N.E. Miller and G.J. Miller, editors
Clinical and Metabolic Aspects of High-density Lipoproteins

CHAPTER 5

Diet and HDL

MARTIJN B. KATAN*

Department of Human Nutrition, Agricultural University, De Dreijen 12, 6703 BC Wageningen, The Netherlands

1. Introduction

Diet is probably an important determinant of the concentration of high-density lipoprotein (HDL) cholesterol in plasma. This is especially so if alcohol consumption and energy balance are included in the definition of diet; but other dietary factors also affect HDL. This chapter reviews the major dietary influences on HDL. However, it should be pointed out that it is still uncertain whether increasing the HDL concentration by dietary means will decrease the risk of coronary heart disease. It is still conceivable that the apparent protection afforded by HDL is in reality due to some other underlying factor, and this unknown factor might not react to dietary change in the same way as the HDL cholesterol concentration. In addition, many dietary interventions that affect HDL also affect the concentrations of low-density (LDL) and very-low-density lipoprotein (VLDL). The reader should thus keep in mind that dietary changes that increase HDL levels are not necessarily beneficial, and those that decrease HDL levels are not necessarily deleterious.

Each section of this chapter starts with an introduction to the role of a particular dietary component in nutrition, and then goes on to discuss the effect of this component on the concentration of HDL cholesterol in plasma in humans. The final section presents an overall summary and an attempt to combine into a coherent model the various factors that affect the HDL concentration.

Influences on HDL are discussed here in terms of total HDL cholesterol, because information about dietary effects on apolipoproteins and other HDL components is still very incomplete. In principle, it would be important to differentiate between effects on HDL_2 and on HDL_3, because these subclasses of HDL have

*Established Investigator, Netherlands Heart Foundation.

different relations with the risk of atherosclerotic disease. In practice, when subclasses were measured in diet studies, changes were usually found in HDL_2 cholesterol, while HDL_3 cholesterol remained relatively constant. Thus, little information is lost by limiting the discussion to effects on total HDL cholesterol and ignoring effects on subclasses. The review is limited to studies of humans.

2. Alcohol

2.1. Introduction

Within a given population most persons have somewhat similar long-term average intakes of the various nutrients. Indeed, the differences between such long-term individual averages are often smaller than the day-to-day fluctuations of the intake within one individual (Keys, 1965; Beaton et al., 1979). Alcohol, however, is an exception in that some people drink while others do not drink at all, and in those who do drink the mean intake can vary greatly. Thus, in the North American populations studied in the Lipid Research Clinics prevalence study (Lipid Research Clinics, 1982), male drinkers on average admitted to a consumption of 40–50 g per day (as ethanol), and females 20–30 g per day; these figures represent a contribution to the daily energy intake of about 10%. In surveys of alcohol consumption under-reporting is the rule, and one may safely assume that true intakes were even higher (Kaelber and Mills, 1981). Thus, for many people alcohol is a major source of dietary energy.

2.2. Effect of alcohol on HDL levels

People who drink beer, wine or spirits have higher HDL levels than people who do not. A relationship between alcohol intake and serum HDL cholesterol concentration has been found very consistently in epidemiological surveys (Castelli et al., 1977; Ernst et al., 1980b; Hulley and Gordon, 1981; Arab et al., 1982); the increment is about 0.03–0.05 mmol/l for every 10 g of alcohol consumed per day. Alcoholics can have very high HDL cholesterol concentrations (Johansson and Medhus, 1974; Laporte et al., 1981; Ekman et al., 1981; Taskinen et al., 1982). Very low levels, however, have been reported in alcoholic liver disease (Sabesin, 1981). After alcohol withdrawal HDL decreases, and reaches normal levels in 1–4 weeks.

Controlled experiments show that there is a direct cause-and-effect relation between alcohol consumption and elevation of HDL: addition of 63 g (Berg and Johansson, 1973) or 75 g (Belfrage et al., 1977) of alcohol per day to the diet of student volunteers caused an increase of 25–30% in the concentration of alpha-lipoprotein in plasma, measured by electrophoresis. When alcohol was withdrawn, alpha-lipoprotein levels came down again, although slowly. HDL cholesterol was

not measured in these studies, but if one assumes that it changed in the same proportion as alpha-lipoprotein, then one can calculate that the increase was about 0.35 mmol/l, or about 0.05 mmol/l for each additional 10 g of alcohol per day. This is in good agreement with the epidemiological observations.

A more recent metabolic ward experiment of Glueck et al. (1980a) appeared to contradict these findings. These workers put seven college students on alcohol-free diets for 2 weeks, and then gave the subjects 15 g of alcohol (35 g of Vodka) per day for 1 week and 22.5 g/day for a further week. (In the paper the terms 'alcohol' and 'Vodka' are used interchangeably. However, 35 g of 100 proof Vodka contains only 15 g of alcohol.) No significant effect on HDL cholesterol was seen. However, over such a short period and with such a low dosage one could not expect much of an effect. Thus, this experiment does not contradict the results of Berg and Johansson (1973) and of Belfrage et al. (1977), which were obtained over longer periods and with higher intakes of alcohol. In addition, Glueck et al. (1980a) did not report how much alcohol the subjects were in the habit of consuming before the experiment. Even if they consumed only a moderate amount, the alcohol-free baseline period may have been too short to obtain stable new HDL levels.

2.3. Conclusions

The balance of the evidence suggests that every additional drink per day, corresponding with an extra alcohol intake of 10–15 g, will raise the serum HDL cholesterol concentration by about 0.04–0.07 mmol/l. On the other hand, alcohol-induced liver disease is associated with low HDL levels.

Excessive alcohol consumption not only causes liver disease, but also a host of other health-threatening conditions. Therefore, restraint should be exercised in encouraging alcohol consumption as a way to avoid heart disease.

3. Proportion of fat and carbohydrate

3.1. Introduction

Most populations derive on average 80–90% of their dietary energy from fats and carbohydrates. The remainder is made up by protein and alcohol. In poor populations complex carbohydrates are the main source of energy, but as affluence increases, consumption of starchy foods declines and the intake of meat, cheese and fat-rich processed food products goes up. As a result, most affluent populations derive about 40% of their energy from fat and another 40% from carbohydrates; half of the latter are sugars (mainly mono- and disaccharides) and the other half complex carbohydrates (mainly starch).

If both energy expenditure and body weight are held constant, then changes in carbohydrate consumption can only be achieved by reciprocal changes in fat

intake. Thus, 'low-fat' and 'high-carbohydrate' are two ways of describing the same diet, and it is very difficult to distinguish which of these two aspects is responsible for any observed effects on serum lipids.

3.2. Fat/carbohydrate ratio and HDL: controlled trials

Replacement of dietary fat by carbohydrate causes increased concentrations of triglyceride-rich lipoproteins, i.e., VLDL, in fasting serum (Ahrens et al., 1961). As noted by Levy et al. (1966) and confirmed by other investigators (Wilson and Lees, 1972; Blum et al., 1977; Brussaard et al., 1982; Kashyap et al., 1982), HDL concentrations go down on carbohydrate-rich diets in short-term experiments. Carbohydrate-induced hypertriglyceridaemia, however, appears to be a transient phenomenon, and tends to subside after several months on the high-carbohydrate diet (Antonis and Behrson, 1961); therefore, one might wonder whether the depression of HDL cholesterol is also a temporary matter. Several studies suggest that it is not. Table 1 summarizes these and other studies. The longest controlled trial on this subject is the classic study of Antonis and Behrson in South-African prisoners (Antonis and Behrson, 1961, 1962). This trial lasted 3 years, and consisted of an initial period during which the diet provided only 15% of energy as fat, five periods in which 25% of energy as carbohydrates in the initial diet was replaced by various types of fat, and finally the low-fat diet again. For the purpose of Table 1 the results of all high-fat diets have been combined, and so have the results of the low-fat diet periods. The high-fat diets all caused higher HDL levels than the low-fat diets. During the last high-fat period the mean HDL cholesterol of all subjects combined was 1.43 mmol/l. During the first 4 months of the low-fat period that followed, carbohydrate-induced hypertriglyceridaemia reached a maximum, and HDL cholesterol fell to an average of 1.18 mmol/l. During the final part of the low-fat period, triglyceride levels became fairly normal again, but HDL cholesterol remained low, at 1.14 mmol/l. Thus, the depression of serum HDL cholesterol by the high-carbohydrate, low-fat diet appeared to be permanent, and independent of the transient rise in triglycerides.

This is confirmed by the results of other trials. Brussaard et al. (1982) found that replacement of polyunsaturated fat by starch caused a drop of HDL cholesterol in student volunteers which persisted for the full 13 weeks of the study. Brunner et al. (1979) studied Yemenite agricultural workers in Israel. Addition of butter, margarine and fatty meats to their habitual low-fat diet caused a permanent elevation of HDL cholesterol levels. The cholesterol content of the added foods may, of course, also have contributed to this rise (see section 5). As the LDL cholesterol concentration also increased, the percentage of total serum cholesterol in the high-density fraction remained constant.

Finally, Hulley et al. (1972) described 13 hypertriglyceridaemic men who had consumed the regular American Heart Association diet for 6 months and a high-

TABLE 1

Effect of exchanging fat and carbohydrate in the diet on HDL cholesterol concentrations in controlled trials on healthy subjects

Reference	Number of subjects	Fat content of the diets (% of energy)		Duration (weeks)		ΔHDL cholesterol, high-fat minus low-fat diet (mmol/l)	ΔHDL cholesterol per 10% of energy exchanged ((mmol/l)/10 energy %)
		High-fat diet	Low-fat diet	High-fat diet	Low-fat diet		
Antonis and Behrson (1961)[a]	32	40	15	85	71	0.20	0.08
Blum et al. (1977)	3	40	0	2	2–3	0.41	0.10
Brunner et al. (1979)	26	50	26[b]	30	habitual	0.24	0.10
Brussaard et al. (1980)	29	40	30	5	2.5	0.11	0.11
Brussaard et al. (1982)	17	31	21	2.5	13	0.15[c]	0.15
Kashyap et al. (1982)	9	65	15	3	3	0.23	0.05
All studies							
Range							0.05–0.15
Median							0.10

[a] HDL cholesterol values were calculated from Table III of Antonis and Behrson (1961), as total minus beta-cholesterol. The 'beta'-cholesterol had been determined as the manganese-heparin precipitate, which probably included the pre-beta cholesterol.
[b] The low-fat diet also contained less cholesterol.
[c] Corrected for the change in the concurrent control group.

fat, low-carbohydrate version of the same diet for another 6 months. In the low-carbohydrate diet sugars had been replaced, mostly by polyunsaturated and monounsaturated fatty acids. This diet resulted in a decrease in serum cholesterol and triglycerides, but an increase in the alpha (high-density) lipoprotein concentration.

The magnitude of the effect of the fat/carbohydrate ratio on HDL can be seen in Table 1. The last column of this table presents the mean change in HDL cholesterol concentration standardized for the amount of fat exchanged. Each 10% of energy exchanged caused a change in HDL cholesterol of 0.05–0.15 mmol/l, with little difference between short- and long-term trials. Thus, replacement of carbohydrate by fat raised HDL cholesterol concentrations in both short-term and long-term controlled experiments.

3.3. Fat/carbohydrate ratio and HDL: epidemiological studies

The experimental observations on the fat/carbohydrate ratio reported in the previous section fit remarkably well with epidemiological observations. Within populations, HDL cholesterol levels are inversely correlated with carbohydrate consumption (Ernst et al., 1980b; Arab et al., 1982). The correlation coefficients are low, but this may be due to the known large fluctuations in the composition of the daily menu of free-living subjects. As a result, many subjects will be misclassified as to their carbohydrate consumption, and the underlying relationship with HDL will be partly obscured (Keys, 1965; Beaton et al., 1979).

This problem can be circumvented by studying the mean values of groups of people with widely differing dietary habits. Knuiman et al. (1980) studied groups of school boys in 16 different countries, employing strict standardization of blood collection and analysis. They found that both total and HDL cholesterol were lower in boys in the less developed countries, and that the ratio of HDL cholesterol to total cholesterol was fairly constant over a 2-fold range of absolute concentrations of total cholesterol. Knuiman et al. suggested that a more Western type of diet, characterized by a high-fat intake, causes both higher HDL and total cholesterol concentrations.

This suggestion was tested in an in-depth follow-up study of large groups of school boys in Ghana, The Philippines, Italy, The Netherlands and Finland (Knuiman et al., 1983). As shown in Figure 1, there was a strong negative correlation between the serum HDL cholesterol concentration and the proportion of energy derived from carbohydrates, both for group means (solid circles) and for individual boys (open circles). The dietary differences were mostly due to complex carbohydrates. Multiple regression analysis showed that differences in intake of carbohydrates explained on average 29% of the differences in HDL cholesterol between countries. In addition, there was a small contribution of the body mass index to these differences. In the multiple regression model the regression coeffi-

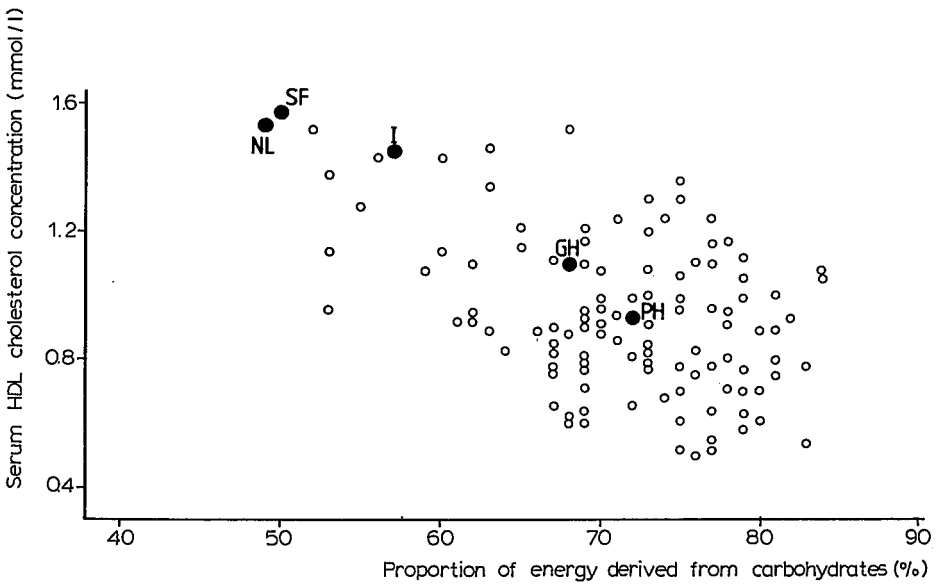

Figure 1. The relationship between the concentration of HDL cholesterol in serum and the proportion of energy (percent) from carbohydrate in young boys. ●, Mean values for Ghana (GH), The Philippines (PH), Italy (I), The Netherlands (NL) and Finland (SF). The Pearson correlation coefficient (r) was –0.98. O, Individual data for the Philippino boys (r = –0.40). Data taken from Knuiman et al. (1983), and supplemented with unpublished figures of Knuiman and West.

cient of HDL cholesterol on carbohydrate intake was −0.07 mmol/l per 10% of energy.

A very similar figure can be calculated from the results of an entirely different epidemiological survey. In the North-American Lipid Research Clinics prevalence study (Ernst et al., 1980b), the regression coefficients of HDL cholesterol on sucrose and on starch consumption combined yielded an overall value of 0.09 mmol/l for each 10% of energy. In the experiments described in the previous section this value ranged from 0.05 to 0.15 mmol/l, with a median of 0.10 mmol/l. The epidemiological and experimental studies are thus remarkably consistent.

In the studies of Knuiman et al. (1980, 1983) an advantage of studying young boys was the absence of confounding factors. Age and sex were constant; smoking, alcohol consumption, drug use and diabetes were negligible or absent; and the body mass index and physical activity were fairly similar between countries.

The effects of such confounders were obvious in groups of adult men studied by the same group (Knuiman et al., 1982); both HDL and total cholesterol were higher in men in affluent countries than in men in less-developed countries, but the relation between the two was weaker than in young boys. The authors suggested that differences in factors such as alcohol consumption, smoking, obesity, drug use

and physical activity cause differences in HDL cholesterol which obscure the effect of diet. Nevertheless, the general trend was still for the men in countries with a higher fat and lower carbohydrate consumption to have higher HDL cholesterol concentrations. It is noteworthy that the highest HDL cholesterol concentrations were found in middle-aged men in eastern Finland, a population that is well-known for its high risk of ischaemic heart disease. This illustrates that effects of diet on HDL should not be seen in isolation. Apparently, these high HDL levels are insufficient to protect this population against the harmful effects of the high LDL levels which accompany them.

3.4. Conclusions

Replacement of carbohydrates, either sugars or starch, by fat raises the HDL cholesterol concentration in controlled experiments. The negative relation between carbohydrate consumption and HDL is confirmed by epidemiological studies both within and between populations. Replacement of 10% of energy as fat by an equivalent amount of carbohydrate will lower HDL cholesterol by about 0.10 mmol/l. There is, however, no evidence that this increases the risk of coronary heart disease, because LDL is also lowered. Indeed, if one compares different populations, a low intake of fat, low values for LDL and HDL and low coronary heart disease incidence often go together.

4. Dietary fatty acid composition

4.1. Introduction

All dietary fats contain saturated, monounsaturated and polyunsaturated fatty acids in differing proportions. In the diet of North Americans saturated fatty acids provide about 15% of energy, monounsaturated fatty acids about 16% and polyunsaturated fatty acids about 7% (Lipid Research Clinics, 1982). Thus, the polyunsaturated/saturated (P/S) ratio is about 0.45. Although this ratio is a convenient short-hand notation, it is insufficient to predict the effect of dietary fatty acid composition on serum lipids, because it does not take into account the proportion of monounsaturated fatty acids. For instance, one can calculate from Keys' formula (Keys et al., 1965) that a diet containing olive oil, P/S ratio 0.6, will actually cause lower cholesterol levels than a diet containing chicken fat, P/S ratio 0.7, if all other nutrients are held constant. The reason is that olive oil has only 13.5 g of saturated fatty acids per 100 g while chicken fat has 30 g. Thus, the P/S ratio by itself gives insufficient information, and it is unfortunate that so many studies report only the P/S ratios of the various diets and not the separate fatty acids.

4.2. Fatty acids and HDL: controlled trials

In theory, the fatty acid composition of the diet can be changed without changing the intake of total fat or cholesterol. In practice, diets with a high polyunsaturate content usually contain less total fat and cholesterol than more saturated diets, because products with a high fat and cholesterol content, such as full-fat milk, cheese and meat, are eliminated. Several investigators have, however, studied the specific effects of fatty acids, using diets that differed in fatty acid composition but not in the content of total fat, cholesterol or other nutrients. Table 2 summarizes a number of such studies.

There is almost unanimous agreement that the concentration of LDL in serum decreases if saturated fatty acids in the diet are replaced by polyunsaturated fatty acids. There is less agreement about the effect of polyunsaturated fatty acids on HDL.

A reduction of HDL concentration by polyunsaturated fatty acids was reported by Shepherd et al. (1980). On a diet rich in safflower oil, with a P/S ratio of 4.0, HDL cholesterol was 0.23 mmol/l lower than on a diet with dairy products. What is strange about this study is that it actually consisted of two parts with dissimilar results. In the first four subjects (Shepherd et al., 1978) HDL cholesterol declined by 0.39 mmol/l, a very large change indeed. However, the second group of four men studied by the same protocol showed a decrease in HDL of only 0.08 mg/dl (Shepherd et al., 1980). The reason for this discrepancy is unclear.

Diets with a very high P/S ratio were also used in two studies employing liquid formula diets. According to Spritz and Mishkel (1969), the HDL cholesterol concentration was the same whether saturated or highly polyunsaturated fat was given. However, their findings are at variance with the more recent results of Vega et al. (1982), who did find a reduction of HDL cholesterol in a study of very similar design.

Thus, there are some indications that HDL is lowered by diets containing extreme amounts of polyunsaturated fatty acids. Such diets can be very useful in metabolic studies, but it is hazardous to extrapolate their effects to everyday situations. Indeed, as Table 2 shows, most studies suggest that with less extreme diets changes in the fatty acid composition have little or no influence on HDL cholesterol.

One of the earlier studies of this kind was that of Von Lossonczy et al. (1978), who fed diets rich in either mackerel or cheese to convent inhabitants. The fatty fish caused a fall in total serum cholesterol, which in view of its polyunsaturated fatty acid content was to be expected. More pertinent to this review was the slight but significant rise in HDL cholesterol on the fish diet.

Studies using other sources of fat confirmed that in a normal diet changes in the fatty acid composition will cause changes in LDL and VLDL concentrations but not in HDL. Thus, Schwandt et al. (1982) reported a 2 × 3 months cross-over

TABLE 2

Effect of the fatty acid composition of the diet on HDL cholesterol concentrations in controlled studies

Reference	Subjects		Diet type[a]; fat sources	P/S ratio		Δserum cholesterol, high-P/S minus low-P/S diet (mmol/l)		
	Number	Type		High-P/S diet	Low-P/S diet	Δtotal	ΔLDL	ΔHDL
Spritz and Mishkel (1969)	8	patients, vascular disease	liquid; coconut or butter vs. corn or safflower oil	5.5–10.7	0.1	–2.17	–1.26	0.00
Shepherd et al. (1978, 1980)	8	young men	solid; dairy products vs. safflower oil	4.0	0.3	–1.16	–0.78	–0.23
Von Lossonczy et al. (1978)	42	monks and nuns	solid; cheese vs. fatty fish	0.7	0.2	–0.41		+0.09
Vessby et al. (1980a)	7	patients, type IIa	solid; mixed	2.0	0.2	–1.16	–0.62	–0.18
	5	patients, type IIb	solid: mixed	2.0	0.2	–1.38	–0.85	–0.05
	18	patients, type IV	solid; mixed	2.0	0.2	–0.70	–0.32	0.00
Brussaard et al. (1980)	29	students	solid; mixed	1.7	0.2	–0.36	–0.18	–0.02
Schwandt et al. (1982)	30	prisoners	solid; mixed	1.0	0.3	–0.59	–0.52	0.00
Laine et al. (1982)	24	students	solid; palm vs. corn or soy oil	2.0	0.2	–0.67	–0.71	0.00
Vega et al. (1982)	8	hyperchol-esterolaemic patients	liquid; lard vs. safflower oil	8.0[b]	0.3[b]	–2.15	–1.65	–0.20

[a] 'Liquid' denotes liquid formula diets and 'solid' mixed solid diets. In the various studies the percentage of energy provided by fat ranged from 35 to 45% and the daily cholesterol intake from 0 to about 700 mg/day.

[b] Calculated from United States Department of Agriculture (1979).

study in 30 male prisoners. They received diets which had P/S ratios of either 0.3 or 1.0, but were almost identical in all other respects. On the high P/S diet the LDL cholesterol concentration in serum fell by 14%, but HDL cholesterol concentrations were unaffected. Vessby et al. (1980a) fed 30 hyperlipoproteinaemic patients, who were hospitalized in a metabolic ward, first a diet high in saturated and then a diet high in polyunsaturated fatty acids. HDL cholesterol decreased by 0.18 mmol/1 in patients with type IIa hyperlipoproteinaemia but showed little or no change in patients with type IIb or type IV hyperlipoproteinaemia. Reductions in total cholesterol ranged from 9 to 15%. A difference of 10% in total cholesterol with no change in HDL was reported by Brussaard et al. (1980) for students given diets with different P/S ratios. The absolute effects on total and LDL cholesterol were much smaller in these healthy young people, probably because the initial levels were less than half those in the hyperlipoproteinaemic patients. Finally, Laine et al. (1982), in a carefully designed 10-week controlled trial, compared the effects of vegetable oils and fats of various fatty acid composition on serum lipoproteins in students. The corn oil and soy oil diets caused an average reduction in LDL cholesterol of about 24% compared with the palm oil diet, which had a P/S ratio of 0.2. HDL cholesterol was again unchanged.

4.3. Conclusions

Taken together, these studies suggest that in normal mixed diets replacement of saturated by polyunsaturated fatty acids to the extent recommended for the prevention of coronary heart disease (Grundy et al., 1982) will lower total and LDL cholesterol concentrations in plasma but will leave HDL cholesterol levels essentially unchanged.

5. Dietary cholesterol

5.1. Introduction

A large proportion of cholesterol in the diet is provided by dairy products, meat and other fat-rich foods of animal origin, and as a result the effects of dietary cholesterol are difficult to disentangle from the effects of dietary fat. Therefore, many epidemiological studies give no clue to the specific effects of dietary cholesterol on serum HDL, and we have to depend on clinical trials for this information. Most of these trials have lasted no more than a few weeks, and almost all of them have employed eggs or egg yolk as the source of dietary cholesterol. This causes some complications, because egg yolk contains a considerable amount of fat. If, for instance, a subject with an energy intake of 10 MJ per day (2400 kcal/day), 40% of it as fat and 40% as carbohydrate, adds six egg yolks to his diet and leaves out a corresponding amount of carbohydrate, then his fat intake will increase to 53% of

energy and his carbohydrate intake diminish to 24% of energy. Thus, in studies of the specific effect of cholesterol, the fat, protein and carbohydrate intake ought to be balanced between the control and the test diet.

5.2. Dietary cholesterol and HDL: controlled trials

In properly designed trials egg yolk cholesterol usually causes an increase in serum cholesterol concentration (Glueck and Connor, 1978; Liebman, 1982), although exceptions are known (Ginsberg et al., 1981). When separate serum lipoprotein fractions were measured, increases were usually found in both LDL and HDL cholesterol. Thus, Mistry et al. (1981) added three or six egg yolks to the habitual diet of students and laboratory staff members, and measured plasma lipoproteins by sequential ultracentrifugation. They found that the egg yolks caused an increase in HDL cholesterol concentration of 0.16–0.21 mmol/l, while total cholesterol rose by 13–15%.

Raymond et al. (1977), in a carefully controlled metabolic ward study, fed diets that provided either less than 50 mg cholesterol per day or 1000 mg per day to four subjects, and found a rise in HDL cholesterol of 0.16–0.21 mmol/l, concomitant with a very large rise in LDL cholesterol. In a similar study in Tarahumara Indians, a people habituated to a low-cholesterol diet, 1000 mg of cholesterol per day caused HDL cholesterol levels to increase by 0.10 mmol/l (McMurry et al., 1982).

Schonfeld et al. (1982) fed controlled diets containing 300, 1050 or 1800 mg of cholesterol as egg yolks to student volunteers, and measured HDL cholesterol in serum after precipitation of other lipoproteins with the manganese-heparin reagent. HDL cholesterol increased by 0.08–0.16 mmol/l on the high-cholesterol diets.

Nestel et al. (1982) observed a mean increase of 0.18 mmol/l in the concentration of HDL cholesterol in a metabolic ward study when an extra 1500 mg of cholesterol/day was given as egg yolks; the egg yolk fatty acids were balanced by a mix of fats and oils, such as peanut butter (Nestel, P.J., personal communication). Stasse-Wolthuis et al. (1979), in a controlled experiment on dietary fibre, found that HDL cholesterol levels were on average 0.10 mmol/l higher in students receiving high-cholesterol diets than in subjects on low-cholesterol diets of otherwise similar composition.

Finally, Katan et al. (1984) found a slight but significant increase of 0.06 mmol/l in HDL cholesterol when subjects in a controlled study were switched from a diet providing 110 mg cholesterol/day to one providing 610 mg cholesterol/day, other nutrients being kept constant.

Thus, an increase in HDL cholesterol concentrations is seen consistently after feeding of cholesterol as egg yolk.

One might wonder whether the extra HDL has the same composition as the HDL that is normally present, because Mahley and coworkers (1975) have shown

that in animals cholesterol feeding causes the appearance of HDL_c, an abnormal form of HDL that is rich in cholesterol and apolipoprotein E. They have also presented indirect evidence that a similar particle is present in the serum of cholesterol-fed human volunteers (Mahley et al., 1978). On the other hand, several groups (Stasse-Wolthuis et al., 1979; Nestel et al., 1982; Schonfeld et al., 1982; Katan et al., 1984) have reported an increase in HDL cholesterol determined with the manganese-heparin reagent. Since this method may be specific for HDL particles which do not contain apolipoprotein E, the nature of the HDL formed upon egg yolk feeding awaits clarification.

5.3. Conclusions

Feeding of cholesterol as egg yolk increases the plasma cholesterol concentration, and part of this increase is due to an increase in the concentration of HDL cholesterol. It is unclear to what extent this reflects an increased concentration of HDL_c.

6. Protein, vitamins, minerals and lecithin

6.1. Protein

Of the four macronutrients (protein, fat, carbohydrate and alcohol), protein is the most difficult to study in isolation, because in human foodstuffs protein rarely occurs alone. Thus, products high in plant protein content are usually lower in saturated fatty acids and cholesterol and higher in dietary fibre than products containing animal protein. Van Raaij et al. (1981, 1982) managed to circumvent this problem by incorporating highly purified casein and soy protein into a range of special foodstuffs. These were then fed to large groups of volunteers under controlled conditions. In both studies, the soy protein diet caused slightly, but significantly, higher HDL cholesterol and lower LDL cholesterol levels than the casein diet. This interesting observation awaits confirmation from other workers.

6.2. Vitamins and minerals

The effects of vitamins and minerals on HDL in humans have been studied less extensively than those of macronutrients, and reliable information is scarce. This situation may change, however, because of the increased interest in trace element metabolism in man. It has been reported, for instance, that chromium supplementation will increase HDL cholesterol concentrations in adult men (Riales and Albrink, 1981). Because consistent information on humans is still limited, the subject is not discussed further here.

6.3. Lecithin

Lecithin is the trivial name for a class of phospholipids referred to as phosphatidylcholines. It has the structure of a triglyceride in which one fatty acid moiety has been replaced by phosphocholine. Phosphatidylcholine forms an important component of biomembranes and of the outer, hydrophilic coat of lipoproteins. It is synthesized in the human body, and generally is not considered an essential nutrient.

Although lecithin was originally isolated from egg yolk, at present soy beans are the main source. Commercial preparations vary widely in composition, and some of them actually contain very little true lecithin, i.e., phosphatidylcholine.

Lecithin preparations are widely consumed for health reasons. They are thought to have favourable effects on cholesterol metabolism and other processes (Peeters, 1976), but properly controlled trials of their action in humans are rare. A few such trials are discussed below.

Ter Welle et al. (1974) tested a soya lecithin preparation, fortified with vitamins, in 12 outpatients with severe hypercholesterolaemia. The patients received 1.2 g of the lecithin preparation per day for 4 months and then 2.4 g/day for another 4 months. Compared with pre- and post-experimental values, there was a slight decrease of total serum cholesterol during the lecithin regime, which the authors considered clinically irrelevant. Most of the decrease in cholesterol appeared to be in the LDL fraction.

Childs et al. (1981) compared the action of 36 g per day of a crude soya phospholipid product with an equivalent amount of corn oil in outpatients. Relative to the corn oil, the phospholipid product caused an increase of 0.10 mmol/l in HDL cholesterol and of 0.13 in LDL cholesterol in 12 normal subjects. In six hypercholesterolaemic patients, the respective figures were 0.03 and 0.52 mmol/l.

Greten et al. (1980) compared the effect of 18 g of lecithin with an equivalent amount of soya oil in patients in a metabolic ward. LDL cholesterol concentrations were slightly lower and HDL cholesterol concentrations slightly higher on lecithin, but the effects were not significant. However, lecithin did cause a remarkable increase in the faecal excretion of cholesterol and its bacterial metabolites. This agrees with a study of Beil and Grundy (1980), who found that infusion of lecithin into the duodenum in humans markedly decreased the absorption of cholesterol in the upper part of the small intestine.

There is, thus, some evidence that large amounts of lecithin may interfere with cholesterol absorption. However, there is at present no proof that oral lecithin in the amounts usually consumed has a specific beneficial effect on plasma lipoprotein concentrations.

7. Energy intake and body mass

7.1. Introduction

Food intake, energy expenditure and body fatness are three terms of the same equation. When energy intake exceeds expenditure, the excess is added to the stores of the body as fat. A fat person has, therefore, at some time in his past expended less energy than he has consumed.

Obese people have lower serum HDL cholesterol concentrations than lean persons (Carlson and Ericsson, 1975; Rhoads et al., 1976; Albrink et al., 1980; Glueck et al., 1980b). The association between HDL cholesterol and body mass indices remains significant after correction for other known determinants of HDL, such as smoking, alcohol intake, age and hormone use (Heiss et al., 1980; see also section 8.4.). However, convincing evidence that excess body fat by itself is a cause of low HDL concentrations can only be obtained from controlled experiments. This question can be tackled by increasing energy expenditure or reducing energy intake in obese patients and comparing HDL values after weight loss with pre-experimental concentrations. An untreated control group is desirable in such a trial, but unfortunately is often omitted. (A cross-back design, employing weight reduction followed by weight gain, would be even more convincing, but is untenable for ethical reasons.)

As discussed elsewhere in this volume, there is indeed evidence that an increase in energy expenditure will raise the plasma HDL cholesterol concentration. Trials in which reduction of body mass was achieved primarily by reducing food intake have also been performed, but the results are often difficult to interpret. First of all, it is very difficult for a fat person to reach and maintain a stable lower body weight, and those who manage to reduce may not be at all representative of obese people as a group. Secondly, reaching a new equilibrium situation takes longer than is feasible for most metabolic ward studies, and therefore one has to resort to designs employing outpatients. As a result, food intake, energy expenditure, smoking and alcohol consumption can no longer be controlled precisely, and interpretation of changes in serum lipoproteins becomes difficult. Thirdly, in studying the specific effect of caloric restriction on HDL it would be preferable if the composition of the weight-reducing diet and the control or pre-experimental diet were the same, with only the amount of food being restricted. However, the usual weight-reducing diets involve rather drastic changes in the intake of fat, cholesterol and alcohol. As a result, it often is not possible to tell whether the observed changes in lipoprotein concentrations are due to the loss of body fat or to the changes in the proportions of the various dietary components.

With these limitations in mind, we will now consider some experiments with reducing diets.

7.2. *Trials of reducing diets and HDL*

Wilson and Lees (1972) reported that weight reduction increased the concentration of HDL. They instructed an unspecified number of obese patients to follow a weight-reducing diet, and presented lipoprotein data for those six patients in whom VLDL had gone down appreciably. In these patients HDL concentrations had increased by 68%. However, the selection that was employed and the lack of information on the weight-reduction regime and its outcome make this report less than convincing. Also, the values reported for HDL cholesterol in two healthy young women are unusually low. This makes one wonder whether HDL as measured in this study is really equivalent to what is commonly regarded as HDL.

More recent investigations have shown quite the opposite effect of weight reduction on HDL. For instance, Thompson et al. (1979) studied obese women who participated in a weight-loss program. 15 of the subjects continued in the program for 10 weeks and had post-treatment blood samples taken. Their mean body weight had decreased by 8.6 kg, and their HDL cholesterol levels had decreased by 0.10 mmol/l compared with pretreatment values. 11 women were measured again 8 months after the start of the program. Their body weights had decreased somewhat further, while HDL values were now slightly higher than initially. However, confounding effects of increased alcohol intake and exercise could not be excluded.

Several other studies also failed to observe a significant increase in HDL cholesterol concentrations after weight reduction (Larosa et al., 1980; Weltman et al., 1980; Wolf and Grundy, 1980; Oster et al., 1981). Each of these studies suffered from one or more of the limitations outlined at the beginning of this section, and accordingly they should not be taken as proof.

More encouraging results were reported by Contaldo et al. (1980). They subjected nine massively obese patients to a severe long-term reducing regime. On average, the patients lost 22 kg in weight. Post-treatment blood samples were obtained after 15 months; by then, body weights had been stable with an uncontrolled food intake for at least 6 months, and HDL cholesterol had increased from an average of 0.88 mmol/l to 1.37 mmol/l.

Streja et al. (1980) also found that grossly obese patients showed an increase in HDL cholesterol levels after losing on average 16 kg in weight. Again, post-treatment values were obtained after the body weights had stabilized. The authors suggested that a considerable amount of weight must be lost to produce a significant increase in HDL cholesterol concentration.

In the Multiple Risk Factor Intervention Trial (MRFIT; Caggiula et al., 1981), the men who lost weight showed a slight increase and those who gained weight a very slight decrease in HDL cholesterol. Changes in LDL cholesterol were also more favourable in men who lost weight. However, these men also showed better adherence to the diet, and thus the study did not strictly show a cause-and-effect relation: It did show, however, that in a real-life situation a fat-restricted, cholesterol-lowering diet can reduce LDL levels without affecting HDL. This same

experience was obtained in another large intervention trial, the Oslo Study (Hjermann et al., 1979).

7.3. Conclusions

People who are overweight tend to have lower HDL cholesterol concentrations than lean people, but it is still uncertain whether reduction of weight by dietary measures will remedy this. HDL cholesterol levels certainly do not rise while weight is being lost on reducing diets. Increases in HDL levels have been found in people after they had managed to achieve and maintain a large reduction in body fatness, but the possibility remains that this was due to changes in their physical activity, in the composition of their diet or in other aspects of their lifestyle.

8. Combined diets

8.1. Introduction

The previous sections have dealt mostly with experiments in which only a single dietary component was changed. Such studies help to identify the components which affect serum lipoproteins most strongly. In practice, however, lipid-lowering diets usually involve multiple changes in nutrient composition. In the classic diets for the treatment of hyperlipoproteinaemia, products high in saturated fat and cholesterol, such as whole milk, butter, cheese, fat-rich meats, and baked goods, are restricted, and consumption of vegetable foodstuffs is encouraged. Alcohol consumption may also be restricted. As a result, cholesterol consumption goes down, the proportion of energy derived from carbohydrates increases at the expense of fat and/or alcohol, the P/S ratio increases, and the consumption of complex carbohydrates and dietary fibre may also rise.

In multifactorial prevention trials body weight, smoking habits, and amount of physical exercise may also change; under such conditions changes in HDL become even more difficult to interpret. On the other hand, such studies do tell us what a realistic combination of intervention measures can achieve in practice.

Epidemiological observations of people with special dietary habits are one more step away from controlled experiments and towards real life. Their advantage is that they relate to long-term effects in large numbers of people and to dietary habits that have proved attractive in practice. The drawback of such studies is, of course, that one can never tell what else is special about such persons besides their diet, and therefore epidemiological observations should always be checked against the results of controlled experiments.

Nevertheless, as shown hereafter, the agreement between the results of these various approaches is quite satisfactory.

8.2. *Effect of multiple dietary changes on HDL*

There can be no doubt that classic fat-restricted, lipid-lowering diets will cause decreases in both LDL and HDL concentrations (Ernst et al., 1980a; Vessby et al., 1980b; Lewis et al., 1981). However, it would be wrong to conclude that such diets therefore will not affect the risk of coronary heart disease. The studies that showed a protective effect of high HDL concentrations were all performed in populations with high mean LDL cholesterol levels. HDL levels might become less relevant for the risk for coronary heart disease once the concentration of LDL has been reduced (Knuiman and West, 1983).

As argued in sections 3–5, the effect on HDL of lipid-lowering diets can be explained by the restriction in total fat and cholesterol intake, and is not necessarily caused by the replacement of saturated by polyunsaturated fatty acids. This is shown by studies of high-fat diets with a high proportion of polyunsaturated fatty acids: such diets will often lower LDL and VLDL without lowering HDL (Hulley et al., 1972; Chait et al., 1974; Lewis et al., 1981; Brussaard et al., 1980).

The extent to which fat-restricted diets will lower HDL relative to LDL or total cholesterol is not clear; it may depend on the lipid status of the subjects (Boberg et al., 1981) and on the particulars of the diet. Thus, Lewis et al. (1981) found that inclusion of fruit, vegetables, pulses and other fibre-rich products in a lipid-lowering diet limited the decrease in HDL and caused a distinct improvement in the ratio of LDL cholesterol to HDL_2 cholesterol. More studies of this effect would certainly be worthwhile.

8.3. *HDL in multifactorial intervention trials*

The Oslo Study was a controlled intervention trial of the effect of diet and smoking on coronary heart disease in middle-aged men with a high risk of coronary heart disease. The effect of diet on HDL has been reported for 23 selected diet-responders, who were compared with 23 matched controls (Hjermann et al., 1979). The dietary change consisted of a decreased intake of cholesterol and saturated and monounsaturated fatty acids, and a slight increase in linoleic acid. Total fat consumption was reduced to 28% of energy, the deficit being made up mostly by complex carbohydrates. The intervention and the control groups started at the same levels, but after 4 years of intervention HDL cholesterol in the treated group was 0.20 mmol/l higher and LDL cholesterol 1.84 mmol/l lower than in the control group. The treated group also reduced their mean body weight by about 4 kg, and it seems likely that they smoked less. Thus, any effect of the fat-limited, lipid-lowering diet on HDL was offset by the positive effects of smoking cessation and body weight reduction.

One should be careful in extrapolating these results, because persons who adhere well to treatment might be a very special group. However, similar effects were seen in the MRFIT study (Caggiula et al., 1981), in which multiple intervention also led to an increase in HDL cholesterol. This suggests that in patients with

a high risk of coronary heart disease, a lipid-lowering diet, when combined with a reduction of overweight and smoking, will reduce the concentrations of atherogenic lipoproteins and maintain or increase HDL levels.

8.4. Epidemiological studies of HDL in people with special dietary habits

Comparisons between vegetarians and omnivores within Western societies are a valuable supplement to international studies, because differences in genetic background, in the prevalence of infectious diseases and in various aspects of lifestyle are much less within one society. Several studies of lipoproteins in vegetarians are available. Sacks et al. (1975) reported that persons who followed a macrobiotic vegetarian diet had a mean LDL cholesterol concentration of 1.89 mmol/l and an HDL of 1.11 mmol/l, as opposed to 3.05 and 1.27 mmol/l, respectively, in age- and sex-matched controls. Thus, in spite of their high carbohydrate and low fat intakes, the depression of HDL in these macrobiotics was quite limited, and their HDL cholesterol to total cholesterol ratio was more favourable than in controls. Burslem et al. (1978) and Knuiman and West (1982) also reported a more favourable HDL/LDL or HDL/total cholesterol ratio in vegetarians. In the lactovegetarians studied by Knuiman and West, the absolute HDL cholesterol concentration was even higher than in controls.

The vegetarians were usually thinner than omnivores; this partly explains why they had fairly normal HDL cholesterol concentrations on a low-fat, low-cholesterol diet with a high ratio of polyunsaturated to saturated fatty acids. In addition, the high fibre content of their diet deserves attention: a well-controlled study by Lewis et al. (1981) showed that addition of fruit, vegetables, pulses and other fibre-rich foods to a lipid-lowering diet antagonised its depressing effect on HDL cholesterol.

Remarkably high values for alpha-lipoproteins (HDL) were found in Greenland Eskimos by Bang and Dyerberg (1972). Beta- and especially pre-beta-lipoproteins (VLDL), on the other hand, were lower than in Danish controls. The diet of these Eskimos (Bang et al., 1980) would lead one to expect such values: it is low in saturated and high in polyunsaturated fatty acids, which should cause low LDL and VLDL levels, and high in total fat and cholesterol, which agrees with the high HDL levels. However, the lack of reliable information on other factors, especially energy expenditure, should temper these conclusions.

8.5. Conclusions

The results from experiments with lipid-lowering diets, multifactorial prevention trials and epidemiological observations agree in that restriction of total dietary fat and cholesterol intake tends to diminish the concentration of HDL cholesterol along with that of other lipoprotein classes. The decrease in HDL can, however, be counteracted by other changes in lifestyle, such as increased activity, cessation of smoking and perhaps weight reduction.

9. Summary and conclusions

9.1. Attempt at a coherent model

Multiple factors, dietary and otherwise, influence the concentration of HDL cholesterol in plasma. In this final section I will attempt to point out the common underlying mechanisms of action which these seemingly unconnected factors might share.

9.1.1. Role of HDL in triglyceride catabolism

High-density lipoproteins are involved in the catabolism of triglyceride-rich lipoproteins in two different ways: as activators and as products.

The main protein component of HDL, apolipoprotein A-I (ApoA-I), is originally synthesized in intestinal cells as part of chylomicrons during fat absorption (Glickman and Green, 1977). As the chylomicrons are broken down by lipoprotein lipase, they lose ApoA-I and other surface materials, which are transferred to the HDL density range and give rise to mature HDL particles through the further action of the cholesterol-esterifying enzyme lecithin:cholesterol acyltransferase (LCAT) (Tall and Small, 1980). Figure 2 visualises this process. Nikkilä (1978) has made a case for the concept that HDL is a 'second remnant' of the action of lipoprotein lipase on triglyceride-rich lipoproteins, and for a crucial role of lipoprotein lipase activity in determining the level of HDL in plasma. The importance of lipoprotein lipase is illustrated by the low level of HDL in patients with type I hyperlipoproteinaemia, who lack this enzyme and thus lack normal catabolism of triglyceride-rich lipoproteins (Herbert and Henderson, 1979). On the other hand, stimulation of lipoprotein lipase activity by heparin infusion in normal subjects causes a reduction of serum triglycerides and an increase in HDL concentration (Levy et al., 1966).

High-density lipoproteins, however, are not only products but also tools in fat catabolism. Chylomicrons obtain from HDL the ApoC-II, which is essential for the breakdown of triglyceride-rich particles by lipoprotein lipase. This is illustrated by the massive hypertriglyceridaemia in persons with homozygous familial ApoC-II deficiency. A further illustration of the need for HDL in this breakdown is provided by observations on Tangier disease patients, who have a hereditary lack of normal HDL. After a fat-rich meal these patients develop much higher levels of triglycerides in plasma than do normal subjects. However, if exogenous HDL is infused prior to the meal the alimentary hyperlipaemia is much reduced (Assmann, 1978).

Thus, high HDL levels may be associated with rapid breakdown of fat-rich lipoproteins, both because they are a prerequisite for rapid catabolism and because they are produced in the process. At present it is unclear whether or not these two different functions are fulfilled by different subpopulations of high-density lipoproteins.

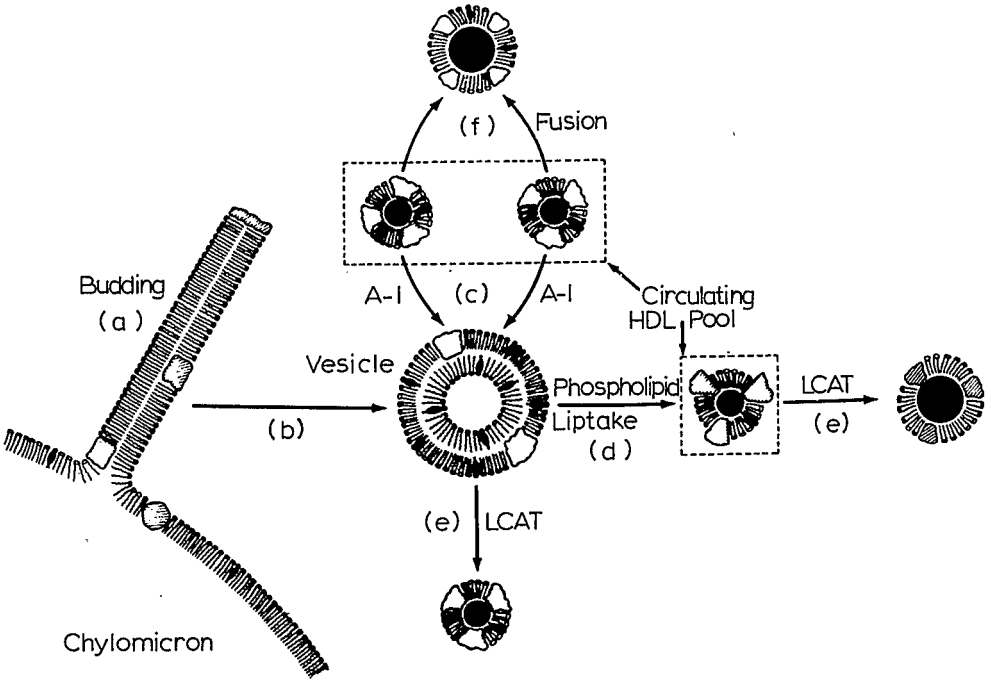

Figure 2. Possible mechanisms for the formation of new HDL from chylomicron surface by interaction with pre-existing HDL. As lipoprotein lipase decreases the triglyceride mass, the chylomicron surface becomes redundant and buds bilayers (a). These bilayers break off in sheets and rapidly fuse as vesicles containing phospholipid, free cholesterol and possibly small amounts of soluble chylomicron apolipoproteins (b). Vesicles interact with HDL in the circulating pool, accepting apolipoproteins A-I (c) or donating phospholipids to circulating HDL (d). Both types of interaction produce ApoA-I-containing phospholipid-rich particles which will then act as substrate for LCAT. This enzyme combines acyl chains from surface phospholipids with cholesterol from other lipoproteins or cell membranes. The cholesterol esters that are produced fill the core of the particle, which is thus converted to HDL, mostly of the larger HDL_2 type. The HDL particles that have given up ApoA-I become unstable and fuse (f). (After Tall and Small (1980); reproduced with permission.)

9.1.2. Dietary fat and cholesterol

Dietary factors that influence HDL concentrations could fit into the above model as follows.

An iso-energetic replacement of dietary fat by carbohydrate should lead to a decrease in the amount of triglyceride-rich lipoprotein entering the lipoprotein lipase pathway, because part of the dietary carbohydrate is going to be taken up directly by the tissues as glucose and will not be converted to triglyceride. Even at constant lipoprotein lipase activity this decreased supply of substrate should lead to a lower rate of production of surface remnants, and thus of HDL, assuming that the surface to volume ratios of triglyceride-rich particles on the two diets are not

greatly different. In fact, the activity of lipoprotein lipase also falls when fat in the diet is replaced by carbohydrate (Lithell et al., 1982); whether this is a reaction to the decreased supply of substrate is not clear.

One might speculate that the decrease in HDL concentration after reduction of cholesterol consumption proceeds in the same way: a reduced production of lipid-rich lipoproteins, in this case from dietary cholesterol, followed by a reduced production of surface remnants, and thus of HDL, from such lipoproteins. As yet, there is little experimental evidence to support or refute this speculation.

These considerations on the metabolism of dietary fat and cholesterol help to rationalise the epidemiological observations on diet, HDL and coronary heart disease described in section 3.3. In affluent societies the high HDL levels observed in low-risk subjects might reflect the competent handling of large daily amounts of dietary fat. The low HDL levels in subjects prone to coronary heart disease could point to a reduced ability of lipoprotein lipase and/or its activators to handle the large supply of chylomicrons and other triglyceride-rich lipoproteins which the diet in affluent societies provides. In populations with a low-fat intake, however, the low HDL concentrations observed (Knuiman et al., 1980, 1982) simply reflect a reduced flux of triglyceride-rich lipoproteins, without any defect in the underlying metabolic machinery. In such populations coronary heart disease is rare because the concentration of atherogenic lipoproteins in plasma is low, and HDL is less relevant.

In this model diet influences HDL concentrations because the amount and type of food eaten affects the supply of triglyceride-rich lipoproteins, and perhaps also the activity of lipoprotein lipase.

9.1.3. Obesity, energy intake and energy expenditure

Tissue lipoprotein lipase activity is low in obese people and high in people who are physically active, and this correlates well with their HDL concentrations (Nikkilä, 1978). In this respect, the supply of triglyceride-rich lipoproteins deserves attention. There are reports that obese people eat less than their lean counterparts (Baecke et al., 1983), which could mean that the amount of substrate offered to lipoprotein lipase is less in obese than in lean persons. True food intake in obese subjects is difficult to measure, but the reduction in HDL observed on weight-reducing diets also agrees with a model in which a reduced supply of triglyceride-rich lipoproteins derived from dietary fat causes a reduced production of HDL.

The opposite effect is seen in physical exercise, where the increased energy demand must be met by a higher food intake. Thus, Wood et al. (1983) found in a randomized controlled study that in people who took up exercise the increase in HDL cholesterol was significantly correlated with the increase in caloric intake. The increased intake of food, be it as fat or as carbohydrates, could again lead to an increased production of triglyceride-rich lipoproteins. As lipoprotein lipase

activity is also increased by regular exercise (Nikkilä, 1978) no increase in plasma triglycerides is seen, but HDL production could be much higher.

If differences in energy intake should turn out to be major determinants of differences in HDL between obese and lean persons, then an increase of HDL levels in the obese might be attainable only through an increase in energy expenditure, and not by dietary restrictions.

9.1.4. Alcohol and smoking

The energy provided by alcohol is made available to the body by the liver as triglyceride in the form of VLDL (Lewis, 1976). Lipoprotein lipase is also stimulated by alcohol consumption (Belfrage et al., 1977). Thus, the rise of the HDL concentration when alcohol intake is increased can be explained by the increased supply of substrate for lipoprotein lipase and the increase in the activity of the enzyme, which together make for an increased production of HDL as the 'second remnant' (Nikkilä, 1978) of lipolysis. Alternative explanations of the HDL-raising effect of alcohol, such as inhibition of the breakdown of HDL by liver triglyceride lipase (Nikkilä, 1978), cannot, however, be excluded.

Smoking is known to suppress feelings of hunger, and obesity caused by overeating is a well-known consequence of smoking cessation. Stubbe et al. (1982) reported that heavy smokers increased their caloric intake by an average of 7–9% after they had stopped smoking. The rise in HDL cholesterol concentration after smoking was stopped was strongly correlated with the increase in fat consumption, and the authors suggested that the changes in lipoprotein concentrations after smoking cessation might have been partly related to nutritional changes.

9.1.5. Conclusions

A simplified model has been presented in which high HDL levels reflect a high flux of triglyceride-rich lipoproteins, and thus a high rate of production of surface remnants that are converted into HDL. Consumption of dietary fat, cholesterol and alcohol are suggested to increase HDL because they increase the production of triglyceride-rich lipoproteins and the activity of lipoprotein lipase. Smoking, obesity and lack of physical activity are all associated with low absolute intakes of food, and this in turn is suggested to cause a decreased production of triglyceride-rich lipoproteins and a decreased activity of lipoprotein lipase. Although this model will certainly turn out to be incomplete and over simplified, it provides a connection between determinants of HDL that commonly are viewed separately.

9.2. General overview of the results obtained

If diet is defined to include energy balance and alcohol consumption, then it should be reckoned a major determinant of the concentration of HDL cholesterol in plasma.

Both epidemiological and experimental studies have shown convincingly that alcohol will raise HDL cholesterol; one to three drinks a day will cause an increase of about 0.04–0.12 mmol/l (1.5–4.5 mg/dl).

The effect of the carbohydrate-to-fat ratio has also been established fairly convincingly. A very crude estimate shows that replacement of 10% of energy as fat by an equivalent amount of carbohydrate will lower HDL cholesterol by 0.08 mmol/l (3–4 mg/dl). The effects of sugars and of complex carbohydrates are in the same direction, but a quantitative comparison is not available.

There are strong indications that dietary cholesterol in the form of egg yolk raises the HDL cholesterol concentration, in addition to its well-established effect on the concentration of atherogenic lipoproteins. It is unclear to what extent this is caused by the formation of abnormally high concentrations of HDL_c.

Under conditions where total fat and cholesterol consumption are forcibly held constant the effect of exchanging saturated for polyunsaturated fatty acids on HDL is small or nil. In several well-controlled trials the changes in serum lipoproteins caused by such diets were limited to VLDL and LDL.

Specific effects of protein, vitamins, minerals and lecithin are not yet sufficiently documented.

Obese people have lower HDL cholesterol levels than their lean counterparts. A rise of HDL cholesterol upon weight reduction would be expected, but has not yet been proven convincingly, especially in the case where energy expenditure is not increased but only intake is reduced.

Results of multifactorial prevention studies and of epidemiological observations on vegetarians agree with the conclusion that restriction of total dietary fat and cholesterol tends to decrease the concentration of HDL cholesterol along with that of other lipoproteins. On the other hand, they suggest that the decrease in HDL can be prevented by other changes in lifestyle, such as increased activity, cessation of smoking and perhaps weight reduction. The addition of fruits, vegetables and pulses to a lipid-lowering diet might also cause a more specific lowering of atherogenic lipoproteins alone.

10. Acknowledgements

I am grateful to Drs. Clive West and Anton Beynen for critically reading the manuscript, to them and to my other colleagues in the Department, especially Drs. Jan Knuiman and Tineke Brussaard for discussions on diet and lipoproteins, and to Drs. Knuiman and West for allowing me to use their unpublished material.

11. References

Ahrens, E.H., Hirsch J., Oette, K., Farquhar, J.W. and Stein, Y. (1961) Carbohydrate-induced and fat-induced hyperlipemia. Trans. Ass. Am. Physicians 74, 134–146.

Albrink, M.J., Krauss, R.M., Lindgren, F.T., Von der Groeben, J., Pan. S. and Wood, P.D. (1980) Intercorrelations among plasma high density lipoprotein, obesity and triglycerides in a normal population. Lipids 14, 668–676.

Antonis, A. and Behrson, I. (1961) The influence of diet on serum-triglycerides in South African white and Bantu prisoners. Lancet 1, 3–9.

Antonis, A. and Behrson, I. (1962) The influence of diets on serum lipids in South African white and Bantu prisoners. Am. J. Clin. Nutr. 10, 484–499.

Arab, L., Schellenberg, B. and Schlierf, G. (1982) Nutrition and health – A survey of young men and women in Heidelberg. Ann. Nutr. Metab. 26 (Suppl. 1), 1–244.

Assmann, G. (1978) The metabolic role of high density lipoproteins: perspectives from Tangier disease. In: A.M. Gotto, N.E. Miller and M.F. Oliver (Eds.), High Density Lipoproteins and Atherosclerosis. Elsevier, Amsterdam, pp. 77–89.

Baecke, J.A.H., Van Staveren, W.A. and Burema, J. (1983) Food consumption, habitual physical activity, and body fatness in young Dutch adults. Am. J. Clin. Nutr. 37, 278–286.

Bang, H.O. and Dyerberg, J. (1972) Plasma lipids and lipoproteins in Greenlandic west coast Eskimos. Act. Med. Scand. 192, 85–94.

Bang, H.O., Dyerberg, J and Sinclair, H.M.M. (1980) The composition of the Eskimo food in North Western Greenland. Am. J. Clin. Nutr. 33, 2657–2662.

Beaton, G.H., Milner J., Corey, P., McGuire, V., Cousins, M., Stewart, E., De Ramos, M., Hewitt, D., Grambsch, P.V., Kassim, N. and Little, J.A. (1979) Sources of variance in 24-hour dietary recall data: implications for nutrition study design and interpretation. Am. J. Clin. Nutr. 32, 2546–2559.

Beil, F.U. and Grundy, S.M. (1980) Studies on plasma lipoproteins during absorption of exogenous lecithin in man. J. Lipid Res. 21, 525–536.

Belfrage, P., Berg, B., Haegerstrand, I., Nilsson-Ehle, P., Tornquist, H. and Wiebe, T. (1977) Alterations of lipid metabolism in healthy volunteers during long-term ethanol intake. Eur. J. Clin. Invest. 7, 127–131.

Berg, B. and Johansson, B.G. (1973) Effects on parameters of liver function, plasma lipid concentrations and lipoprotein patterns. Acta Med. Scand. Suppl. 552, 13–18.

Blum, C.B., Levy, R.I., Eisenberg, S., Hall, M., Goebel, R.H. and Berman, M. (1977) High density lipoprotein metabolism in man. J. Clin. Invest. 60, 795–807.

Boberg, J., Gustafsson, I.B., Karlström, B., Lithell, H., Vessby, B. and Werner, I. (1981) Treatment of hyperlipoproteinaemia with 'Type-specific' diets under metabolic ward conditions – effects on serum lipoproteins and serum lipid esters. Ann. Nutr. Metab. 25, 320–333.

Brunner, D., Weisbort, J., Fischer, M., Bearman, J.E., Loebl, K., Schwartz, S. and Levin, S. (1979) Serum lipid response to a high-caloric high-fat diet in agricultural workers during 12 months. Am. J. Clin. Nutr. 32, 1342–1349.

Brussaard, J.H., Dallinga-Thie, G., Groot, P.H.E. and Katan, M.B. (1980) Effects of amount and type of dietary fat on serum lipids, lipoproteins and apolipoproteins in man – a controlled 8-week trial. Atherosclerosis 36, 515–527.

Brussaard, J.H., Katan, M.B., Groot, P.H.E., Havekes, L.M. and Hautvast, J.G.A.J. (1982) Serum lipoproteins of healthy persons fed a low fat diet or a polyunsaturated fat diet for three months: a comparison of two cholesterol-lowering diets. Atherosclerosis 42, 205–219.

Burslem, J., Schonfeld, G., Howald, M.A., Weidman, S. and Miller, J.P. (1978) Plasma apoprotein and lipoprotein lipid levels in vegetarians. Metabolism 27, 711–719.

Caggiula, A.W., Christakis, G., Farrand, M., Hulley, S.B., Johnson, R., Lasser, N.L., Stamler, J. and Widdowson, G. (1981) The multiple risk factor intervention trial (MRFIT) – IV. Intervention on blood lipids. Prev. Med. 10, 443–475.

Carlson, L.A. and Ericsson, M. (1975) Quantitative and qualitative serum lipoprotein analysis. Part I. Studies in healthy men and women. Atherosclerosis 21, 417–433.

Castelli, W.P., Doyle, J.T., Gordon, T., Hames, C.G., Hjortland, M.C., Hulley, S.B., Kagan, A. and Zukel, W.J. (1977) Alcohol and blood lipids – The cooperative lipoprotein phenotyping study. Lancet 2, 153–155.

Chait, A., Onitiri, A., Nicoll, A., Rabaya, E., Davies, J. and Lewis, B. (1974) Reduction of serum triglyceride levels by polyunsaturated fat – studies of the mode of action and on very low density lipoprotein composition. Atherosclerosis 20, 347–364.

Childs, M.T., Bowlin, J.A., Ogilvie, J.T., Hazzard, W.R. and Albers, J.J. (1981) The contrasting effects of a dietary soya lecithin product and corn oil on lipoprotein lipids in normolipidemic and familiar hypercholesterolemic subjects. Atherosclerosis 38, 217–228.

Contaldo, F., Strazzulo, P., Postiglione, A., Riccardi, G., Patti, L., Di Biase, G. and Mancini, M. (1980) Plasma high density lipoprotein in severe obesity after stable weight loss. Atherosclerosis 37, 163–167.

Ekman, R., Fex, G., Johansson, B.G., Nilsson-Ehle, P. and Wadstein, J. (1981) Changes in plasma high density lipoproteins and lipolytic enzymes after long-term, heavy ethanol consumption. Scand. J. Clin. Lab. Invest. 41, 709–715.

Ernst, N., Fischer, M., Bowen, P., Schaefer, E.J. and Levy, R.I. (1980a) Changes in plasma lipids and lipoproteins after a modified fat diet. Lancet 2, 111–113.

Ernst, N., Fischer, M., Smith, W., Gordon, T., Rifkind, B.M., Little, J.A., Mishkel, M.A. and Williams, O.D. (1980b) The association of plasma high-density lipoprotein cholesterol with dietary intake and alcohol consumption. Circulation 62 (Suppl. IV), 41–52.

Ginsberg, H., Le, N.A., Mays, C., Gibson, J. and Brown, W.V. (1981) Lipoprotein metabolism in nonresponders to increased dietary cholesterol. Arteriosclerosis 1, 463–470.

Glickman, R.M. and Green, P.H.R. (1977) The intestine as a source of apolipoprotein A-I. Proc. Natl. Acad. Sci. U.S.A. 74, 2569–2573.

Glueck, C.J. and Connor, W.E. (1978) Diet-coronary heart disease relationships reconnoitered. Am. J. Clin. Nutr. 32, 727–737.

Glueck, C.J., Hogg, E., Allen, C. and Gartside, P.S. (1980a) Effects of alcohol on lipids and lipoproteins in normal men: isocaloric metabolic studies. Am. J. Clin. Nutr. 33, 2287–2293.

Glueck, C.J., Taylor, H.L., Jacobs, D., Morrison, J.A., Beaglehole, R. and Williams, O.D. (1980b) Plasma high-density lipoprotein cholesterol: association with body mass. The Lipid Research Clinics program prevalence study. Circulation 62 (Suppl. IV), 62–69.

Greten, H., Raetzer, H., Stiehl, A. and Schettler, G. (1980) The effect of polyunsaturated phosphatidylcholine on plasma lipids and fecal sterol excretion. Atherosclerosis 36, 81–88.

Grundy, S.M., Bilheimer, D., Blackburn, H., Brown, W.V., Kwiterovich, P.O., Mattson, F., Schonfeld, G. and Weidman, W.H. (1982) Rationale of the Diet-Heart statement of the American Heart Association – Report of Nutrition Committee. Circulation 65, 839A-854A.

Heiss, G. Johnson, N.J., Reiland, S., Davis, C.E. and Tyroler, H.A. (1980) The epidemiology of plasma high-density lipoprotein cholesterol levels. The Lipid Research Clinics program prevalence study. Circulation 62 (Suppl. IV), 116–136.

Herbert, P. and Henderson, L.O. (1979) Plasma triglycerides do not regulate high-density lipoprotein concentrations. Lancet 1, 1368–1370.

Hjermann, I., Enger, S.C., Helgeland, A., Holme, I., Leren, P. and Trygg, K. (1979) The effect of dietary changes on high density lipoprotein cholesterol: The Oslo Study. Am. J. Med. 66, 105–109.

Hulley, S.B. and Gordon, S. (1981) Alcohol and high-density lipoprotein cholesterol – causal inference from diverse study designs. Circulation 64 (Suppl. III), 57–63.

Hulley, S.B., Wilson, W.S., Burrows, M.I. and Nichaman, M.Z. (1972) Lipid and lipoprotein responses of hypertriglyceridaemic outpatients to a low-carbohydrate modification of the A.H.A. fat-controlled diet. Lancet 2, 551–555.

Johansson, B.G. and Medhus, A. (1974) Increase in plasma α-lipoproteins in chronic alcoholics after acute abuse. Acta Med. Scand. 195, 273–277.

Kaelber, C. and Mills, G. (1981) Alcohol consumption and cardiovascular diseases: introductory remarks. Circulation 64 (Suppl. III), 1–6.

Kashyap, M.L., Barnhart, R.L., Srivastava, L.S., Perisutti, G., Vink, P., Allen, C., Hogg, E., Brady, D., Glueck, C.J. and Jackson, R.L. (1982). Effects of dietary carbohydrate and fat on plasma lipoproteins and apolipoproteins C-II and C-III in healthy men. J. Lipid Res. 23, 877–886.

Katan, M.B., Beynen, A.C., De Vries, J.H.M. and Nobels, A. (1984) Existence of consistent hyper- and hyporesponders to dietary cholesterol in man. Am. J. Clin. Nutr., submitted.

Keys, A. (1965) Dietary survey methods in studies on cardiovascular epidemiology. Voeding 26, 464–483.

Keys, A., Anderson, J.T. and Grande, F. (1965) Serum cholesterol response to changes in the diet. IV. Particular saturated fatty acids in the diet. Metabolism 14, 776–787.

Knuiman, J.T. and West, C.E. (1982) The concentration of cholesterol in serum and in various serum lipoproteins in macrobiotic, vegetarian and non-vegetarian men and boys. Atherosclerosis 43, 71–82.

Knuiman, J.T. and West, C.E. (1983) Differences in HDL cholesterol between populations: no paradox? Lancet 1, 296.

Knuiman, J.T., Hermus, R.J.J. and Hautvast, J.G.A.J. (1980) Serum total and high density lipoprotein (HDL) cholesterol concentrations in rural and urban boys from 16 countries. Atherosclerosis 36, 529–537.

Knuiman, J.T., West, C.E. and Burema, J. (1982) Serum total and high density lipoprotein cholesterol concentrations and body mass index in adult men from 13 countries. Am. J. Epidemiol. 116, 631–642.

Knuiman, J.T., Westenbrink, S., Van der Heijden, L., West, C.E., Burema, J., De Boer, J., Hautvast, J.G.A.J., Räsänen, L., Virkkunen, L., Viikari, J., Lokko, P., Pobee, J.O.M., Ferro-Luzi, A., Ferrini, A.M., Saccacini, C., Sette, S., Villavieja, G.M. and Bulatao-Jayme, J. (1983) Determinants of total and high density lipoprotein cholesterol in boys from Finland, The Netherlands, Italy, The Philippines and Ghana with special reference to diet. Human Nutrition: Clin. Nutr. 37C, 237–254.

Laine, D.C., Snodgrass, C.M., Dawson, E.A., Ener, M.A., Kuba, K. and Frantz, I.D. (1982) Lightly hydrogenated soy oil versus other vegetable oils as a lipid-lowering dietary constituent. Am. J. Clin. Nutr. 35, 683–690.

Laporte, R., Valvo-Gerard, L., Kuller, L., Dai, W., Bates, M., Cresanta, J., Williams, K. and Palkin, D. (1981) The relationship between alcohol consumption, liver enzymes and high-density lipoprotein cholesterol. Circulation 64 (Suppl. III), 67–72.

Larosa, J.C., Gordon Fry, A., Muesing, R. and Rosing, D.R. (1980) Effect of high-protein, low-carbohydrate dieting on plasma lipoproteins and body weight. J. Am. Diet. Ass. 77, 264–270.

Levy, R.I., Lees, R.S. and Fredrickson, D.S. (1966) The nature of pre-beta (very low density) lipoproteins. J. Clin. Invest. 45, 63–77.

Lewis, B. (1976) The Hyperlipidaemias. Clinical and Laboratory Practice. Blackwell, London.

Lewis, B., Hammet, F., Katan, M.B., Kay, R.M., Merkx, I., Nobels, A., Miller, N.E. and Swan, A.V. (1981) Towards an improved lipid-lowering diet: additive effects of changes in nutrient intake. Lancet 2, 1310–1313.

Liebman, B.F. (1982) Poor design undercuts cholesterol study results. Am. J. Clin. Nutr. 35, 1041.

Lipid Research Clinics (1982) Population Studies Data Book, Volume II. The prevalence study – Nutrient intake. National Heart, Lung and Blood Institute (DHHS Publications No. NIH 82–2014).

Lithell, H., Jacobs, I., Vessby, B., Hellsing, K. and Karlsson, J. (1982) Decrease of lipoprotein lipase activity in skeletal muscle in man during a short-term carbohydrate-rich dietary regime. With special reference to HDL-cholesterol, apolipoprotein and insulin concentrations. Metabolism 31, 994–998.

Mahley, R.W., Weisgraber, K.H., Innerarity, T., Brewer, H.B. and Assmann, G. (1975) Swine lipoproteins and atherosclerosis. Changes in the plasma lipoproteins and apoproteins induced by cholesterol feeding. Biochemistry 14, 2817–2823.

Mahley, R.W., Innerarity, T.L., Bersot, T.P., Lipson, A. and Margolis, S. (1978) Alterations in human high density lipoproteins with or without increased plasma cholesterol, induced by diets high in cholesterol. Lancet 2, 807–809.

McMurry, M.P., Connor, W.E. and Cerqueira, M.T. (1982) Dietary cholesterol and the plasma lipids and lipoproteins in the Tarahumara Indians: a people habituated to a low cholesterol diet after weaning. Am. J. Clin. Nutr. 35, 741–744.

Mistry, P., Miller, N.E., Laker, M., Hazzard, W.R. and Lewis, B. (1981) Individual variations in the effects of dietary cholesterol on plasma lipoproteins and cellular cholesterol homeostasis in man. J. Clin. Invest. 67, 493–502.

Nestel, P., Tada, N., Billington, T., Huff, M. and Fidge, N. (1982) Changes in very low density lipoproteins with cholesterol loading in man. Metabolism 31, 398–405.

Nikkilä, E.A. (1978) Metabolic and endocrine control of plasma high density lipoprotein concentration – Relation to catabolism of triglyceride-rich lipoproteins. In: A.M. Gotto, N.E. Miller and M.F. Oliver (Eds.), High Density Lipoproteins and Atherosclerosis. Elsevier, Amsterdam, pp. 177–192.

Oster, P., Schlierf, G., Heuck, C.C., Hahn, S., Szymanski, H. and Schellenberg, B. (1981) Diet and high density lipoproteins. Lipids 16, 93–97.

Peeters, H. (1976) The biological significance of the plasma phospholipids. In: H. Peeters (Ed.), Phosphatidylcholine – Biochemical and Clinical Aspects of Essential Phospholipids. Springer Verlag, Berlin, pp. 10–33.

Raymond, T.L., Connor, W.E., Lin, D.S., Warner, S., Fry, M.M. and Connor, S.L. (1977) The interaction of dietary fibers and cholesterol upon the plasma lipids and lipoproteins, sterol balance and bowel function in human subjects. J. Clin. Invest. 60, 1429–1437.

Rhoads, G.G., Gulbrandsen, C.L. and Kagan, A. (1976) Serum lipoproteins and coronary heart disease in a population study of Hawaii Japanese men. N. Engl. J. Med. 294, 293–298.

Riales, R. and Albrink, M.J. (1981) Effect of chromium chloride supplementation on glucose tolerance and serum lipids including high density lipoprotein of adult men. Am. J. Clin. Nutr. 34, 2670–2678.

Sabesin, S.M. (1981) Lipid and lipoprotein abnormalities in alcoholic liver disease. Circulation 64 (Suppl. III), 72–84.

Sacks, F.M., Castelli, W.P., Donner, A. and Kass, E.H. (1975) Plasma lipids and lipoproteins in vegetarians and controls. N. Engl. J. Med. 292, 1148–1151.

Schonfeld, G., Patsch, W., Rudel, L.L., Nelson, C., Epstein, M. and Olson, R.E. (1982) Effects of dietary cholesterol and fatty acids on plasma lipoproteins. J. Clin. Invest. 69, 1072–1080.

Schwandt, P., Janetschek, P. and Weisweiler, P. (1982) High density lipoproteins unaffected by dietary fat modification. Atherosclerosis 44, 9–17.

Shepherd, J., Packard, C.J., Patsch, J.R., Gotto, A.M. and Taunton, O.D. (1978) Effects of dietary polyunsaturated and saturated fat on the proporties of high density lipoproteins and the metabolism of apolipoprotein A-1. J. Clin. Invest. 61, 1582–1592.

Shepherd, J., Packard, C.J., Grundy, S.M., Yeshurun, D., Gotto, A.M. and Taunton, O.D. (1980) Effects of saturated and polyunsaturated fat diets on the chemical composition and metabolism of low density lipoproteins. J. Lipid Res. 21, 91–99.

Spritz, N. and Mishkel, M.A. (1969) Effects of dietary fats on plasma lipids and lipoproteins: a hypothesis for the lipid-lowering effect of unsaturated fatty acids. J. Clin. Invest. 48, 78–86.

Stasse-Wolthuis, M., Hautvast, J.G.A.J., Hermus, R.J.J., Katan, M.B., Bausch, J.E., Rietberg-Brussaard, J.H., Velema, J.P., Zondervan, J.H., Eastwood, M.A. and Brydon, W.G. (1979) The effect of a natural high-fiber diet on serum lipids, fecal lipids and colonic function. Am. J. Clin. Nutr. 32, 1881–1888.

Streja, D.A., Boyko, E. and Rabkin, S.W. (1980) Changes in plasma high-density lipoprotein cholesterol concentration after weight reduction in grossly obese subjects. Br. Med. J. 281, 770–772.

Stubbe, I., Eskilsson, J. and Nilsson-Ehle, P. (1982) High-density lipoprotein concentrations increase after stopping smoking. Br. Med. J. 284, 1511–1513.

Tall, A.R. and Small, D.M. (1980) Body cholesterol removal: role of plasma high-density lipoproteins. Adv. Lipid Res. 17, 1–51.

Taskinen, M.J., Välimäki, M., Nikkilä, E.A., Kuusi, T., Ehnholm, C. and Ylikahri, R. (1982) High density lipoprotein subfractions and postheparin plasma lipases in alcoholic men before and after ethanol withdrawal. Metabolism 31, 1168–1174.

Ter Welle, H.F., Van Gent, C.M., Dekker, W. and Willebrands, A.F. (1974) The effect of soya lecithin on serum lipid values in type II hyperlipoproteinaemia. Acta Med. Scand. 195, 267–271.

Thompson, P.D., Jeffery, R.W., Wing, R.R. and Wood, P.D. (1979) Unexpected decrease in plasma high density lipoprotein cholesterol with weight loss. Am. J. Clin. Nutr. 32, 2016–2021.

United States Department of Agriculture (1979) Composition of Foods – Fats and Oils, Raw, Processed, Prepared. Agriculture Handbook No. 8-4. Washington DC: U.S. Government Printing Office.

Van Raaij, J.M.A., Katan, M.B., Hautvast, J.G.A.J. and Hermus, R.J.J. (1981) Effects of casein versus soy protein diets on serum cholesterol and lipoproteins in young healthy volunteers. Am. J. Clin. Nutr. 34, 1261–1271.

Van Raaij, J.M.A., Katan, M.B., West, C.E. and Hautvast, J.G.A.J. (1982) Influence of diets containing casein, soy isolate and soy concentrate on serum cholesterol and lipoproteins in middle-aged volunteers. Am. J. Clin. Nutr. 35, 925–934.

Vega, G.L., Groszek, E., Wolf, E. and Grundy, S.M. (1982) Influence of polyunsaturated fats on composition of plasma lipoproteins and apolipoproteins. J. Lipid Res. 23, 811–822.

Vessby, B., Gustafsson, I.B., Boberg, J., Karlström, B., Lithell, H. and Werner, I. (1980a) Substituting polyunsaturated for saturated fat as a single change in a Swedish diet: effects on serum lipoprotein metabolism and glucose tolerance in patients with hyperlipoproteinaemia. Eur. J. Clin. Invest. 10, 193–202.

Vessby, B., Boberg, J. Gustafsson, I.B., Karlström, B., Lithell, H. and Östlund-Lundquist, A.M. (1980b) Reduction of high density lipoprotein cholesterol and apolipoprotein A-I concentrations by a lipid-lowering diet. Atherosclerosis 35, 21–27.

Von Lossonczy, T., Ruiter, A., Bronsgeest-Schoute, H.C., Van Gent, C.M. and Hermus, R.J.J. (1978) The effect of a fish diet on serum lipids in healthy human subjects. Am. J. Clin. Nutr. 32, 1340–1346.

Weltman, A., Matter, S. and Stamford, B.A. (1980) Caloric restriction and/or mild exercise: effects on serum lipids and body composition. Am. J. Clin. Nutr. 33, 1002–1009.

Wilson, D.E. and Lees, R.S. (1972) Metabolic relationships among the plasma lipoproteins. J. Clin. Invest. 51, 1051–1057.

Wolf, R.N. and Grundy, S.M. (1980) Effects of caloric restriction on plasma lipids and lipoproteins. Clin. Res. 28, 55A.

Wood, P.D., Haskell, W.L., Blair, S.N., Williams, P.T., Krauss, R.M., Lindgren, F.T., Albers, J.J., Ho, P.H. and Farquhar, J.W. (1983) Increased exercise level and plasma lipoprotein concentrations: a one-year, randomized, controlled study in sedentary, middle-aged men. Metabolism 32, 31–39.