The influence of dietary protein on serum cholesterol in man and experimental animals¹⁾

By C. E. West, J. M. A. van Raaij, A. C. Beynen, J. G. A. J. Hautvast, M. B. Katan, M. W. Kuyvenhoven, K. E. Scholz² and A. H. M. Terpstra³
Department of Human Nutrition, Agricultural University, Wageningen, Netherlands

1. Introduction

While studying the effect of dietary protein derived from animal sources on the structure and function of parenchymous organs in rabbits, Ignatowski (1) in 1909 discovered fortuitously that rabbits fed meat, milk and eggs developed arterial lesions. The resemblance of these lesions to human atherosclerosis was immediately recognized. Great interest was aroused by the findings of Ignatowski (1) since now an experimental model for studying human atherosclerosis was provided. Furthermore, he had demonstrated that atherosclerosis could be produced by dietary means. The changes in the vessels were initially ascribed to the injurious effects of animal protein (1). However, Stuckey (2) tested different foodstuffs of animal origin and found that the feeding of egg yolk to rabbits resulted in atheromatous changes in the intima, whereas other animal products, such as milk, egg white and meat juice had no effect. These findings together with the observation that feeding egg yolk resulted in deposition of large amounts of fatty substances in the liver and aorta, prompted the hypothesis that the lipid in the egg yolk was responsible and that the protein in the diet had little to do with atherosclerosis. Further studies on rabbits fed egg yolk by Wesselkin (3) provided evidence that the fatty substances deposited in the liver and aorta contained mainly cholesteryl esters. This prompted the idea that in the diet the cholesterol from the egg yolk was the culprit. This early work was rounded off by Anitschkow and Chalatow (4) and Wacker and Hueck (5) who demonstrated independently that feeding to rabbits crystalline cholesterol dissolved in sunflower oil resulted in similar arterial lesions as did the feeding of egg yolk. Therefore, the view of Ignatowski (1) that the arterial lesions in rabbits fed animal products could be attributed to animal protein, was largely abandoned. From then on the inclusion of cholesterol in the diet was generally considered as a prerequisite for the production of experimental atherosclerosis in rabbits. Nevertheless, a number of investigators over the years have still adhered to the idea that dietary protein might play an important role in the etiology of atherosclerosis. Newburgh (6) observed in 1919 that high casein diets were able to produce atherosclerosis whereas the feeding of soybeans could not. Similar results were reported by Meeker and Kesten (7) in 1941 and by Lambert et al. (8) in 1958, and by Wigand in 1959 (9).

The induction of atherosclerosis in rabbits fed casein was associated with a marked increase of the concentration of cholesterol in the serum (7–10). When the rabbits were fed soy protein, the level of serum cholesterol remained low. We have obtained similar results in our studies with cholesterol-free, semipurified diets in which the protein source was the only variable (Fig. 1). When the rabbits on the casein diet were transferred to the diet containing soy protein (Fig. 1), a rapid decrease in serum cholesterol occurred. Conversely, changing the rabbits from the diet containing soy protein to the casein diet

¹⁾ Invited Paper, Symposium on Role of Milk Proteins in Human Nutrition, Kiel 1983

²⁾ Present address: Institute for Nutritional Physiology and Biochemistry, Federal Dairy Research Centre Kiel, F. R. Germany

³⁾ Present address: Division of Nutrition and Metabolism, Brown University, Providence, Rhode Island, USA.

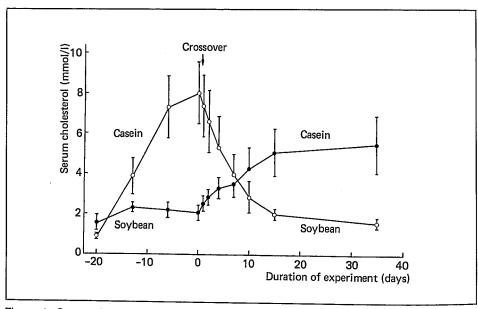


Figure 1: Serum cholesterol concentrations in rabbits fed cholesterol-free, semipurified diets containing either 40% (w, w) casein or 40% (w, w) soy protein. ○, group receiving diet containing casein before the cross-over and soy protein after the cross-over; ●, soy protein and casein, respectively. Each point denotes the mean from 6 rabbits, aged 13 weeks at the beginning of the experiment; the vertical bars correspond to 1 SE. Reproduced from reference (11), with permission from the publishers.

resulted in a significant increase in the concentration of serum cholesterol after only one day (11).

2. The nature of dietary protein and serum cholesterol in rabbits

Carroll and Hamilton (12, 13) have reported the results of a series of feeding trials designed to test the effect of different proteins on plasma cholesterol levels. Some protein sources, such as extracted whole egg, skim milk powder and casein produced rather high concentrations of serum cholesterol, whereas other sources of protein, such as wheat gluten, peanut meal and soybean protein were able to maintain low levels of serum cholesterol (Fig. 2).

Table 1: Concentration of serum cholesterol in rabbits fed semipurified diets containing various sources of protein or amino acid mixtures (25%, w, w)

Protein and amino acid source	Amino acids composition equivalent to:	Number of animals	Serum cholesterol (mmol/l)
Casein Amino acids Soybean protein Amino acids	Casein Casein Soybean protein Soybean protein	6 9 6 10	5.72±0.98 5.52±1.09 1.76±0.36 3.21±0.78

Results are expressed as means \pm SE.

The diets were fed for 28 days to rabbits aged about 10 weeks at the beginning of the experiment. Data are taken from reference (14).

It cannot be decided from the data presented in Figure 2 whether the differing effects of dietary proteins on plasma cholesterol in rabbits are due to the proteins themselves or to other constituents of the protein preparations. Most of the preparations used in the reported experiments contained very little fat, but the protein content was often no more than 60 to 65 percent of the total. Even the purest preparations of casein and isolated soy protein contained up to 20 percent of nonprotein material.

To see whether the protein itself determines the level of serum cholesterol, rabbits were fed semipurified diets containing an amino acid mixture resembling the composition of either casein or soy protein (14). It was found that the amino acid mixture

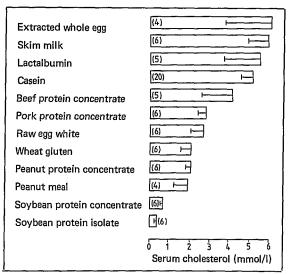


Figure 2: Concentrations of plasma cholesterol in rabbits fed semipurified diets containing 4.23% (w, w) of N from various animal and plant proteins. Based on data reported by Carroll and Hamilton (12, 13). The rabbits, aged 8–12 weeks at the beginning of the experiment, were fed the diets for 28 days. Figures in parantheses refer to the number of animals; horizontal bars represent the standard error of the mean.

equivalent in composition to casein produced concentrations of serum cholesterol similar to those obtained with casein, whereas the mixture imitating soy protein induced higher levels of serum cholesterol than the intact protein, but the levels were still lower than those seen with casein (Table 1). Thus, at least part of the differential effect of casein and soy protein on serum cholesterol appears to be related to differences in the amino acid composition of these proteins.

Kritchevsky et al. (15) suggested that the differential effects of casein and soy protein on serum cholesterol levels and atherosclerosis in rabbits are due to the different ratios in the protein of lysine to arginine (casein, 2.04; soy protein, 0.88 on a weight basis). Indeed they found that addition of lysine to soy protein increased the level of serum cholesterol, but addition of arginine to casein gave equivocal results (15). Although addition of arginine plus glycine plus alanine to casein does produce some lowering of serum cholesterol levels, no clear relation with the lysine: arginine ratio is observed (14, 16, 17). When the results of feeding trials with amino acid mixtures were combined, and the lysine: arginine ratio was plotted *versus* the level of plasma cholesterol, only a very scattered graph was obtained (18). Furthermore, we found that increasing the amount of casein in both diets with and without added cholesterol further increased serum cholesterol levels (19), while the lysine: arginine ratio obviously remained constant.

There is evidence that amino acids other than lysine and arginine also play a role in determining serum cholesterol levels in rabbits. Glycine, when added to a semipurified diet containing casein, counteracted the hypercholesterolemic response (16, 17). Methionine, when added in relatively large amounts to a soy protein diet, elevated serum cholesterol (12).

Table 2: Serum cholesterol and body weight of rabbits fed semipurified diets containing formaldehyde-treated proteins.

Dietary protein	Body w	eight (g)	Serum cholesterol (mmol/lj	
(weight %)		final	initial final	
21% casein + 21% soy	2204±67	2875±50		3.90±0.42 ^a
42% casein	2204±44	2818±59		10.41±1.74 ^b
21% casein + 24.2% F-soy	2200±51	2928±60		3.33±0.55 ^a
21% casein + 23% F-casein	2195±69	2702±60		5.58±1.24 ^{ac}

Results are expressed as means \pm SE for 10 animals per group. The animals, aged about 12 weeks at the beginning of the experiment, were fed the diets for 8 weeks. F = formaldehyde-treated; figures bearing a different superscript are significantly different (P<0.05).

Data from unpublished observations of C. E. West, A. C. Beynen, A. H. M., Terpstra, K. E., Scholz, J. B., Schutte, K., Deuring and L. G. M. van Gils.

It is clear that the serum cholesterol level in rabbits can be modified by the amino acid composition of the diet. However, it follows from the data in Table 1 that other factors such as the structure and digestibility of the proteins are almost certainly also involved.

The possibility that the cholesterolemic responses to casein and soy protein are effected by the structure of the proteins was tested by modifying their structure by formaldehyde-treatment. The formaldehyde-treated proteins were incorporated into semipurified diets and fed to New Zealand white rabbits. The data in Table 2 show that formaldehyde-treatment of the proteins did not significantly affect growth of the rabbits. However, the hypercholesterolemic effect of casein is markedly reduced after formal-dehyde-treatment. The addition of formaldehyde (0.4%, w/w) per se to the 42%-casein diet did not significantly affect the level of serum cholesterol. We conclude that the tertiary structure of casein is an important factor in determining the cholesterolemic response in rabbits to this protein.

Table 3: Concentration of cholesterol in lipoprotein fractions of rabbits fed semipurified diets containing either soy protein or casein.

Lipoprotein fraction	Cholesterol concentra	ation (mmol/l serum)
	Soy protein diet	Casein diet
$\begin{array}{l} \text{VLDL } (\varrho 20 < 1.006) \\ \text{IDL}_1 \ (1.006 < \varrho 20 < 1.012) \\ \text{IDL}_2 \ (1.012 < \varrho 20 < 1.019) \\ \text{LDL}_1 \ (1.019 < \varrho 20 < 1.040) \\ \text{LDL}_2 \ (1.040 < \varrho 20 < 1.063) \\ \text{HDL}_1 \ (1.063 < \varrho 20 < 1.092) \\ \text{HDL}_2 \ (1.092 < \varrho 20 < 1.125) \\ \text{HDL}_3 \ (1.125 < \varrho 20 < 1.210) \\ \end{array}$	0.15±0.04 0.03±0.01 0.18±0.02 0.77±0.13 0.17±0.04 0.29±0.08 0.36±0.09 0.21±0.02	0.26±0.06 0.19±0.11 ^a 0.52±0.25 ^b 1.74±0.38 ^b 0.34±0.05 ^c 0.44±0.09 0.50±0.07 0.25±0.02
Serum total cholesterol (mmol/l)	2.27±0.32	4.71±0.90°

Results are expressed as mean \pm SE for 9 rabbits in each dietary group. All rabbits were fed the semipurified diet containing soy protein (21%, w/w) for 4 weeks when 9 animals, aged about 14 weeks at that time, were allocated to the semipurified diet containing casein (21%, w/w). Blood samples were taken 36 days after this allocation to the dietary groups.

Significantly different (two-tailed Wilcoxon test) from the soy-fed group: a, P<0.01; b, P<0.05, c, P<0.10. Data are taken from reference (20).

3. Effects of casein and soy protein on the cholesterol concentration in serum lipoproteins of rabbits

The cholesterol concentrations in the different serum-lipoprotein fractions of rabbits fed casein and soyprotein diets are given in Table 3. The increase in serum cholesterol of the casein-fed animals was reflected in all fractions, except for the fraction with density limits $1.125 < \varrho_{20} < 1.210$ kg/l, which is the HDL $_3$ fraction. However, only the increases in the IDL $_1$ (1.006 $< \varrho_{20} < 1.019$ kg/l) and LDL $_1$ and LDL $_2$ (1.019 $< \varrho_{20} < 1.063$ kg/l) fractions reached statistical significance.

We have studied the time course of the changes in the concentration of cholesterol in the LDL and VLDL fraction of rabbits fed casein (21). It appeared that the cholesterol concentration increased first in the LDL fraction and subsequently in the VLDL fraction. The VLDL fraction in rabbits fed casein becomes markedly enriched with app E (21).

4. Mechanism of action of dietary protein

Feeding casein to rabbits has been shown to reduce the faecal enterior of steroids compared to that of soy protein (22), an effect paralleling, if not preceeding the elevation of serum cholesterol (23). Subsequently, the number of hepatic LDL receptors decrease (24), which aggravates the degree of hypercholesterolemia and which may further reduce biliary steroid output. Thus the accumulation of serum cholesterol in the casein-fed rabbit most likely is the result of a decreased clearance of plasma cholesterol.

Total body cholesterol synthesis in rabbits fed casein has been found to be reduced when compared to animals on a diet containing soy protein (22). The depressed synthesis of cholesterol in rabbits fed casein is most likely the result of feed-back inhibition effected by the increased level of serum cholesterol (25). This regulatory device, however, only protects the animals against further development of the hypercholesterolemia. The depressed synthesis of cholesterol and the diminished faecal excretion of steroids in casein-fed rabbits results in a reduced turnover of cholesterol when compared with rabbits fed soy protein.

5. The rabbit and other laboratory animals as experimental model to study the effects of dietary protein on serum cholesterol levels

It has to be stressed that the concept of casein as a hypercholesterolemic protein in rabbits has several limitations. The hypercholesterolemic response of rabbits to a cholesterol-free, casein containing diet, depends on several other components of the diet, such as carbohydrates, fiber (12), fats (26) and possibly salts (27). Furthermore, the hypercholesterolemic effect of casein in a cholesterol-free diet was only observed in young growing rabbits and not in their mature counterparts (28). When 0.25% (w, w) cholesterol was added to the semipurified diet, the differential effect of casein and soy protein was also seen in mature rabbits (29). In rats (30), mice (31), guinea pigs (32), chickens (33) and calves (34) fed cholesterol-free diets, casein did not significantly affect serum cholesterol levels when compared with soy protein. However, when cholesterol was added to the diets, a hypercholesterolemic effect of casein was observed in female lean Zucker rats, but not in the males (35) or chickens (36). In chickens (36), we have observed that increasing the level of protein, irrespective of whether it was casein or soy protein, decreased the concentration of cholesterol in serum.

The lack of hypercholesterolemic effect of casein *versus* soy protein in essentially cholesterol-free diets with mature rabbits (29), rats (30), mice (31), guinea pigs (32), chickens (33) and calves (34), may be due to the composition of the diets used with respect to components other than protein. In rats, Nagata *et al.* (37) have found that the

Table 4: Serum cholesterol concentration (mmol/l) of male Wistar rats fed cholesterol-free, semipurified diets containing either casein of soybean protein.

	initial	day 29	day — 15	day — 1	day + 14	day + 28	day + 33
Soy-casein group	2.13±0.11	1.91±0.09	2.02±0.09	2.19±0.04	2.87±0.24	2.57±0.09	2.96±0.12
Casein-soy group	2.16±0.03	2.48±0.10 ^a	2.70±0.15 ^a	2.73±0.15 ^b	2.32±0.12 ^b	2.24±0.10 ^b	2.57±0.19

Rats, aged about 6 weeks and raised on a commercial rat diet, were fed the semipurified diet containing soybean protein for 23 days until day -43 of the experiment. Then, one group was allocated to the casein diet (casein-soy group) and the other group remained on the soybean-protein diet (soy-casein group) until the cross-over (day 0), when the diets were changed. The initial serum-cholesterol value refers to day -49 of the experiment. Results are expressed as means \pm SE for 6 or 7 animals in each group. a, statistically different P<0.01 from the soy-caseingroup; b, P<0.05. The diets contained 21% (w, w) casein or soybean protein and 1% (w, w) corn oil as fat source. Data taken from unpublished observations of A. C. Beynen, A. H. M. Terpstra, C. E. West and G. van Tintelen.

amount of fat in the cholesterol-free diet must be as low as 1% (w, w) in order to demonstrate a hypercholesterolemic effect of casein. We have recently reproduced this observation in male Wistar rats (Table 4).

We have also studied the effects of dietary casein and soybean protein on the concentration of serum cholesterol in rhesus monkeys. Ten mature female rhesus monkeys were alternately fed semipurified diets containing either casein or soybean protein. The diets contained 26 energy % protein, 13 energy % fat and 300 mg cholesterol per 4.18 MJ (1000 kcal). In addition, a restricted amount of fruit and vegetables were fed, providing 2.2 g protein per day. All together, the animals received a diet containing 21–24 energy % protein of which 92–95% was provided by the test protein. The results in Table 5 show that the feeding of diets containing casein produced a marked elevation of serum cholesterol levels, whereas the replacement of casein by soybean protein had the opposite effect. The initial increase in serum cholesterol level observed when the animals were transferred from the commercial diet to the semipurified diet can be explained by the increased concentration of cholesterol in the latter diet. The results of this study suggest that the hypercholesterolemic effect of casein in comparison with soybean protein is not merely a phenomenon observed in experimental animals such as rabbits and rats, but is a more general phenomenon also observed in species more akin to man.

6. Dietary protein and serum cholesterol in man

The ultimate aim of the studies with experimental animals is to provide further insight into practical means of decreasing the level of serum cholesterol in humans by means of

Table 5: Concentration of serum cholesterol in rhesus monkeys fed alternately semipurified diets containing casein or soybean protein.

Diet	Weeks on diet	Serum chole	sterol (mmol/l)
		Final	Change
 Commercial Soybean protein Casein Soybean protein Casein 	13 15 17 17	3.92±0.24 4.44±0.28 5.81±0.45 4.18±0.31 5.46±0.50	$+0.51\pm0.24^{b}$ $+1.38\pm0.32^{a}$ -1.63 ± 0.37^{a} $+1.28\pm0.37^{a}$

Results are expressed as means \pm SE for 10 animals.

Change significantly different from zero: a, P<0.01; b, P<0.05. Data taken from unpublished studies of A. H. M. Terpstra, C. E. West, J. T. C. M. Fennis, J. A. Schouten and E. A. van der Veen.

Table 6: Effects of casein and soybean protein on serum cholesterol concentration in healthy human subjects.

	10000 1000)						
Age of	Number Diet	Dietary protein		Comp	Composition of diets	diets		Serum cholesterol (mmol/l)	terol (mmol/l)
subjects			Protein Fat (energy %)	Fat (energy %)	P/S	Chole- sterol (mg/day)	Test- period (days)	Initial value	Final value
Exp. 1									
18-28 yr	52	casein	13	37	9.0	387	58	3.93±0.14	3.85±0.12
	24	soybean protein isolate	13	37	9.0	365	78	3.95±0.13	3.88±0.12
Exp. 2									
29-60 yr	17	casein	16	35	0.5	374	58	5.35±0.23	5.30±0.22
	20	soybean protein isolate	16	35	0.5	381	28	5.30±0.23	5.09±0.25
	8	soybean protein concentrate	16	32	0.5	382	28	5.14 ± 0.20	5.17±0.22

The initial values in Exp. 1 were measured after a control period of 10 days during which all the subjects received a diet containing a 2:1 mixture of casein and soybean protein. In Exp. 2 the control period lasted 17 days during which all the subjects received the casein diet. The data are taken from references (45) and (46).

dietary alterations. A decrease in the level of serum cholesterol would probably lead to a decrease in the incidence of atherosclerotic diseases.

It was shown by Hodges et al. (38) that the substitution of vegetable proteins (mainly soybean protein) for animal proteins in the diet of hypercholesterolemic subjects markedly lowered plasma cholesterol levels. Further studies have also shown a reduction (by 10-25%) in the concentration of plasma cholesterol in individuals with varying degrees of hypercholesterolemia (39-41). However, in all these studies the transfer of the subjects from their habitual, mixed protein diet to the diet containing predominantly soybean protein, involved a marked increase in the ratio of dietary polyunsaturated fatty acids to saturated fatty acids (P/S ratio) and/or a decrease in cholesterol intake. The soybean protein diets were most likely also relatively rich in complex carbohydrates and dietary fiber. In one study (38) a tremendous increase in the intake of the plant sterol, β -sitosterol, was found to be associated with the diet containing soybean proteins. These changes in the diet, namely an increased P/S ratio, a decreased content of cholesterol and an increased content of β -sitosterol are all known to lower plasma cholesterol levels. Thus it is likely that changes in these dietary factors and not the soybean protein component had caused the reported (39-41) lowering of plasma cholesterol. This is substantiated by the work of investigators who used two experimental diets with a relatively high P/S ratio and low cholesterol content, which differed only in their protein constituents. It was then found that both diets, when compared to the habitual diet, lowered plasma cholesterol in hypercholesterolemic individuals and that the response was identical, irrespective of whether animal protein or soybean protein was the main protein source (42, 43). Goldberg et al. (44), who used a similar experimental design, reported that soybean protein, when compared to animal protein, resulted in an additional reduction in the plasma concentrations of total cholesterol by $3.5\pm5.5\%$ (n = 12).

Strictly controlled studies in our laboratory with young healthy volunteers (45) and also with middle-aged volunteers (46) have demonstrated that soybean protein, when compared to the animal protein casein has little or no effect on the serum level of cholesterol (Table 6). In these two studies, diets were used in which 60 or 65% of the protein in the diet consisted of either soybean protein or of casein. The similarity achieved in other components of the diets such as in cholesterol and fat content and in P/S ratio of the fat was optimal. Although it was not possible to demonstrate a difference in the level of total cholesterol in plasma between the diets containing soybean protein and casein, the soybean protein diet produced a shift in the cholesterol from the low density lipoproteins (LDL) to the high density lipoproteins (HDL). Such an effect is generally regarded as being favourable in the prevention of coronary heart disease. No effect on the level of cholesterol and other components in serum was also found by Lembke *et al.* (47) when soybean protein was compared with casein in a controlled experiment with adult volunteers.

Walker et al. (48) did demonstrate that a mixed vegetable protein diet did give lower plasma cholesterol values in normocholesterolemic women than a diet containing animal protein. In this study (48) the animal protein diet contained meat, cheese and milk as opposed to cereals, rice, beans and legumes in the vegetable protein diet. Thus the animal protein diet must have contained more cholesterol than the vegetable protein diet. Carroll et al. (49) found that replacement of animal protein by soybean protein significantly lowers (by 5%) plasma cholesterol in healthy young women. In order to balance the experimental diets for their cholesterol content, Carroll et al. (49) added crystalline cholesterol to the diet containing soybean protein. Since pure cholesterol is not always absorbed as well as cholesterol in animal foodstuffs, the soybean protein diet may have contained effectively less cholesterol, which may explain the somewhat lower plasma cholesterol levels observed on this diet. Thus the specific effect of soybean protein versus

casein on the concentration of total cholesterol of serum in healthy humans, if any, cannot be very great.

Why does the type of dietary protein affect the plasma concentration of total cholesterol in laboratory animals, including rhesus monkeys, but not in humans? There are several ways to explain this difference. First of all, in the animal experiments diets are formulated especially so as to maximize the hypercholesterolemic response to casein. Casein is much less effective if it is part of a normal mixed animal feed. Secondly, in the human being it could be a matter of a species-dependent resistance to the dietary protein source. Furthermore, in most animal experiments young animals are used which are fed the test diets during a considerable part of their life span, whereas the above mentioned trials with humans lasted 2—6 weeks. Possibly, long-term experiments starting at an early age will show an effect of dietary protein on the level of plasma cholesterol in man. This would be compatible with the observation that the hypercholesterolemic effect of casein was only observed in young growing rabbits and not in their mature counterparts (28).

An important difference between the experiments with humans and animals relates to the amount of test protein in the diets. With animals the diets contained relatively high proportions of protein. In our experiments with humans only about 60% of the dietary protein could be replaced by either casein or soy protein; further replacement would only have been possible by the use of liquid-formula diets, analogous to semipurified diets in animals. Possibly, with a higher degree of replacement of proteins and/or higher amounts of protein in the diets of humans, the type of protein does affect the level of serum cholesterol. In any case, the striking effects on serum cholesterol concentrations of dietary casein and soy protein *per se* seen in laboratory animals have until now not been observed in man.

7. References

- (1) Ignatowski, A.: Virchows Arch. path. Anat. Physiol. klin. Med. 198 248-270 (1909)
- (2) Stuckey, N. W.: Zbl. allg. Path. path. Anat. 23 910-911 (1912)
- (3) Wesselkin, N. W.: Virchows Arch. path. Anat. Physiol. klin. Med. 212 225-235 (1913)
- (4) Anitschkow, N., Chalatow, S.: Zbl. allg. Path. path. Anat. 24 1-9 (1913)
- (5) Wacker, L., Hueck, W.: Münch. med. Wochenschr. 60 2097-2100 (1913)
- (6) Newburgh, L. H.: Arch. Intern. Med. 24 359-377 (1919)
- (7) Meeker, D. R., Kesten, H. D.: Arch. Path. 31 147-162 (1941)
- (8) Lambert, G. F., Miller, J. P., Olsen, R. T., Frost, D. V.: Proc. Soc. Exp. Biol. 97 544-549 (1958)
- (9) Wigand, G.: Acta Med. Scand. (Suppl. 351) 166 1-91 (1959)
- (10) Hermus, R. J. J.: Experimental atherosclerosis in rabbits on diets with milk fat and different proteins. Centre for Agricultural Publications and Documentation, Wageningen – The Netherlands (1975)
- (11) Terpstra, A. H. M., Woodward, C. J. H., West, C. E., van Boven, H. G.: Br. J. Nutr. 47 213-221 (1982)
- (12) Carroll, K. K., Hamilton, R. M. G.: J. Food Sci. 40 18-23 (1975)
- (13) Hamilton, R. M. G., Carroll, K. K.: Atherosclerosis 24 47-62 (1976)
- (14) Huff, M. W., Carroll, K. K.: J. Nutr. 110 1676-1685 (1980)
- (15) Kritchevsky, D.; J. Am. Oil. Chem. Soc. 56 135-140 (1979)
- (16) Hermus, R. J. J., Dallinga-Thie, G. M.: Lancet II 48 (1979)
- (17) Katan, M. B., Vroomen, L. H. M., Hermus, R. J. J.: Atherosclerosis 43 381-391 (1982)
- (18) Carroll, K. K.: J. Am. Oil. Chem. Soc. 58 416-419 (1981)
- (19) Terpstra, A. H. M., Harkes, L., van der Veen, F. H.: Lipids 16 114-119 (1981)
- (20) Beynen, A. C., den Engelsman, G., Scholz, K. E., West, C. E.: Ann. Nutr. Metab. 27 117-124 (1983)
- (21) Scholz, K. E., Beynen, A. C., West, C. E.: Atherosclerosis 44 85-97 (1982)
- (22) Huff, M. W., Carroll, K. K.: J. Lipid Res. 21 546-558 (1980)
- (23) Beynen, A. C., Winnubst, E. N. W., West, C. E.: Z. Tierphysiol., Tierernährg. u. Futtermittelkde 49 43-49 (1983)
- (24) Chao, Y., Yamin, T.-T., Alberts, A. W.: J. Biol. Chem. 257 3623-3627 (1982)
- (25) Dietschy, J. M., Wilson, J. D.: New Engl. J. Med. 282 1128-1138 (1970)
- (26) Beynen, A. C., West, C. E.: Z. Tierphysiol., Tierernährg. u. Futtermittelkde 46 233-239 (1981)
- (27) Beynen, A. C., van Wanrooy-Stroeken, C. T. M.: Z. Tierphysiol., Tierernährg. u. Futtermittelkde 46 240-246 (1981)

- (28) West, C. E., Deuring, K., Schutte, J. B., Terpstra, A. H. M.: J. Nutr. 112 1287-1295 (1982)
- (29) Terpstra, A. H. M., Deuring, K., West, C. E.: Nutr. Rep. Int. 26 389-394 (1982)
- (30) Sautier, C., Doucet, C., Flament, C., Lemonnier, D.: Atherosclerosis 34 233-241 (1979)
- (31) Raheja, K. L., Linscheer, W. G.: Ann. Nutr. Metab. 26 44-49 (1975)
- (32) Terpstra, A. H. M., van Tintelen, G., West, C. E.: Nutr. Rep. Int. 25 725-731 (1982)
- (33) Moi, M. A. E., de Smet, R. C., Terpstra, A. H. M., West, C. E.: J. Nutr. 112 1029-1037 (1982)
- (34) Beynen, A. C., van Gils, L. G. M.: Z. Tierphysiol., Tierernährg u. Futtermittelkde 49 49-56 (1983)
- (35) Terpstra, A. H. M., van Tintelen, G., West, C. E.: Atherosclerosis 42 85-95 (1982)
- (36) Terpstra, A. H. M., Schutte, J. B., West, C. E.: Atherosclerosis 46 95-104 (1983)
- (37) Nagata, Y., Imaizu, K., Sugano, M.: Br. J. Nutr. 44 113-121 (1980)
- (38) Hodges, R. E., Krehl, W. A., Stone, D. B., Lopez, A.: Am. J. Clin. Nutr. 20 198-208 (1967)
- (39) Sirtori, C. R, Agradi, E., Conti, F., Mantero, O.: Lancet i 275-277 (1977)
- (40) Descovich, G. C., Ceredi, C., Gaddi, A., Benassi, M. S., Mannino, G., Colombo, L., Cattin, L., Fontana, G., Senin, U., Mannarino, E., Caruzzo, C., Bertelli, E., Fragiacomo, C., Noseda, G., Sirtori, M., Sirtori, C. R.: Lancet ii 709-712 (1980)
- (41) Vessby, B., Karlström, B., Lithell, H., Gustafsson, I.-B., Werner, I.: Human Nutr. Appl. Nutr. **36A** 179–189 (1982)
- (42) Holmes, W. L., Rubel, G. B., Hood, S. S.: Atherosclerosis 36 379-387 (1980)
- (43) Shorey, R. A. L., Bazan, B., Lo, G. S., Steinke, F. H.: Am. J. Clin. Nutr. 34 1769-1778 (1981)
- (44) Goldberg, A. P., Lim, A., Kolar, J. B., Grundhauser, J. J., Steinke, F. H., Schonfeld, G.: Atherosclerosis 43 355-368 (1982)
- (45) van Raaij, J. M. A., Katan. M. B., Hautvast, J. G. A. J., Hermus, R. J. J.: Am. J. Clin. Nutr. 34 1261 1271 (1981)
- (46) van Raaij, J. M. A., Katan, M. B., West, C. E., Hautvast, J. G. A. J.: Am. J. Clin. Nutr. 35 925-934 (1982)
- (47) Lembke, A., Greggersen, H., Kay, H., Rathjen, G.: Milchwissenschaft 36 (9) 557-561 (1981)
- (48) Walker, G. R., Morse, E. H., Overley, V. A.: J. Nutr. 72 317-321 (1960)
- (49) Carroll, K. K., Giovanetti, P. M., Huff, M. W., Moase, O., Roberts, D. C. K., Wolfe, B. M.: Am. J. Clin. Nutr. 31 1312-1321 (1978)

8. Summary

West, C. E., van Raaij, J. M. A., Beynen, A. C., Hautvast, J. G. A. J., Katan, M. B., Kuyvenhoven, M. W., Scholz, K. E., Terpstra, A. H. M.: **The influence of dietary protein on serum cholesterol in man and experimental animals.** Kieler Milchwirtschaftliche Forschungsberichte **35** (3) 397–407 (1983)

14 Proteins (metabolism, cholesterol)

Studies in experimental animals have shown that the nature of dietary protein can influence the concentration of cholesterol in serum. The replacement of soy protein in semipurified diets of rabbits and rats by casein results in higher levels of serum cholesterol. The effect appears to be associated not only with the amino acid composition, but also with the structure of the proteins although the precise mechanisms involved are not clearly understood. The hypercholesterolemic effect of dietary casein when compared with soy protein has also been found in rhesus monkeys. Thus the effect is not merely a phenomenon observed in experimental animals such as rabbits and rats but is more general as it is also observed in species more akin to man. Much attention has been directed towards the role of dietary protein in determining serum cholesterol levels in man because a decrease in the level of serum cholesterol would probably lead to a decrease in the incidence of atherosclerotic disease. Strictly controlled studies in our laboratory with healthy young volunteers and also with middle-aged volunteers have demonstrated that soybean protein, when compared to casein has little or no effect on the level of total cholesterol in serum. Several studies have demonstrated an apparent effect but often the effects can be attributed to other functions such as differences in the P/S ratio of the dietary fat and the cholesterol content of the test diets and not to the nature of the dietary protein. Thus the striking effects on serum cholesterol concentrations of dietary casein and soy protein per se seen in laboratory animals have not up until now been observed in man.

West, C. E., van Raaij, J. M. A., Beynen, A. C., Hautvast, J. G. A. J., Katan, M. B., Kuyvenhoven, M. W., Scholz, K. E., Terpstra, A. H. M.: **Der Einfluß von Nahrungsproteinen auf Serumcholesterin beim Menschen und bei Versuchstieren.** Kieler Milchwirtschaftliche Forschungsberichte **35** (3) 397–407 (1983)

14 Proteine (Stoffwechsel, Cholesterin)

Untersuchungen an Tieren haben ergeben, daß die Beschaffenheit des Nahrungsproteins den Cholesteringehalt im Serum beeinflussen kann. Wird Sojaprotein in halbgereinigten Diäten für Kaninchen und Ratten durch Casein ersetzt, erhöht sich der Serumcholesteringehalt. Diese Wirkung hängt nicht nur mit der Zusammensetzung der Aminosäuren zusammen, sondern auch mit der Proteinstruktur, obwohl die hier beteiligten Mechanismen nicht genau erklärbar sind. Der Hypercholesterinämie-Effekt von Nahrungscasein, verglichen mit Sojaprotein, wurde auch bei Rhesusaffen nachgewiesen. Folglich ist der Effekt nicht nur ein bei Versuchstieren wie Kaninchen und Ratten beobachtetes Phänomen, sondern läßt sich auch bei Arten, die dem Menschen näher verwandt sind, feststellen. Dem Einfluß des Nahrungsproteins auf die Höhe des Serumcholesteringehaltes beim Menschen wurde besondere Beachtung geschenkt, da eine Verringerung des Serumcholesteringehaltes die Entwicklung der Atherosklerose beeinflussen könnte. Untersuchungen, die in unserem Labor unter streng kontrollierten Bedingungen mit gesunden freiwilligen jungen Probanden und Versuchspersonen mittleren Alters durchgeführt wurden, haben gezeigt, daß Sojaprotein, verglichen mit Casein, einen geringen oder keinen Einfluß auf den Gesamt-Cholesteringehalt im Serum hat. In verschiedenen Untersuchungen wurde ein offensichtlicher Einfluß nachgewiesen, jedoch können die Einflüsse oftmals auf andere Faktoren, wie Unterschiede im P/S-Quotient des Nahrungsfettes und den Cholesteringehalt der Testdiäten, jedoch nicht auf die Beschaffenheit des Nahrungsproteins zurückgeführt werden. Der bei Versuchstieren auffallende Einfluß von Casein und Sojaprotein auf den Serumcholesteringehalt ist beim Menschen bislang nicht festgestellt worden.

West, C. E., van Raaij, J. M. A., Beynen, A. C., Hautvast, J. G. A. J., Katan, M. B., Kuyvenhoven, M. W., Scholz, K. E., Terpstra, A. H. M.: Effet de la protéine diététique sur le cholestérol du sérum chez l'homme et les animaux. Kieler Milchwirtschaftliche Forschungsberichte 35 (3) 397–407 (1983)

14 Protéines (métabolisme, cholestérol)