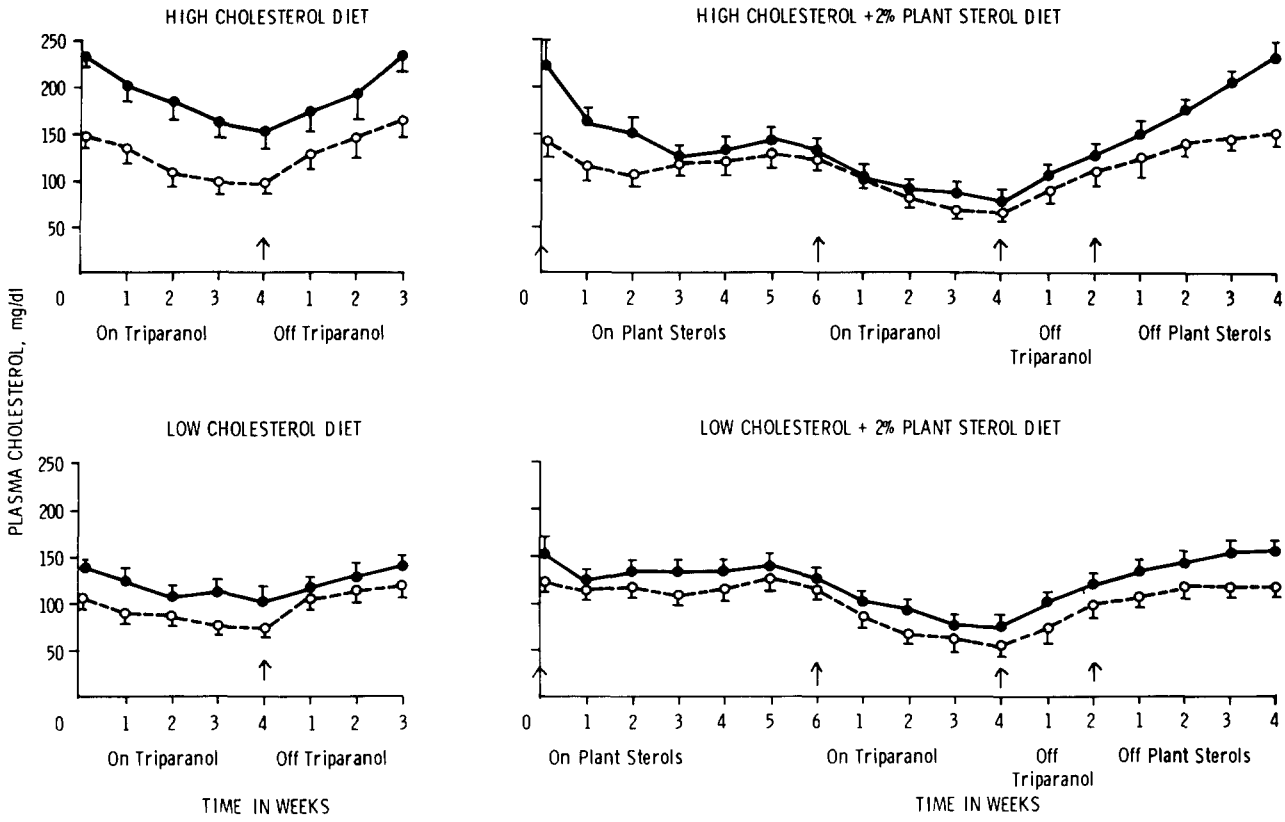

Fig. 3. Mean plasma cholesterol concentrations (±S.E.M.) in six high-responding (closed circles) and five low-responding rhesus monkeys (open circles) fed triparanol (T) for 28 days along with high cholesterol, low plant sterol diet (upper left); high cholesterol, high plant sterol diet (upper right); low cholesterol, low plant sterol diet (lower left); and low cholesterol, high plant sterol diet (lower right). The arrows indicate the starting and withdrawal of triparanol or plant sterols.

low-responders than in the high-responders on all diets, however the difference between groups was statistically significant only on the diets low in plant sterols. In both groups of animals the effect of adding plant sterols to the diet was to increase the initial slope of the plasma desmosterol build up. The effect was, however, statistically significant only for the high-cholesterol diet.

Plasma cholesterol concentrations

On both high- and low-cholesterol diets, the high-responders had higher mean plasma cholesterol levels than the low-responders, with a mean ± S.E.M. of 235 ± 14 and 147 ± 13 mg/dl, respectively, ($P < 0.005$) on the high-cholesterol diet and 140 ± 9 versus 107 ± 9 mg/dl, respectively, ($P < 0.05$) on the low-cholesterol diet (**Fig. 3**). Triparanol feeding decreased plasma cholesterol levels significantly in both groups on both diets; however, the decrease in the low-responding group was smaller than that in the high-responding group. On withdrawal of triparanol, plasma cholesterol levels returned to initial levels in both groups on both diets.

The mean plasma cholesterol concentrations (Fig. 3) in the high- and low-responding animals just before the addition of 2% plant sterols to the high-cholesterol diet were 230 and 142 mg/dl, respectively ($P < 0.01$); on the low-cholesterol diet, they were 154 and 124 mg/dl, respectively ($P < 0.05$). In the high-responders, adding 2% plant sterols to the high-cholesterol diet produced a decrease of 43% in mean plasma cholesterol levels by 6 weeks (from 230 to 132 mg/dl) that was statistically significant ($P < 0.025$). In the low-responders, however, the decrease was only 13% (from 142 to 123 mg/dl, which was not statistically significant). Addition of 2% plant sterols to the low-cholesterol diet decreased the mean plasma cholesterol in high- and low-responding groups by 17% and 6%, respectively; however, neither of these decreases was statistically significant. Thus, on either diet adding plant sterols decreased the difference in plasma cholesterol between groups to the point that it was no longer statistically significant. Addition of 0.05% triparanol to either of the diets containing high levels of plant sterols further decreased plasma cholesterol levels in both groups by an average of 44%

on the high-cholesterol diet and by about 49% on the low-cholesterol diet. With the withdrawal of triparanol, the plasma cholesterol concentrations returned by 2 weeks to pre-drug levels. Furthermore, plasma cholesterol levels in both groups of animals returned to the initial levels within 4 weeks after withdrawal of plant sterols from either high- or low-cholesterol diets.

Cholesterol absorption

At low levels of plant sterols on either high- or low-cholesterol diets, the mean percentage absorption of luminal cholesterol in the high-responders was significantly higher than that of the low-responders (**Table 2**). Addition of 2% plant sterols to either the high- or low-cholesterol diets reduced significantly the percent absorption of cholesterol so that it became essentially the same in the two groups (Table 2). Further, the percentage cholesterol absorption in both high- and low-responding groups was significantly higher on the low-cholesterol diet than on the high-cholesterol diet. In other words, the percent of luminal cholesterol absorbed decreased on adding cholesterol to the diets.

TABLE 2. Percent cholesterol absorbed in high- and low-responding rhesus monkeys on low or high cholesterol diet with or without 2% plant sterols

Group and Animal No.	Diets: High Cholesterol Low PS[a]	High Cholesterol High PS	Low Cholesterol Low PS	Low Cholesterol High PS
High-responders				
1	59.5	36.8	81.4	50.6
2	74.1	42.9	91.9	36.0
3	76.3	47.5	83.1	37.0
4	75.9	41.2	80.7	43.0
5	82.3	43.3	88.8	37.8
6	69.7	45.0	86.6	36.9
Mean ± S.E.M.	73.0 ± 3.2	42.8 ± 1.5	85.4 ± 1.8	40.3 ± 2.3
Low-responders				
7	70.6	—[b]	84.5	45.5
8	48.4	41.5	71.7	36.4
9	62.5	41.2	75.1	37.3
10	48.9	29.8	79.0	41.0
11	62.5	52.2	67.1	53.6
Mean ± S.E.M.	58.6 ± 4.3	41.2 ± 4.1	75.6 ± 3.0	42.8 ± 3.1

Statistical Significance—*P* Values

Between high- and low-responders[c]	*Low PS diet*	*High PS diet*
On high cholesterol diet	<0.025	NS[d]
On low cholesterol diet	<0.025	NS
Between diets[e]	*High-responders*	*Low-responders*
High cholesterol vs. low cholesterol	<0.01	<0.025
High cholesterol vs. high cholesterol + 2% PS	<0.001	<0.05
High cholesterol + 2% PS vs. low cholesterol + 2% PS	NS	NS
Low cholesterol vs. low cholesterol + 2% PS	<0.001	<0.005

[a] PS, plant sterols.
[b] Data not obtained due to technical difficulties.
[c] By *t*-test of difference between means.
[d] NS, not significant.
[e] By *t*-test of paired observations.

DISCUSSION

The present study was designed to test the hypothesis that high-responding rhesus monkeys, because of their higher percentage absorption of cholesterol than that of low-responding animals, should have a greater degree of feedback inhibition of hepatic cholesterol biosynthesis. The method used to assess cholesterol synthesis was the "desmosterol suppression" technique of Bricker, Weis, and Siperstein (6). In this technique triparanol is administered to an animal and the plasma desmosterol concentration is measured. Triparanol is a drug known to block cholesterol biosynthesis at the point of conversion of desmosterol to cholesterol (7, 8). Because desmosterol is not consumed in the diet, the rate of accumulation of desmosterol in the plasma during triparanol feeding is an index of rate of endogenous sterol synthesis. As seen in Table 1 and Fig. 1, adding triparanol to either the high- or low-cholesterol diet caused a less rapid build up of plasma desmosterol concentration in high-responders than in low-responders. This finding indicated that the rate of sterol synthesis was less in the high-responders than in the low-responders. Because the percentage absorption of cholesterol in the high-responders was higher than in the low-responders on both high- and low-cholesterol diets (Table 2), these results showed that the high-responders had a greater degree of feedback inhibition of cholesterol biosynthesis than did the low-responding animals.

Further support for this hypothesis was obtained when plant sterols were fed. Plant sterols, particularly β-sitosterol, are known inhibitors of intestinal cholesterol absorption (12); feeding high levels of plant sterols should release the feedback inhibition mechanism with an increase in the rate of cholesterol synthesis. With the higher levels of plant sterol in the diet, the initial rate of build-up of plasma desmosterol with triparanol feeding should be increased, and this increase in rate should be greater in high- than in low-responders. Our results show that addition of plant sterols to either the high- or low-cholesterol diet did

produce a more rapid build-up of plasma desmosterol concentration and that the increase was greater for high- than low-responders (Fig. 1 and Table 1). We also showed that there were significant decreases in the percentage absorption of cholesterol in both groups of animals on either diet when plant sterols were added to the diet (Table 2). This finding indicated that adding plant sterols to the diet released the feedback inhibition of cholesterol synthesis by interfering with cholesterol absorption.

On the basis of our previous studies (2–4), we suggested that one mechanism of the severe hypercholesterolemic response of the high-responders when fed cholesterol is that these animals absorb significantly more cholesterol than do the low-responders. The results of the present study are also unequivocal in that on both high- and low-cholesterol diets, the high-responders absorbed a significantly higher percentage of cholesterol than did the low-responders (Table 2). Besides the difference in the absorption of cholesterol between the high- and low-responders to date, no other differences in cholesterol metabolism have been observed that might explain the large difference in plasma cholesterol response to dietary cholesterol (2, 4).

In a previous study using less direct kinetic methods, we also found that when fed cholesterol the high-responders had a lower rate of cholesterol biosynthesis than did low-responders (4), which in effect would tend to lower plasma cholesterol concentration rather than to increase it during cholesterol feeding. Therefore, the difference in the intestinal absorption of cholesterol remains the only difference observed that might explain the differential response of plasma cholesterol concentration to dietary cholesterol between these two groups of rhesus monkeys. Jones et al. (13) also reported that hyperresponding squirrel monkeys had greater absorption of cholesterol than the hyporesponding monkeys. Recently, Parks et al. (14) reported that the cholesterol-fed African green monkeys with higher serum cholesterol response compared with those with lower response, derived a larger fraction of cholesterol from the diet. Because these investigators did not find the estimated values for cholesterol absorption (in mg/kg/day) significantly correlated with plasma cholesterol concentration, they argued that gross alterations in cholesterol absorption, synthesis, or excretion cannot explain fully the large variability of serum cholesterol response to dietary cholesterol in non-human primates.

We disagree with the conclusions of Parks et al. (14) because our study showed that, during interference in cholesterol absorption by plant sterol feeding, the difference in plasma cholesterol concentration between the high- and low-responders was greatly diminished to the extent that they were no longer statistically significant (Fig. 3). This equalization in plasma cholesterol between the two groups coincided with a large reduction in differences in absorption of cholesterol (Table 2) and in the rate of sterol synthesis (Table 1 and Figure 1). In other words, by greatly reducing the difference in cholesterol absorption, the difference in plasma cholesterol concentration between the high- and the low-responders was nearly eliminated. Therefore, we believe that the difference in cholesterol absorption that we have consistently found between the high- and low-responding rhesus monkeys is a primary factor contributing to the difference among animals in the response of plasma cholesterol to dietary cholesterol.

Our study also supports the view that absorbed cholesterol in the form of lipoproteins of intestinal origin mediates the feedback inhibition of hepatic cholesterol biosynthesis (5), and that intestinal absorption of both endogenous and exogenous cholesterol is effective in this process. This is so because during the very low cholesterol diet period the intestinal luminal cholesterol is derived almost entirely from the endogenous sources, i.e., from the bile, from locally synthesized cholesterol that may be excreted by the intestinal mucosal cells, and from the sloughed mucosal cells. When the absorption of this endogenously derived cholesterol was blocked by plant sterol feeding, the rate of sterol synthesis increased in the animals, as evidenced by an increased rate of accumulation of desmosterol in the plasma upon feeding triparanol. Similarly, when much higher levels of cholesterol were present in the diet, blockage of cholesterol absorption by plant sterols also produced increased plasma cholesterol concentrations on triparanol feeding (Table 1).

Plant sterols, particularly β-sitosterol, are known to inhibit cholesterol absorption (12). Our study confirmed this observation for the rhesus monkeys; we observed a large and statistically significant reduction in cholesterol absorption in both groups of animals on feeding plant sterols. Our study, however, extends the observations further because it shows that plant sterols interfere not only with dietary (exogenous) cholesterol absorption but also with the absorption of endogenously derived intestinal luminal cholesterol. This is so because the percentage of cholesterol absorbed decreased by more than 50% with the addition of plant sterols to the low cholesterol diet, i.e., during the time when the intestinal luminal cholesterol was derived almost entirely from the endogenous sources as discussed above. The decrease in the percent absorption of endogenous cholesterol oc-

curred to similar extent in both high- and low-responding rhesus monkeys.

Plant sterol feeding resulted in a decrease in the mean plasma cholesterol level in both groups and on both diets; however, the decrease was significant only in the high-responding group while it was fed the high-cholesterol diet. These observations are consistent with the reported hypocholesterolemic effect of plant sterols in humans (15). The observed effect in the monkeys fed the low-cholesterol diet is, however, at variance with observations reported by Bhattacharyya and Lopez in rabbits (16). When the rabbits were fed 2% plant sterols for 10 weeks along with a low cholesterol diet, their plasma cholesterol concentration increased by about 60%. Thus there is apparently a species difference in the effect of plant sterol feeding during low-cholesterol diets. As was suggested by studies in rabbits, either the endogenous neutral sterol excretion in feces did not increase or any increase could not keep pace with increased biosynthesis of cholesterol (16). In any event, the results of the present study show that plant sterol feeding will produce a larger reduction in plasma cholesterol levels that are elevated by dietary cholesterol than in basal levels. Further, the reduction in plasma cholesterol concentration with plant sterol feeding occurred in the face of an increased cholesterol biosynthesis as evidenced by more rapid plasma desmosterol build-up (Tables 1 and 2). Thus, in the effect on plasma cholesterol, the increase in cholesterol biosynthesis did not compensate for the large decrease in cholesterol absorption. Because the latter affects the former and the reverse is not true, it is suggested that cholesterol absorption rather than cholesterol biosynthesis plays a greater role in the maintenance of the plasma cholesterol level in the rhesus monkey under a constant diet.

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