Vegetable Protein and Atherosclerosis

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ABSTRACT

A number of studies purport to demonstrate that animal protein (usually casein) is more cholesteremic and atherogenic than vegetable protein (usually soy protein). These findings are generally true, but the effect of any single dietary component may be influenced by any other one. Thus, when the carbohydrate is dextrose, casein is more cholesteremic in rabbits than is soy protein, but when the carbohydrate is raw potato starch, the two proteins are equivalent. Similarly, a casein-cellulose diet is more cholesteremic and atherogenic for rabbits than is one containing soy protein and cellulose. Substitution of alfalfa for cellulose renders the two proteins virtually the same. In man, too, vegetable protein appears to be less cholesteremic than animal protein. The difference persists even in the face of saturated fat. In seeking a mechanism to explain the differences in atherogenicity, we have hypothesized that a high ratio of lysine to arginine may be important. The lysine/arginine ratio of casein is 2.0 and that of soy protein is 0.90. Addition of enough lysine to a soy protein diet to raise the lysine/arginine ratio to 2.0 also increases the atherogenicity of that diet.

In 1909 Ignatowski (1) provided a clear demonstration that diet could affect atherosclerosis. He hypothesized that diets rich in animal protein led to atherosclerosis and tested this thesis by feeding rabbits diets containing meat, eggs and animal products. Rabbits fed these diets showed less than optimum weight gain, became anemic and cirrhotic, and exhibited aortic atherosclerosis. Ignatowski's work appeared at the same time that Anitschkow (2) was reporting that addition of cholesterol to a rabbit's diet led to atherosclerosis. Since the substances in Ignatowski's atherogenic diet all contained cholesterol, it was concluded that this substance had been responsible for the observed effects, and the role of dietary protein was ignored.

In the 1920s Newburgh and his colleagues investigated the effects of dietary protein on atherogenesis in rabbits (3,4). A diet containing meat led to some atherosclerosis in 4 weeks. Thirty g/day of casein was atherogenic if fed for 11 months. Powdered beef fed at a level that provided 27% protein was atherogenic if fed for a year. When the level of proteins was raised to 36%, the atherogenic effect was seen much earlier. The 27% powdered beef diet provided about 30 mg of cholesterol per day.

Meeker and Kesten (5,6) compared the effects of 38% casein or 39% soy protein in rabbits given 60 or 250 mg of cholesterol daily. The basal diet contained white flour, alfalfa meal, linseed oil meal, ground carrots and salt. The protein/carbohydrate/fat (PCF) ratio of the basal diet was 15:55:5. The casein diet introduced casein at the expense of some flour and alfalfa meal, and the linseed oil meal was deleted. Its PCF was 38:39:4. The soy diet dispensed with the white flour and replaced it with soy flour. Its PCF was 39:34:3. Ground carrot was the major (50%) ingredient of all three diets. The soy diet was reportedly more cholesteremic but resulted in lower incidence and severity of atherosclerosis (Table I). In the absence of cholesterol, only the casein diet was atherogenic.

Lofland and his collaborators (7,8) studied the effects of different combinations of fats and proteins on atherosclerosis in pigeons and squirrel monkeys. They (8) noted that any single dietary component may be influenced by other dietary ingredients and that the effects are not always additive. Table II summarizes an experiment in which the effects of wheat gluten and casein-lactalbumin (85:15) were compared. The difference between the two types of protein was dependent, in part, on the type of fat in the diet. Level

TABLE I

Effects of Casein and Soy Protein on Atherosclerosis in Rabbits (5,6)

Diet[a]	Survival No.	Mg cholesterol/day	Average atherosclerosis[b]
Basal	8/8	---	0.0
Casein	6/6	---	0.67
Casein	6/8	---	0.83
Basal	9/10	60	0.89
Casein	5/5	60	2.20
Casein	8/8	60	2.00
Soy	8/8	---	0.0
Basal	9/9	60	0.89
Soy	6/8	60	0.33
Basal	6/6	250	1.50
Soy	6/6	250	0.67
Basal[c]	6/6	250	1.50
Soy[c]	4/6	250	0.25

[a]Description of diets in text.

[b]Graded on a 0-3 scale.

[c]Three month feeding, all others 6 months.

TABLE II

Serum Cholesterol (mg/dl) and Atherosclerotic Index of White Carneau Pigeons as a Function of Dietary Protein and Fat (8)

Fat[a]	Protein[b]	
	Casein-Lactalbumin (85:15)	Wheat gluten
Butter[c]		
SC	472 ± 22	419 ± 23
AI	5.1	3.5
INC	89	100
Corn oil		
SC	345 ± 41	492 ± 32
AI	5.2	5.7
INC	100	78
Crisco		
SC	577 ± 98	495 ± 45
AI	3.5	4.3
INC	89	85
Margarine		
SC	375 ± 24	442 ± 32
AI	3.0	2.0
INC	73	60

[a]Percent of calories.

[b]30% of calories.

[c]SC, serum cholesterol; AI, atherosclerotic index; INC, incidence (% birds with lesions).

TABLE III

Plasma Cholesterol Levels in Rabbits Fed Different Proteins (12)[a]

Diet	No.	Weight gain (g/day)	Feed intake (g/day)	Plasma cholesterol (mg/dl)	
				14 days	28 days
Commercial	22	27 ± 1	105 ± 5	65 ± 2	70 ± 5
Casein	20	62 ± 4	62 ± 4	140 ± 21	200 ± 22
Skim milk	6	18 ± 3	59 ± 5	185 ± 14	230 ± 40
Lactalbumin	5	9 ± 2	46 ± 14	115 ± 32	215 ± 69
Extracted egg	4	-1 ± 0.7	65 ± 10	150 ± 16	235 ± 89
Beef protein conc.	5	20 ± 2	54 ± 15	150 ± 28	160 ± 60
Pork protein conc.	6	25 ± 1	45 ± 7	140 ± 21	110 ± 17
Raw egg white	6	9 ± 2	40 ± 14	110 ± 36	105 ± 28
Wheat gluten	6	3 ± 1	25 ± 4	65 ± 11	80 ± 21
Peanut protein conc.	6	15 ± 2	40 ± 10	90 ± 23	80 ± 10
Peanut meal	4	24 ± 2	25 ± 6	85 ± 18	75 ± 27
Soy protein conc	6	12 ± 2	24 ± 8	75 ± 23	25 ± 5
Soy protein isolate	6	4 ± 1	15 ± 7	30 ± 14	15 ± 5

[a]Diets contained about 30% protein; 60% dextrose; 4% salt mix; 5% cellulose and 1% corn oil. Beef, pork and egg had been extracted and contained 0.17, 0.10 and 0.22 mg cholesterol/g, respectively.

TABLE IV

Influence of Dietary Carbohydrate on Plasma Cholesterol Levels of Rats (14)

Diet	No. of rats	Plasma cholesterol[a] (mg/dl ± SEM)
Commercial	7	52 ± 4a,b
Semipurified[b]		
Dextrose	6	61 ± 5c
Wheat starch	6	77 ± 5a,d
Rice starch	6	62 ± 3e
Potato starch, raw	8	54 ± 1c,d,e,f
Potato starch, cooked	6	69 ± 4b,f

[a]Values bearing same letter are significantly different.

[b]60% carbohydrate; 27% casein; 1% fat.

of protein may also be of importance. In the absence of cholesterol, a diet containing 15% protein was more atherogenic than diets containing 5 or 30% protein, but in the presence of 0.25% cholesterol the 30% protein diet was the most atherogenic (9). Strong and McGill (10) fed baboons diets containing 8 or 20% of calories as casein, 0.01 or 0.5% cholesterol and 40% of calories as saturated (iodine value 53) or unsaturated (iodine value 109) fat. The design of the experiment gave eight dietary combinations: high cholesterol plus high or low protein and saturated or unsaturated fat and low cholesterol plus the different levels of protein and different fats. Only in the high cholesterol-saturated fat group did the low protein level lead to a greater level of aortic sudanophilia.

Carroll and his coworkers have carried out studies on the effects of animal or vegetable protein on cholesterol levels in rabbits (11-13). Some of their findings are summarized in Table III. It is evident that there are striking differences among animal and vegetable proteins, which suggests that the actual protein composition may be of importance.

Carroll et al. (11,14) have also found, as did Lofland et al. (8), that other components of the diet can affect the results obtained with protein. Thus, when the diets containing semipurified casein or soy protein included dextrose as the source of carbohydrate, casein was significantly more cholestermic (220 mg/dl vs. 70 mg/dl). Replacement of the dextrose by wheat starch did not affect serum cholesterol levels in the casein-fed rabbits, but reduced them to about 50 mg/dl in the soy-fed group. When the carbohydrate source was raw potato starch, serum cholesterol levels in both protein groups were about 50 mg/dl. In rats, raw potato starch gave lower cholesterol levels than did cooked starch (Table IV).

We (15) have found that the type of fiber present in the diet will affect cholesteremia and atherosclerosis in rabbits fed semipurified diets containing either casein or soy protein (Table V).

In these experiments we used a cholesterol-free, semi-

TABLE V

Effect of Fiber on Lipids and Atherosclerosis in Rabbits Fed Casein or Soy Protein (15)

Diet[a]		No. of	Serum lipids (mg/dl ± SEM)		Average atheroma[b]	
Protein	Fiber	rabbits	Cholesterol	Triglyceride	Arch	Thoracic
Casein	Cellulose	8	402 ± 40	164 ± 45	1.81	1.19
Soy	Cellulose	5	248 ± 44	41 ± 8	1.50	1.00
Casein	Wheat straw	12	375 ± 42	94 ± 19	1.17	0.88
Soy	Wheat straw	13	254 ± 35	66 ± 9	1.04	0.77
Casein	Alfalfa	10	193 ± 34	60 ± 8	0.70	0.55
Soy	Alfalfa	13	159 ± 20	62 ± 17	0.88	0.58

[a]Diets contained 40% sucrose, 25% protein, 15% fiber, 14% hydrogenated coconut oil, 5% salt mix and 1% vitamin mix. Fed for 10 months.

[b]Graded on a 0-4 scale.

TABLE VI

Influence of Beef, Textured Vegetable Protein or Casein and Beef Tallow on Atherosclerosis in Rabbits (18)

	Group[a]			
	B-BT	TVP-BT	BTVP-BT	C-BT
Number of rabbits	12	9	11	11
Weight change, g	339	987	218	165
Liver weight, g	48.4	43.9	40.4	54.6
Serum lipids, mg/dl ± SEM				
Cholesterol	185 ± 24	37 ± 4	61 ± 6	200 ± 18
% Esterified	72.3	64.3	63.9	66.8
Triglyceride	59 ± 8	58 ± 7	70 ± 13	92 ± 10
Phospholipid	92 ± 8	67 ± 5	70 ± 5	125 ± 8
Liver lipids, g/100 g ± SEM				
Cholesterol	0.77 ± 0.90	0.28 ± 0.01	0.47 ± 0.04	0.38 ± 0.06
% Esterified	68.8	64.3	60.5	70.1
Triglyceride	0.77 ± 0.08	1.16 ± 0.39	0.72 ± 0.12	0.55 ± 0.08
Phospholipid	1.46 ± 0.06	1.18 ± 0.07	1.58 ± 0.04	1.41 ± 0.06
Average atheromata[b]				
Arch	1.3 ± 0.2	0.7 ± 0.1	0.7 ± 0.1	1.3 ± 0.2
Thoracic	0.8 ± 0.1	0.2 ± 0.1	0.4 ± 0.1	0.9 ± 0.2

[a]B-BT = frozen beef plus beef tallow; TVP-BT = textured vegetable protein plus beef tallow; BTVP-BT = textured vegetable protein (1:1) plus beef tallow; C-BT = casein plus beef tallow. Beef contains 74% protein and 20.4% fat; TVP contains 54% protein and 0.6% fat. All diets adjusted to contain 40% sucrose, 25% protein, 15% cellulose, 14% fat, 5% salt mix and 1% vitamin mix. Diets fed for 8 months.

[b]Aortas graded on a 0-4 scale.

TABLE VII

Effect of Protein on Serum Cholesterol Levels in Conventional and Germ-free Chickens (22)

Group[a]	Protein[b]	No. of chickens	Wt. (g)	Liver Wt. (g)	Serum Cholesterol mg/dl
Experiment 1					
C	Soy	10	218	6.2	365
C	Casein	10	305	8.5	539
GF	Soy	10	193	6.3	521
GF	Casein	10	300	11.3	627
Experiment 2					
C	Soy	11	227	7.4	286
C	Casein	10	193	6.5	713
GF	Soy	11	233	6.9	565
GF	Casein	10	348	10.1	819

[a]C = conventional; GF = germ-free.

[b]Diets contained 54% glucose; 25% protein; 6.6% salt mix; 5% corn oil; 3% cellulose; 3% cholesterol; 1.5% glycine; 1% arginine; 0.5% methionine and vitamins to 100%.

purified diet that is atherogenic for rabbits (16,17). This diet results in endogenous hyperbetalipoproteinemia and atherosclerosis and vitiates one argument against the use of the rabbit in atherosclerosis research, namely the inappropriate model of feeding cholesterol to a herbivore. When the fiber is cellulose, casein is more cholesteremic and atherogenic than is soy protein. Substitution of wheat straw for cellulose does not affect cholesteremia in either the casein or soy groups but reduces atherogenicity. Casein, however, is still more atherogenic than is soy protein. When the fiber is alfalfa, serum cholesterol levels and severity of atherosclerosis are reduced in both groups and similar to each other.

To test the effects of fat in these experiments, we carried out another study in which the source of fat was beef tallow rather than coconut oil. As the source of protein, we fed either freeze-dried beef, soy protein, a beef-soy mixture of casein (18). As Table VI shows, the beef or casein-containing diets were more atherogenic than was vegetable protein. Dilution of the beef with soy protein

TABLE VIII

Effect of Lysine and Arginine Addition to Soy Protein and Casein on Experimental Atherosclerosis in Rabbits (25)

GP[a]	No. of rabbits	Serum lipids, mg/dl ± SEM		Liver lipids g/100 g ± SEM		Average atheromata[b]	
		Cholesterol	Triglyceride	Cholesterol	Triglyceride	Arch	Thoracic
Experiment 1							
C	7	174 ± 30	133 ± 17	1.81 ± 0.19	3.17 ± 0.76	2.2 ± 0.5	1.5 ± 0.4
S	6	59 ± 14	95 ± 20	1.70 ± 0.11	1.31 ± 0.40	0.8 ± 0.4	0.5 ± 0.2
CA	6	129 ± 12	186 ± 20	2.05 ± 0.31	1.21 ± 0.52	1.4 ± 0.4	0.8 ± 0.3
SL	6	106 ± 29	101 ± 14	1.86 ± 0.19	2.25 ± 0.76	1.6 ± 0.4	1.1 ± 0.2
Experiment 2							
C	8	214 ± 27	81 ± 11	1.08 ± 0.13	1.57 ± 0.25	1.1 ± 0.3	0.8 ± 0.3
S	11	171 ± 18	54 ± 7	1.26 ± 0.27	1.90 ± 0.26	0.5 ± 0.2	0.4 ± 0.1
CA	7	281 ± 63	59 ± 5	1.05 ± 0.09	1.88 ± 0.22	1.3 ± 0.4	0.9 ± 0.3
SL	11	197 ± 16	70 ± 7	1.08 ± 0.11	2.39 ± 0.28	0.7 ± 0.2	0.5 ± 0.2

[a]C = casein; S = soy; CA = casein and arginine; SL = soy + lysine. Arginine added to give diet arginine/lysine ratio equal to soy protein. Lysine added to give arginine/lysine ratio equal to casein. Diets contained: 40% sucrose; 25% protein; 15% cellulose; 14% hydrogenated coconut oil; 5% salt mix; 1% vitamin mix. Fed for 8 months.

[b]Aortas graded on a 0-4 scale.

TABLE IX

Influence of Corn Protein, Wheat Gluten and Lactalbumin on Atherosclerosis in Rabbits (18)

	Diets[a]		
	Corn protein	Wheat gluten	Lactalbumin
Number	7	8	7
Weight change, g	-560	-72	-287
Liver weight, g	37.3	45.0	40.8
Serum lipids, mg/dl ± SEM			
Cholesterol	158 ± 25	152 ± 18	312 ± 79
% Esterified	75.3	69.7	70.8
Triglyceride	94 ± 9	98 ± 14	122 ± 52
Phospholipid	84 ± 3	91 ± 3	84 ± 3
Liver lipids, g/100 g ± SEM			
Cholesterol	1.08 ± 0.18	1.11 ± 0.14	1.05 ± 0.12
% Esterified	55.6	48.6	49.5
Triglyceride	2.38 ± 0.25	2.48 ± 0.24	2.39 ± 0.22
Phospholipid	1.83 ± 0.04	1.97 ± 0.04	1.91 ± 0.06
Average atheromata ± SEM[b]			
Arch	0.4 ± 0.2	0.6 ± 0.2	1.1 ± 0.4
Thoracic	0.2 ± 0.2	0.4 ± 0.1	0.6 ± 0.2

[a]Diets contained 40% sucrose, 25% protein, 15% cellulose, 14% hydrogenated coconut oil, 5% salt mix and 1% vitamin mix.

[b]Aortas graded on a 0-4 scale.

TABLE X

Influence of Fat Saturation on Hypolipidemic Effect of a Diet High in Soya Protein (30)

	Cholesterol, mg/dl ± SEM				Triglycerides
	Total	VLDL	LDL	HDL	mg/dl ± SEM
Experiment 1 (7 subjects)					
Baseline	333 ± 12	57 ± 12	247 ± 8	32 ± 2	218 ± 39
P/S 2.7 (3 weeks)[a]	261 ± 12	50 ± 11	184 ± 14	28 ± 2	185 ± 35
P/S 0.1 (3 weeks)	295 ± 11	67 ± 18	197 ± 20	32 ± 2	207 ± 39
Experiment 2 (5 subjects)					
Baseline	350 ± 66	52 ± 8	263 ± 65	32 ± 3	182 ± 26
P/S 0.1 (3 weeks)	311 ± 63	49 ± 5	230 ± 58	33 ± 2	165 ± 12
P/S 2.7 (3 weeks)	295 ± 63	49 ± 6	209 ± 57	31 ± 3	169 ± 16

[a]Diets contained 53% carbohydrate, 21% protein (13.2% soy protein, 6.3% other vegetable protein, 1.5% animal protein), 26% fat with P/S ratio 2.7 or 0.1. VLDL = very low density lipoprotein; LDL = low density lipoprotein; HDL = high density lipoprotein.

reduced the atherogenicity of the diet. Hermus (19) found that a diet containing 20% casein was more atherogenic for rabbits than were diets in which the protein was 12% casein and 8% gelatin, or 7.5% casein, 5% gelatin and 7.5% fish protein.

The mechanism of action by which animal protein exerts its hypercholesteremic effect is not clear. In experiments comparing the different cholesteremic effects of various sugars it was shown that the hypocholesteremic action of certain sugars was abolished if the diet contained a sulfa drug (20) or an antibiotic (21). To test this possibility, we fed diets containing 3% cholesterol and 25% casein or soy protein to conventional or germ-free chickens (22). Table VII shows that although cholesterol levels were increased in

germ-free chickens, casein was still more cholesteremic than was soy protein. However, the difference between the two dietary groups was smaller when the experiment was performed in germ-free chickens.

Another possible source of the difference between casein and soy protein might be in their amino acid ratios. Huff et al. (13) had found that when the proteins were partially hydrolyzed the differences in cholesteremia persisted, but that this was not the case when total hydrolysates or component amino acids were fed. Examination of the amino acid spectra of casein and soy protein revealed that the ratio of lysine to arginine in the former was twice that of the latter. Lysine inhibits liver arginase activity (23), and we hypothesized that in animals fed casein more arginine might be available to be incorporated into the arginine-rich apoprotein, which is a constituent of the lipoprotein, which is atherogenic for rabbits (24).

We have carried out two experiments in which we added enough arginine to the casein diet to approximate the lysine/arginine ratio of soy protein and enough lysine to the soy protein diet to give the lysine/arginine ratio usually seen in casein. In both experiments (Table VIII), the addition of lysine to soy protein enhanced the atherogenicity of the diet containing that preparation (25). Results with the arginine-casein mixture have been equivocal. The serum lipoprotein spectra of the sera of the rabbits fed the various diets are under study. These experiments suggest that there is an inherent constitutional difference between casein and soy protein, and further work will indicate whether the lysine/arginine ratio alone can explain the differences in the mode of action of other proteins.

We have investigated the effects of wheat gluten, corn protein and lactalbumin on atherogenesis in rabbits (18), and differences are evident (Table IX). One possible reason for the observed differences in atherogenicities could be the ratio of lysine to arginine in the protein. The lysine/arginine ratios of casein and soy protein are 2.00 and 0.90, respectively, and casein has been consistently found to be more atherogenic than soy protein. The lysine/arginine ratios of corn protein, wheat gluten and lactalbumin are 0.58, 0.43 and 2.63, respectively. Another possibility is that the actual level of lysine or arginine is the determining factor rather than the ratio of the two. The lysine levels (%) of casein, soy protein, corn protein, wheat gluten and lactalbumin are 6.4, 6.6, 1.4, 1.5 and 8.4, respectively. Arginine levels (%) are: casein, 3.2; soy protein, 7.3; corn protein, 2.4; wheat gluten, 3.5 and lactalbumin, 5.0.

There have been a few studies of the effects of animal or vegetable protein on cholesteremia in man. In 1954 Hardinge and Stare (26) reported that vegetarians exhibited considerably lower serum cholesterol levels than did subjects ingesting a general diet. In an experiment testing different carbohydrates, Hodges et al. (27) fed a variety of diets. The source of dietary protein before and after the study was mixed, but soybean protein was the only source used during the study. Average serum cholesterol levels were about 300 mg/dl at the beginning and end of the experiment but fell to 200 mg/dl when the protein was soy.

Walker et al. (28) reported that a group of young women ingesting a diet containing 50 g of vegetable protein exhibited lower serum cholesterol levels than did a group eating the same quantity of animal protein. There were six women in each group. At the start of the study, the average cholesterol level of the animal protein group was 185 ± 11 mg/dl and that of the vegetable protein group was 182 ±18 mg/dl. Serum cholesterol levels fell in both groups, but fell further in the group fed vegetable protein. After 6 weeks, average serum cholesterol levels in the animal protein- and vegetable protein-fed groups were 157 ± 9 mg/dl and 137 ± 8 mg/dl, respectively.

The most exciting development in this area has been the report of Sirtori et al. (29) that the substitution of vegetable for animal protein in the "prudent" diet fed to hypercholesteremic patients significantly enhanced the lipid-lowering properties of that diet. The usually prescribed diet contains 58% carbohydrate, 21% fat (polyunsaturated/-saturated, P/S, 2.2) and 21% protein (13% animal; 8% vegetable). The Sirtori diet contained 53% carbohydrate, 26% fat (P/S, 2.7) and 21% protein (13.2% soy protein; 6.3% other vegetable protein; 1.5% animal protein). Subjects fed the prudent diet for 3 weeks showed an 11% fall in serum triglycerides and a 5% fall in serum cholesterol. When these individuals were placed on the soy diet, cholesterol levels decreased further by 32% and triglycerides by 16%. When the pattern was reversed, initial administration of the soy diet caused serum cholesterol and triglycerides to fall by 19 and 17%, respectively. When the soy diet was replaced by the prudent diet, triglyceride levels fell further by 8%, but cholesterol levels rose by 9%.

To test the effects of fat in this dietary regimen, Sirtori et al. (30) carried out another study in which patients were either fed a soy protein diet whose P/S ratio was 2.7 for 3 weeks followed by 3 weeks of a diet similar in all respects except that its P/S ratio was 0.1, or were first fed the P/S 0.1 diet for 3 weeks then fed the P/S 2.7 diet. Even on the diet high in saturated fat, the subjects' serum lipids were reduced. The P/S 2.7 diet was, as expected, more hypolipidemic than the P/S 0.1 diet (Table X). On the P/S 2.7 diet, total serum cholesterol fell by 21%, low density lipoprotein (LDL) cholesterol fell by 26%, and triglycerides by 15%. With the P/S 0.1 diet, all the lipid values rose but the total cholesterol, LDL cholesterol and triglycerides were still 11, 20, and 5% below baseline values. When the regimens were reversed, the P/S 0.1 diet caused an 11% decrease in total serum cholesterol, a 13% drop in LDL cholesterol and a 9% drop in triglycerides. When the subjects were then placed on the P/S 2.7 diet, total and LDL cholesterol levels fell further, but triglyceride levels were unchanged.

The foregoing discussion indicates that dietary protein *per se* can play an important role in cholesteremia and atherosclerosis. However, protein interacts with other components of the diet, and it is this interaction that ultimately determines levels of serum lipids and lipoproteins and their effect on the arterial wall.

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