HYPO- AND HYPERRESPONDERS TO DIETARY CHOLESTEROL

A.C. Beynen[1], M.B. Katan[2] and L.F.M. van Zutphen[1]

[1]Department of Laboratory Animal Science, State University, P.O. Box 80.166, 3508 TD Utrecht
[2]Department of Human Nutrition, Agricultural University, De Dreijen 12, 6703 BC Wageningen (The Netherlands)

ABSTRACT

The feeding of cholesterol-rich diets to random-bred animals results in marked inter-individual differences in the response of serum cholesterol. Certain animals show only small responses (hyporesponders), whereas others develop high degrees of hypercholesterolemia (hyperresponders). Inbred strains of rabbits, rats and mice differing in their sensitivity to dietary cholesterol are available. In these animals, and also in monkeys, differences in the responsiveness to high-cholesterol diets have a strong genetic basis. In man the responsiveness to dietary cholesterol also varies among individuals, although less markedly.

The mechanisms underlying hypo- and hyperresponsiveness to dietary cholesterol have not yet been unravelled. We propose that in hyperresponders, compared with hyporesponders there is a higher hepatic efflux of cholesterol in low density lipoproteins (LDL), or its precursors, after cholesterol consumption. This may be caused by unsufficient inhibition of cholesterol biosynthesis in the hyperresponders. The stimulation of LDL production accounts for the increase in LDL cholesterol in serum. The number of hepatic LDL receptors, which may be already decreased in hyperresponders, will decrease further through down regulation. The receptor-mediated LDL clearance decreases, but the absolute amount of LDL cholesterol taken up by the cells via the receptor and by the receptor-independent pathway increases because of the increased level of LDL cholesterol. In this way a new equilibrium is reached in which LDL production equals LDL catabolism.

The phenomenon of hypo- and hyperresponsiveness may have implications for counseling subjects who attempt to lower their serum cholesterol by diet. However, identification of true hyper- and hyporesponders is greatly hampered by within-person fluctuations of the level of serum cholesterol. No simple test is available to discriminate hypo- from hyperresponders. As yet, monitoring a person's response to diet should be based on relatively large numbers of serum cholesterol determinations.

INTRODUCTION

In most questions of diet and health, two alternative approaches are available. If a food component (or its absence) causes metabolic disturbances in a large proportion of the population, then a public health approach is mandated. Measures are taken to protect the whole population from the harmful agent, even though some subjects may be totally insensitive to it. Many food contaminants are regulated in this way.

Nutritional Effects on Cholesterol Metabolism, edited by A. C. Beynen, Transmondial, Voorthuizen, 1986

If, however, the agent affects only a limited number of susceptible subjects, then the usual approach is to screen out these high-risk individuals, and to leave the diet of the general population alone. An example of this is phenylalanine, which is harmless to 99.99% of the population, but causes phenylketonuria in a small minority. This minority is screened out and treated with special diets.

Dietary cholesterol when consumed in excessive amounts can be harmful because it raises plasma cholesterol, which in turn raises the risk of atherosclerotic heart disease. However, people might differ in their susceptibility to dietary cholesterol, and this would argue for a case-finding as opposed to a public-health approach of diet-induced hypercholesterolemia.

Here we review the evidence for the existence of differences in susceptibility to dietary cholesterol in man and in various animal species. Special attention is given to possible mechanisms underlying differences in responsiveness. It is concluded that large differences exist in animals and smaller differences in man, and that the underlying mechanisms are only beginning to be unravelled.

HYPO- AND HYPERRESPONDERS AMONG ANIMALS

The addition of cholesterol to the diet of random-bred rabbits elicits a rise of serum cholesterol, but many investigators have noted that there are marked inter-individual differences in the extent of the response. This indicates that certain animals are hypo-, and others are hyperresponsive to dietary cholesterol. Table I illustrates this.

TABLE I
Effect of dietary cholesterol on serum cholesterol levels in individual, random-bred New Zealand White rabbits

Rabbit no.	Serum cholesterol, mmol/l			
	day -8	day 7	day 14	day 20
1	2.6	1.8	2.5	3.2
2	1.8	3.3	3.2	3.5
3	2.1	3.8	4.1	5.6
4	2.6	5.5	7.1	8.2
5	2.7	6.9	11.0	14.4
6	3.5	9.3	13.5	20.1

Up until day 0 of the experiment the male rabbits were fed a cholesterol-free diet. Then, 0.2% (w/w) of cholesterol was added to the diet. The rabbits were sampled after a 16-h fast. Cholesterol : 1 mmol/l = 38.7 mg/dl.

Extreme differences in the response of serum cholesterol to diet can be found among inbred strains of rabbits (1). Table II shows the levels of serum cholesterol in male rabbits of six inbred strains. The rabbits were sampled while they were on a commercial rabbit chow, and also after

21 days of receiving the same diet to which 0.5% (w/w) cholesterol had been added. The animals with the most extreme response showed almost a 5-fold higher increase in serum cholesterol than the strain with the lowest response.

TABLE II
Effect of dietary cholesterol on plasma cholesterol levels in inbred strains of rabbits

Strain	Plasma cholesterol, mmol/l	
	day 0	day 21
IIIVO/J	0.7 ± 0.1	8.0 ± 1.9
WH/J	0.3 ± 0.0	8.0 ± 0.8
X/J	0.9 ± 0.3	17.3 ± 4.2
ACEP/J	0.7 ± 0.0	18.9 ± 3.5
OS/J	0.8 ± 0.1	29.4 ± 4.8
AX/J	0.6 ± 0.1	33.6 ± 3.1

Results are expressed as means ± SE for five male animals per strain. Up until day 0 of the experiment all rabbits received a cholesterol-free, commercial diet; then, 0.5% (w/w) cholesterol was added to the diet. Data taken from Van Zutphen and Fox (1).

Studies with inbred strains of rats (2), mice (3) and pigeons (4) have also demonstrated marked strain differences in the response of plasma cholesterol to cholesterol-rich diets. These studies indicate that differences in responsiveness have a genetic basis.

Many investigators have also documented the existence of hypo- and hyperresponders in monkeys (5-7). For example, in random-bred squirrel monkeys (Saimiri sciureus) the response of serum cholesterol is stable and reproducible from one experiment to another (5). Animals hypo- or hyperresponsive to a diet fortified with cholesterol showed similar responses after a second challenge six months later. Thus responsiveness in these primates seems to be an innate characteristic of the individual animal. Clarkson et al. (5) calculated that in these wild-type squirrel monkeys about 65% of the variability in serum cholesterol concentration after cholesterol feeding was attributable to genetic factors. From this study and from the studies with inbred strains of laboratory animals it follows that a major part of the inter-individual differences in the response of plasma cholesterol to dietary cholesterol is due to genetic differences.

HUMAN HYPO- AND HYPERRESPONDERS

In the numerous studies which have dealt with the effect of dietary cholesterol on serum cholesterol levels in humans a striking variability in individual response was generally found (8). Certain individuals showed negligible changes in the concentration of serum cholesterol (hyporesponders), whereas others developed elevated concentrations (hyperresponders).

In the literature the concept of human hyper- and hyporesponders became firmly entrenched (9, 10). However, in almost all studies the dietary challenge was only given once and thus the reproducibility of the individual cholesterolemic response was not known.

Studies with a small number of subjects who participated twice in the same type of experiment, did not provide evidence that human hypo- and hyperresponders exist. In 1942 Messinger et al. (11) fed 4 patients with various diseases a daily supplement of 150 g of egg yolk powder (providing 3750 mg cholesterol) emulsified in milk. Typical increases of 6 to 31% in serum cholesterol were observed, but the individual cholesterolemic responses were not reproducible. In fact, a patient who displayed the highest response in the first experiment, showed the lowest response in the second experiment. We have obtained similar results with healthy subjects who consumed six egg yolks (about 1500 mg cholesterol) per day for 10 days in two successive experiments one year apart (12). Three subjects showed entirely different cholesterolemic responses from one year to another. This lack of reproducibility in certain individuals is not unexpected in view of within-person variability in the level of serum cholesterol, which is of the same order of magnitude (13) as the cholesterolemic responses to dietary cholesterol.

It is important to know whether individuals with a consistently low or high serum cholesterol response to dietary cholesterol do exist. Hypercholesterolemia may of course be due to monogenetic disorders, or occur secondary to other diseases or obesity, but the majority of subjects with mild hypercholesterolemia have no clearly defined defect. Many of the latter could conceivably be persons who are hyperresponsive to an affluent diet.

The subject of hypo- and hyperresponsiveness is of both practical and scientific interest. Patients with hypercholesterolemia generally receive dietary advice from clinicians in order to lower their serum cholesterol levels. Frequently, such advice turns out to be ineffective. Although lack of compliance may be involved, it is possible that certain patients are insensitive to cholesterol-lowering diets and need a different form of therapy. It is assumed here that subjects hypo- and hyperresponsive to cholesterol-lowering diets are also hypo- and hyperresponsive, respectively, to hypercholesterolemic diets. From the scientific point of view elucidation of the mechanism underlying hypo- and hyperresponsiveness may shed more light on the relations between dietary components and cholesterol metabolism.

We have carried out three controlled dietary trials with the same subjects to address the question whether individuals do exist with a consistently high or low serum cholesterol response to dietary cholesterol (14). In each trial the volunteers successively consumed a low- and a high-cholesterol diet, the cholesterol component of the diets (provided by egg yolk) being the only variable. Standardized regression coefficients for individual responses in one experiment as a function of the response in a previous experiment ranged from 0.34 to 0.53 ($n=32$, $P<0.05$).

Under less controlled conditions we found similar results. In 1976 Bronsgeest-Schoute et al. (15) studied the serum cholesterol response to

cessation of egg consumption in subjects who habitually consumed at least one egg per day. When eggs were eliminated from the diet, daily cholesterol intake decreased from about 800 mg to 300 mg. Mean serum cholesterol fell only slightly (by 3%), but the individual responses varied from -20% to +8%. In 1982, we re-investigated 34 of these subjects (16), and at our request they again eliminated eggs and egg-containing products from their diet. The differences in serum cholesterol response between individuals were partly reproducible; the individual responses in 1976 and 1982 were positively correlated ($r=0.32$; $n=34$, $P<0.05$).

Thus it appears that at least part of the cholesterolemic response to dietary cholesterol in man is individually determined, although the range of responsiveness is much smaller in man than in laboratory animals. It is also clear that one will always find subjects who appear hyperresponsive in one experiment and hyporesponsive in another. This is caused by the diet-independent within-person variability of serum cholesterol. Nevertheless, from these repeated experiments with the same subjects it can be concluded that human hypo- and hyperresponders to dietary cholesterol do exist.

MECHANISMS UNDERLYING HYPO- AND HYPERRESPONSIVENESS

In man the responses to increased amounts of ingested cholesterol are generally a diminished synthesis of cholesterol in the body and an enhanced excretion of neutral steroids in the feces (17, 18). Sterol balance studies have shown that on high-cholesterol diets there can also be net storage of cholesterol in the body (17). The human gut absorbs a more or less constant fraction of the cholesterol presented to it each day (17-19), but there is probably inter-individual variation. In monkeys, differences in absorption may be involved in hypo- and hyperresponsiveness to dietary cholesterol: hyperresponders showed a higher efficiency of cholesterol absorption than did hyporesponders (6, 20, 21).

In man, the individual variability in cholesterolemic response could theoretically be due to differences in feed-back inhibition of cholesterol synthesis, in fecal steroid excretion or in cholesterol accumulation in the body. We have recently reviewed the evidence that hypo- and hyperresponders differ in their ability to step up the output of neutral steroids and bile acids or to store cholesterol in the body after a cholesterol load (22). We found it less likely that these reactions play a major role. Several lines of evidence however, point to differences in inhibition of cholesterol synthesis being the key to hypo- and hyperresponsiveness in man.

The conjecture that hypo- and hyperresponders differ in the degree of dietary-cholesterol-induced inhibition of cholesterol synthesis is mainly based on the work of Nestel and Poyser (18). These authors studied nine subjects first on a low- and then on a high-cholesterol diet. Table III reveals that the increase in serum cholesterol was related to the decrease in whole-body cholesterol synthesis; the individuals who depressed cholesterol synthesis most markedly showed the smallest increase in serum cholesterol on the cholesterol-rich diet. This agrees with the findings of Mistry et al. (23), who studied the activity of the rate-limiting enzyme in cholesterol synthesis, 3-hydroxy-3-methylglutaryl CoA (HMG-CoA)

TABLE III
Increase in serum cholesterol and decrease in whole-body cholesterol synthesis in human subjects after cholesterol consumption

Subject no.	Increase in serum cholesterol (mmol/l)	Decrease in cholesterol synthesis (mmol/day)
1	0.1	0.6
2	0.2	1.1
3	0.2	0.4
4	0.3	0.7
5	0.3	0.6
6	0.7	0.4
7	1.2	0.2
8	1.7	0.1
9	3.7	0.0

Subjects consumed 300 mg cholesterol per day for 4 to 6 weeks and then 800 mg per day for another 4-6 weeks. Feces were collected during the final 8 days of each period. Cholesterol synthesis equals total fecal steroids excretion minus dietary cholesterol intake. Plasma cholesterol concentrations represent the means of two to three times weekly determinations during both periods. Data taken from Nestel and Poyser (18).

reductase, in freshly isolated blood mononuclear cells. In subjects fed cholesterol the percentual reduction in HMG-CoA reductase was inversely related to the percentual increase in plasma LDL-cholesterol concentration ($r=-0.49$, $n=37$, $P<0.01$).

We ourselves have carried out an experiment with two hyper- and four hyporesponsive subjects; all subjects had shown a reproducible response in two separate experiments (16). In these subjects we have measured serum concentrations of lanosterol, a precursor of cholesterol, and a possible indicator of cholesterol biosynthetic activity (24). Table IV shows that serum lanosterol concentrations increased after removal of cholesterol from the diet in three hypo- but not in the two hyperresponders. This suggests that the rate of cholesterol biosynthesis is regulated by dietary cholesterol in hypo- but not in hyperresponders. However, in these hypo- and hyperresponders we found no clear-cut differences between cholesterol synthesis measured as total fecal steroids excretion minus dietary cholesterol intake.

Studies by Quintão et al. (17) and Maranhão and Quintão (25) failed to demonstrate a relationship between the response of serum cholesterol to dietary cholesterol and the degree of suppression of cholesterol synthesis. This may be related to the extremely large changes in cholesterol intake of the patients in these studies. The baseline diets provided less than 50 mg cholesterol/day, whereas the high-cholesterol diets provided 1350 to about 2500 mg/day. In 10 out of the 21 patients studied

TABLE IV
Serum lanosterol concentrations in hyper- and hyporesponsive subjects on low- and high-cholesterol diets

		Serum lanosterol, µmol/l		
		High-cholesterol diet	Low-cholesterol diet	Increase
Hyporesponders	1	0.36	0.67	0.31
	2	0.44	0.75	0.31
	3	0.44	0.67	0.23
	4	0.47	0.52	0.05
Hyperresponders	1	0.44	0.52	0.08
	2	0.39	0.47	0.08

The 6 subjects received a controlled high-cholesterol diet (67 mg of cholesterol per MJ; average intake was 697 ± 148 mg per day) for 4 weeks, followed by a low-cholesterol diet (10 mg cholesterol per MJ; 109 ± 25 mg of cholesterol per day) for 4 weeks. Cholesterol was the only dietary variable (16). Lanosterol was measured in pools of four serum samples per diet period per subject.

cholesterol synthesis on the high-cholesterol diet could not be calculated from the sterol balance data, as their balances (steroid excretion minus intake) were negative. This implies that the body accumulated cholesterol during this period.

In studies with rhesus monkeys (26), cholesterol biosynthesis was assessed by feeding triparanol, a drug that blocks the conversion of desmosterol into cholesterol, and then determining plasma desmosterol levels. The rate of accumulation of plasma desmosterol, which is a measure of cholesterol biosynthetic rate, was 50% greater in hypo- than in hyperresponders on a low-cholesterol diet. The addition of cholesterol to the diet caused a decrease in desmosterol accumulation in all monkeys, the decrease being 25% greater in the hypo- than hyperresponders (Table V).

Table IV also shows that in our own experiment serum lanosterol on the low-cholesterol diet was three to four-fold higher in the four hyporesponders than in the two hyperresponders. This indicates that hyporesponders have higher basal rates of whole-body cholesterol synthesis than hyperresponders. This is supported by data from one of our controlled dietary trials, where we found that whole-body cholesterol synthesis, measured as the cholesterol balance, was negatively associated ($r=-0.44$, $n=32$, $P<0.05$) with the responsiveness of serum cholesterol to dietary cholesterol. Thus the rate of endogenous cholesterol synthesis is higher in hypo- than hyperresponders. This could be explained by a lower efficiency of cholesterol absorption in the hyporesponders as has been observed in monkeys (6, 20, 21). If cholesterol absorption is lower, then the rate of body cholesterol synthesis must be higher because less cholesterol will reach the tissues from the gut, and synthesis will be less depressed (29).

TABLE V
Plasma desmosterol accumulation following triparanol administration to hypo- and hyperresponsive rhesus monkeys

	Plasma desmosterol accumulation, mg/dl plasma/day		
	Low-cholesterol diet	High-cholesterol diet	Decrease
Hyporesponders (n=5)	3.3 ± 0.2	1.4 ± 0.2	1.9
Hyperresponders (n=6)	2.2 ± 0.4	0.7 ± 0.1	1.5

Results expressed as means ± SE. Plasma cholesterol levels (mean ± SE) on the low-cholesterol diet were 2.8 ± 0.2 and 3.6 ± 0.2 mmol/l for the hypo- and hyperresponders; on the high-cholesterol diet these values were 3.8 ± 0.3 and 6.1 ± 0.4 mmol/l, respectively. Data taken from Bhattacharyya and Eggen (26).

The increase in serum cholesterol after cholesterol feeding of humans is due mostly to an increase in low density lipoprotein (LDL) cholesterol concentration. Why does dietary cholesterol cause an increase in LDL cholesterol in hyperresponders, but not or less so in hyporesponders? Upon an increase in cholesterol consumption more dietary cholesterol carried by the chylomicron remnants could enter the livers of hyper- than hyporesponders. The liver seems to be very efficient at removing chylomicron remnants from the plasma. However, the liver responds to excessive uptake of cholesterol with at least two mechanisms: suppression of endogenous cholesterol synthesis and increased secretion of cholesterol into the blood. If there is a lack of inhibition of cholesterol synthesis in hyperresponders as outlined above, then more cholesterol could be secreted. The increased output of cholesterol by the liver would explain the observed (27) increase in LDL production after cholesterol feeding. LDL may be secreted as such into the plasma from the liver, but in essence it appears initially as its precursors very-low density (VLDL) and intermediate density (IDL) lipoproteins. Nestel and Billington (28) have in fact shown that in man cholesterol feeding caused an increase in IDL-apo B production, and that this increase was directly correlated with the rise in serum cholesterol. Thus, hyperresponders may have increased rates of LDL cholesterol production after cholesterol feeding, and this may explain the elevated concentrations of LDL cholesterol in hyperresponders. Subsequently, the number of LDL receptors will decrease through down regulation (29), as shown in blood mononuclear cells (27, 30). As a result the receptor-mediated fractional clearance of LDL decreases (27) but the absolute amount of LDL cholesterol delivered to the cells by the receptor pathway increases somewhat because the concentration of substrate (LDL) is increased (27). The rise in LDL production will also increase LDL clearance by the receptor-independent scavenger pathway (27). In this way a new equilibrium is reached in which LDL production again equals LDL catabolism.

Mistry et al. (23) have suggested that hyperresponsiveness is explained by a reduced number of LDL receptors. These workers have demonstrated that

human hyperresponders to dietary cholesterol have a lower maximal capacity for LDL receptor activity in blood mononuclear cells than hyporesponders. The increment in plasma cholesterol concentrations after egg-yolk feeding was negatively associated with the LDL receptor activity measured before the dietary challenge in derepressed blood mononuclear cells ($r=-0.74$; $n=18$; $P<0.001$). This suggests that the maximally attainable rate of receptor-mediated catabolism is lower in hyperresponders. A low capacity of the LDL receptor pathway by itself probably does not cause increased sensitivity to dietary cholesterol. Patients with familial hypercholesterolemia, who have drastically reduced numbers of LDL receptors in all tissues, have been shown to produce cholesterolemic responses to dietary cholesterol which are similar to those of healthy subjects (31-33). The key question really is whether there is a difference between hypo- and hyperresponders in the degree of suppression of hepatic LDL receptor activity after cholesterol feeding. At present, this question cannot be answered.

CONCLUSION

We have presented evidence that persons exist with a consistently high (hyperresponders) or low (hyporesponders) response of the concentration of serum cholesterol to a change in diet. This phenomenon may have implications for counseling subjects who attempt to lower their serum cholesterol by diet. However, identification of true hyper- and hyporesponders is greatly hampered by spontaneous, diet-independent within-person fluctuations of the level of serum cholesterol. An improved understanding of the mechanism of hyper- and hyporesponsiveness would help in developing a test to discriminate hyper- from hyporesponders. The use of genetically defined animals with different sensitivity to diet may be of great importance in this respect. As yet, monitoring a person's response to diet should be based on relatively large numbers of serum cholesterol determinations.

ACKNOWLEDGEMENTS

Part of this work was supported by the Netherlands Heart Foundation, grant no. 31.013, and an established investigatorship to M.B.K. We thank I. Zaalmink for typing the manuscript.

REFERENCES

1. Van Zutphen, L.F.M. and Fox, R.R. Strain differences in response to dietary cholesterol by JAX rabbits: correlation with esterase patterns. Atherosclerosis 28, 435 (1977).
2. Van Zutphen, L.F.M. and Den Bieman, M.G.C.W. Cholesterol response in inbred strains of rats, Rattus norvegicus. J. Nutr. 111, 1833 (1981).
3. Beynen, A.C., Katan, M.B. and Van Zutphen, L.F.M. Strain differences in the response of serum cholesterol to diet in inbred rabbits, rats and mice. In: Cholesterol Metabolism in Health and Disease: Studies in the Netherlands, A.C. Beynen et al. (eds) Ponsen & Looijen, Wageningen, p. 158 (1985).
4. Wagner, W.B. and Clarkson, T.B. Mechanisms of the genetic control of plasma cholesterol in selected lines of Show Racer pigeons. Proc. Soc. Exp. Biol. Med. 145, 1050 (1974).

5. Clarkson, T.B., Lofland, H.B., Bullock, B.C. and Goodman, H.O. Genetic control of plasma cholesterol. Studies on squirrel monkeys. Arch. Pathol. 92, 37 (1971).
6. Eggen, D.A. Cholesterol metabolism in groups of rhesus monkeys with high or low response to an atherogenic diet. J. Lipid Res. 17, 663 (1976).
7. Malinow, M.R. Important considerations for nonhuman primate models of diet-induced atherosclerosis. In: Primates in Nutritional Research, K.C. Hayes (ed) Academic Press, New York, p. 199 (1979).
8. McGill Jr., H.C. The relationship of dietary cholesterol to serum cholesterol concentration and to atherosclerosis in man. Am. J. Clin. Nutr. 32, 2664 (1979).
9. Connor, W.E. and Connor, S.L. The key role of nutritional factors in the prevention of coronary heart disease. Prev. Med. 1, 49 (1972).
10. Reiser, R. Oversimplification of diet: coronary heart disease relationships and exaggerated diet recommendations. Am. J. Clin. Nutr. 31, 865 (1978).
11. Messinger, W.J., Porosowska, Y. and Steele, J.M. Effect of feeding egg yolk and cholesterol on serum cholesterol levels. Arch. Intern. Med. 86, 189 (1950).
12. Katan, M.B. and Beynen, A.C. Hyper-response to dietary cholesterol in man. Lancet 1, 1213 (1983).
13. Keys, A. Blood lipids in man: a brief review. J. Am. Diet. Ass. 51, 508 (1967).
14. Katan, M.B., Beynen, A.C., De Vries, J.H.M. and Nobels, A. Existence of consistent hyper- and hyporesponders to dietary cholesterol in man. Am. J. Epidemiol. in press.
15. Bronsgeest-Schoute, D.C., Hermus, R.J.J., Dallinga-Thie, G.M. and Hautvast, J.G.A.J. Dependence of the effects of dietary cholesterol and experimental conditions on serum lipids in man. III. The effect on serum cholesterol of removal of eggs from the diet of free-living habitually egg-eating people. Am. J. Clin. Nutr. 32, 2193 (1979).
16. Beynen, A.C. and Katan, M.B. Reproducibility of the variations between humans in the response of serum cholesterol to cessation of egg consumption. Atherosclerosis 57, 19 (1985).
17. Quintão, E., Grundy, S.M. and Ahrens Jr., E.H. Effects of dietary cholesterol on the regulation of total body cholesterol in man. J. Lipid Res. 12, 233 (1971).
18. Nestel, P.J. and Poyser, A. Changes in cholesterol synthesis and excretion when cholesterol intake is increased. Metabolism 25, 1591 (1976).
19. Connor, W.E. and Lin, D.S. The intestinal absorption of dietary cholesterol by hypercholesterolemic (type II) and normocholesterolemic humans. J. Clin. Invest. 53, 1062 (1974).
20. Bhattacharyya, A.K. and Eggen, D.A. Mechanism of the variability in plasma cholesterol response to cholesterol feeding in rhesus monkeys. Artery 11, 306 (1983).
21. St. Clair, R.W., Wood, L.L. and Clarkson, T.B. Effect of sucrose polyester on plasma lipids and cholesterol absorption in African green monkeys with variable hypercholesterolemic response. Metabolism 30, 176 (1981).
22. Beynen, A.C., Katan, M.B. and Van Zutphen, L.F.M. Hypo- and hyperresponders: Individual differences in the response of serum cholesterol concentration to changes in diet. Adv. Lipid Res. in press.

23. Mistry, P., Miller, N.E., Laker, M., Hazzard, W.R. and Lewis, B. Individual variations in the effects of dietary cholesterol on plasma lipoproteins and cellular cholesterol homeostasis in man. J. Clin. Invest. 67, 493 (1981).
24. Miettinen, T.A. Detection of changes in human cholesterol metabolism. Ann. Clin. Res. 2, 300 (1970).
25. Maranhão, R.C. and Quintão, E.C.R. Long term steroid metabolism balance studies in subjects on cholesterol-free and cholesterol-rich diets: comparison between normal and hypercholesterolemic individuals. J. Lipid Res. 24, 167 (1983).
26. Bhattacharyya, A.K. and Eggen, D.A. Feedback regulation of cholesterol biosynthesis in rhesus monkeys with variable hypercholesterolemic response to dietary cholesterol. J. Lipid Res. 22, 16 (1981).
27. Packard, C.J., McKinney, L., Carr, K. and Shepherd, J. Cholesterol feeding increases low density lipoprotein synthesis. J. Clin. Invest. 72, 45 (1983).
28. Nestel, P.J. and Billington, T. Increased transport of intermediate density lipoprotein (IDL) with cholesterol loading. Metabolism 32, 320 (1983).
29. Brown, M.S. and Goldstein, J.L. Receptor-mediated control of cholesterol metabolism. Science 191, 150 (1976).
30. Applebaum-Bowden, D., Haffner, S.M., Hartsook, E., Luk, K.H., Albers, J.J. and Hazzard, W.R. Down-regulation of the low-density lipoprotein receptor by dietary cholesterol. Am. J. Clin. Nutr. 39, 360 (1984).
31. Martin, G.M. and Nestel, P. Change in cholesterol metabolism with dietary cholesterol in children with familial hypercholesterolaemia. Clin. Sci. 56, 377 (1979).
32. Connor, W.E. and Jagannathan, S.N. The production of hyperbetalipoproteinemia and hypercholesterolemia by dietary cholesterol in normal, type II and type IV subjects. Ann. Intern. Med. 78, 820 (1973).
33. Cole, T.G., Pfleger, B., Hitchins, O. and Schonfeld, G. Effects of high cholesterol high fat diet on plasma lipoproteins in familial hypercholesterolemia. Metabolism 34, 486 (1985).