Lipid metabolism and its pathology. M.J. Halpern, editor.


# INDIVIDUAL DIFFERENCES IN THE CHOLESTEROLEMIC RESPONSE TO CHANGE IN DIET

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## INTRODUCTION

The addition of cholesterol to the diet of random-bred rabbits elicits a rise of serum cholesterol, but there are marked inter-individual differences in the extent of the response (Fig. 1). Certain animals show only small increases in the level of serum cholesterol (hyporesponders), whereas others develop high degrees of hypercholesterolemia (hyperresponders). In a study with inbred strains of rabbits the genetic basis of hypo- and hyperresponsiveness to diet has been clearly demonstrated (Fig. 2). The phenomenon of hypo- and hyperresponsiveness

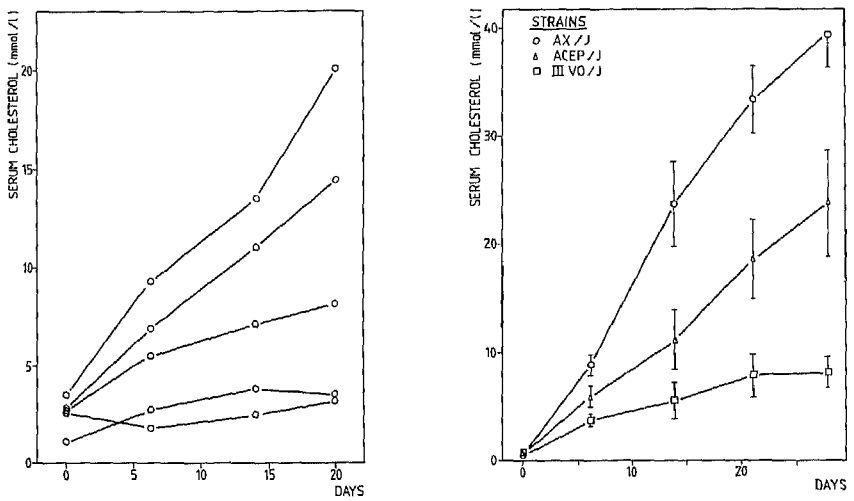



*Fig. 1. Effect of dietary cholesterol (0.2%, w/w) on serum cholesterol levels in individual, random-bred New Zealand White rabbits. Up until day 0 of the experiment the rabbits were fed a cholesterol-free diet. In this experiment cholesterol was the only dietary variable.*

*Fig. 2. Effect of dietary cholesterol (0.5%, w/w) on plasma cholesterol concentrations in three inbred strains of rabbits. Results are expressed as means ± SE for 5 animals per strain. Day 0 levels are pre-experimental values. Based on data taken from Van Zutphen and Fox (1).*

has also been established in inbred strains of rats (2) and pigeons (3).

If the individual variation in cholesterolemic response to dietary cholesterol is a general phenomenon, and if it is genetically determined, then the response

in any given individual should be stable and reproducible from one experiment to another, provided that the experimental conditions are standardized. Indeed, reproducibility of the differential response in individual squirrel monkeys has been demonstrated (4). Figure 3 illustrates that animals hypo- or hyperresponsive to fortification of the diet with cholesterol showed similar responses after a second challenge six months later. Thus the response in these primates seems to be a characteristic of the individual animal. However, when we tested human subjects twice, it was found that a subject hyperresponsive to the addition of six egg yolks (equivalent to about 1500 mg of cholesterol) per day to the diet in one experiment, may appear hyporesponsive in the second experiment and vice versa (Fig. 4). Similar data were published by Messinger and colleagues in 1950 (7). This suggests that the frequently observed (8) differences in response to dietary cholesterol in humans could be due to random fluctuations. Indeed, it is

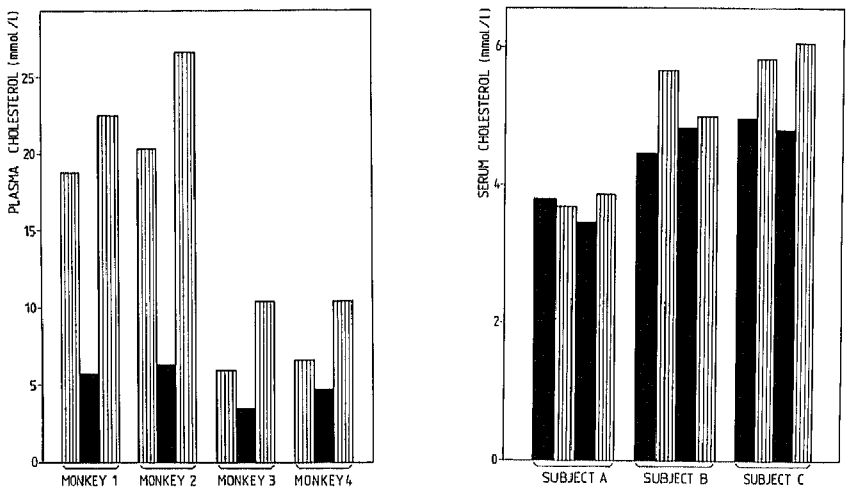



*Fig. 3. Plasma cholesterol levels in four male squirrel monkeys fed a cholesterol-free diet (closed bars) or a diet with 0.5% (w/w) cholesterol (hatched bars). Cholesterol was removed from the diet for a six-month period. Based on data taken from Clarkson et al. (4).*

*Fig. 4. Baseline cholesterol levels (closed bars) and levels after daily consumption of six egg yolks for 10 days (hatched bars) in three healthy subjects. This study was repeated with the same subjects one year later. Based on data taken from references 5 and 6.*

known that diet-independent, so-called "spontaneous" fluctuations in serum cholesterol concentrations in man can be as high as 20% (9). These fluctuations are of the same order of magnitude as the commonly observed response to dietary cholesterol loads. Thus the existence of human hypo- and hyperresponders remains

uncertain.

HUMAN HYPO- AND HYPERRESPONDERS DO EXIST

We have carried out three controlled dietary trials with a large number of the same subjects in order to address the question whether individuals exist with a consistently high or low serum cholesterol response to dietary cholesterol. In each trial the healthy volunteers consumed a low-cholesterol diet (about 120 mg of cholesterol/day) and a high-cholesterol diet (about 650 mg/day in the first and second experiment and about 1000 mg/day in the third trial), the cholesterol component of the diets being the only variable. The extra cholesterol was provided by egg yolk. Seventeen putative hyper- and 15 putative hyporesponding subjects with mean increases of 19 and 0%, respectively, were selected in the first trial and participated in the second and third experiment. Although the response in each subject was only partly reproducible, the selected hyperresponders showed significantly higher serum cholesterol responses in the second and third trial than did the putative hyporesponders (Table 1). Standardized regression coefficients for individual responses in two experiments ranged from 0.34 to 0.53 (n = 32).

TABLE 1

EFFECT OF EGG-YOLK CHOLESTEROL ON SERUM CHOLESTEROL IN THREE CONTROLLED TRIALS WITH THE SAME SUBJECTS

| | Change in serum cholesterol (mmol/l) | |
|---|---|---|
| | Hyporesponders (n = 15) | Hyperresponders (n = 17) |
| Selection trial | -0.01 ± 0.21 | +0.96 ± 0.27 |
| First reproducibility trial | +0.06 ± 0.35 | +0.28 ± 0.38* |
| Second reproducibility trial | +0.47 ± 0.26 | +0.82 ± 0.35** |

*Results are expressed as means ± SD. Change significantly different from that in the hyporesponders (one-tailed Student's t test): *, P < 0.05; **, P < 0.005. Based on data published by Katan and Beynen (5).*

Thus it appears from this work that at least part of the cholesterolemic response to dietary cholesterol in man is individually determined. 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. In our studies in which dietary cholesterol was the only variable, we calculated that the within-person error

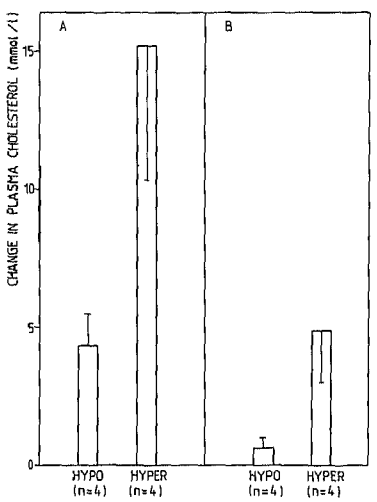
variance was responsible for about 25% of the observed variance in response between subjects. This was found in spite of the fact that we used 12 independent blood samples to determine a person's response to a change in diet. Thus the within-person variation inflates the between-person variation in serum cholesterol response to dietary cholesterol. In other words, the response in an individual in one experiment contains a large error term. This term can only be reduced by doing a large number of serum cholesterol measurements, before and after the dietary challenge, and even then the observed response should be interpreted with caution.

## RESPONSIVENESS TO DIETARY CHOLESTEROL AND TO TYPE OF FAT

In humans the nature of the fat in the diet is more important as a determinant of serum cholesterol concentration than the amount of cholesterol. Thus it seemed relevant to know whether hyperresponders to dietary cholesterol are also hyperresponsive to saturated fatty acids. Such information may also provide clues to the mechanisms underlying the individual variation in the cholesterolemic response to dietary cholesterol.

We have used male rabbits from two fully inbred strains which are hypo- (IIIVO/Ju) or hyperresponsive (AX/Ju) to dietary cholesterol (Fig. 2) and measured the response of their plasma cholesterol to saturated fat (coconut fat) versus polyunsaturated fat (corn oil). Cholesterol-free, semipurified diets were used, and the fat source was the only dietary variable. Figure 5 documents that the replacement of corn oil by coconut fat elicited a significantly higher response of plasma cholesterol in hyper- than in the hyporesponsive rabbits. Thus in these rabbit strains hypo- and hyperresponsiveness to dietary cholesterol and to the type of fatty acids coincide.

Twenty three human subjects who participated in the three controlled trials on the effect of dietary cholesterol (cf. Table 1) were also tested for their response to saturated versus polyunsaturated fatty acids. In this experiment cholesterol intake was kept constant at an average of 41 mg per MJ, but the energy percentage of dietary polyunsaturated fatty acids was kept at 21% for the first 3 and then changed to 5% for the next 3 weeks; the polyunsaturated : saturated fatty acid ratios were 1.91 and 0.22, respectively. The response of serum cholesterol to the change in dietary fatty acid composition in this experiment was compared with the mean response in the three cholesterol experiments combined, which is our best estimate of each person's sensitivity to dietary cholesterol. Figure 6 shows that after dividing the subjects into two groups according to their response to dietary cholesterol, a similar difference in sensitivity to diet remains when the nature of the fat is the variable. This indicates that in humans hyperresponsiveness to dietary cholesterol is associated with



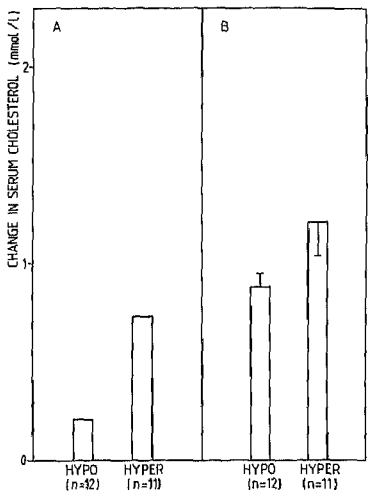




*Fig. 5. Plasma cholesterol responses to 0.3% (w/w) dietary cholesterol versus no cholesterol (panel A) and to coconut fat versus corn oil (panel B) in two inbred strains of rabbits. Results are expressed as means ± SE for 4 animals per strain; the data in panels A and B refer to the same animals.*

*Fig. 6. Serum cholesterol responses to dietary cholesterol (panel A) and to saturated versus polyunsaturated fatty acids (panel B) in healthy human volunteers. The response to dietary cholesterol is the mean of three experiments (cf. Table 1). Subjects were grouped according to their response to dietary cholesterol: below the median ("hyporesponders") or above the median ("hyperresponders"). Results are given as means ± SE.*

hyperresponsiveness to saturated fat. It should be emphasized that spontaneous fluctuations of the level of serum cholesterol cause a relatively smaller error term in cholesterolemic response to dietary fat than the response to dietary cholesterol, as the absolute response to a change in dietary fatty acids is larger.

## 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.

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