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Review

The Garden of Eden—plant based diets, the genetic drive to conserve cholesterol and its implications for heart disease in the 21st century☆

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Abstract

It is likely that plant food consumption throughout much of human evolution shaped the dietary requirements of contemporary humans. Diets would have been high in dietary fiber, vegetable protein, plant sterols and associated phytochemicals, and low in saturated and *trans*-fatty acids and other substrates for cholesterol biosynthesis. To meet the body's needs for cholesterol, we believe genetic differences and polymorphisms were conserved by evolution, which tended to raise serum cholesterol levels. As a result modern man, with a radically different diet and lifestyle, especially in middle age, is now recommended to take medications to lower cholesterol and reduce the risk of cardiovascular disease. Experimental introduction of high intakes of viscous fibers, vegetable proteins and plant sterols in the form of a possible Myocene diet of leafy vegetables, fruit and nuts, lowered serum LDL-cholesterol in healthy volunteers by over 30%, equivalent to first generation statins, the standard cholesterol-lowering medications. Furthermore, supplementation of a modern therapeutic diet in hyperlipidemic subjects with the same components taken as oat, barley and psyllium for viscous fibers, soy and almonds for vegetable proteins and plant sterol-enriched margarine produced similar reductions in LDL-cholesterol as the Myocene-like diet and reduced the majority of subjects' blood lipids concentrations into the normal range. We conclude that reintroduction of plant food components, which would have been present in large quantities in the plant based diets eaten throughout most of human evolution into modern diets can correct the lipid abnormalities associated with contemporary eating patterns and reduce the need for pharmacological interventions.

Keywords: Evolution; Diet; Simian; Neolithic; Portfolio; Genetics; Cholesterol; Plant sterols; Soy protein; Viscous dietary fiber; Almonds; Coronary heart disease

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1. Introduction

We cannot know with certainty the diets of our distant ancestors. However, along the course of human evolution our diets are likely to have changed little until the introduction of new technologies, especially over the last 500 000 years.

Approximately 5–7 million years ago, our clade appears to have split, and our ancestors finally separated from the last of our contemporary great ape cousins, the ancestors of the chimpanzee. The common lineage leading to the gorilla diverged approximately 8 million years ago. The orangutan and gibbon split from the common clade possibly 13 and 20 million years ago, respectively. The shared feature of modern great apes is that their diets are largely vegetarian consisting in the main of large intakes of leafy vegetables, stems and shoots (Milton, 1999; Popovich et al., 1997; Cousins, 1976) fruits (Popovich et al., 1997), seeds and nuts (Lucas et al., 1994). The chimpanzees are more or less omnivorous but this apparently depends very much on the tribe (Whiten et al., 1999). If these diets are reflective of the early ancestors of man, it is likely that throughout a significant time span of hominoid dietary evolution which shaped the human genome, large volumes of plant foods were consumed. Indeed the genetic evolution since 'The Fall', i.e. the separation of the ancestors of man from those of the chimpanzee, gorilla, orangutan and gibbon is likely to have been relatively small since the current difference between man, chimpanzee, gorilla, orangutan and gibbon is estimated to be 2–3% (Kaessmann and Paabo, 2002). Obviously, this difference, though small, cannot be underestimated since it is the difference between staying in the forest or travelling to the moon. Nevertheless, the relative lack of difference emphasizes that the degree to which our genome is changed is likely to be little since the time when it was adapted to a plant-based diet (Kay, 1977; Milton, 1987). The influence of our subsequent changes in diet has acted over a shorter interval of time with shell fish and fish consumption in a lacrustine environment (Broadhurst et al., 2002; Crawford et al., 1999), high protein, brain and marrow fat consumption as scavengers (Cordain et al., 2000, 2002) and later major big game consumers, as hunting weapons became more refined in the later Paleolithic period (Eaton and Konner, 1985). Moreover, there has been little time or evolutionary pressure to adapt to the subsequent agricultural revolution (Cordain, 1999), possibly necessitated by species extinction of big game through progressively effective hunting practices. Even more dramatic has been the rate of dietary change brought on by the industrial and post-industrial revolution in food processing, preservation (canning and refrigeration) and transportation, for which nothing has prepared us previously. Today, the disease group which, together with cancer, is most responsible for premature mortality in western nations is coronary heart disease. For this disease much of the focus has been on cholesterol, in the blood and to a lesser extent in the diet, with the major thrust towards prevention and treatment coming through periodically revised recommendations of the panels of the National Cholesterol Education Program, with international influence (NCEP, 2001). The question, therefore, arises as to why has cholesterol become such a problem now. Why has cholesterol control, especially by drug therapy (and especially the statins) been so successful in saving lives, that it has now been recommended for most middle aged and older men and post-menopausal women in western societies (Downs et al., 1998; Shepherd et al., 1995).

2. Hypothesis

We suggest that for most of human evolution cholesterol was virtually absent from the diet. Few foods were available from which cholesterol could be synthesized within the body, and many foods enhanced cholesterol elimination via the gut. Nevertheless, cholesterol fulfills essential functions in cell membranes, as a component of transport lipoproteins, and for bile acid and steroid hormone synthesis. Human physiology, therefore, developed mechanisms to preserve the total body pool of cholesterol through enhanced cholesterol synthetic ability and efficient retrieval in the terminal ileum of bile acids as the major metabolic end products of cholesterol metabolism (directional selection). Relaxation of evolutionary pressures when dietary cholesterol was plentiful may have favored the retention of single nucleotide polymorphisms (SNPs) which reduced the retention or synthesis of cholesterol. Thus, in the great apes other than man, E4 which favors raised cholesterol is the Apo E apolipoprotein, while in man although E4 is retained, E3 is the wild type and E2 is also present in the gene pool which favors lower

cholesterol. A comparable situation exists in relation to salt and hypertension and the renin–angiotensin regulatory sequence in humans and chimpanzees (Dufour et al., 2000). Thus, human physiology, as presently constituted, along with some of its attendant SNPs for cholesterol homeostasis, is now a liability for those on a Western diet, rich in both dietary cholesterol and possibly more importantly dietary substrates for cholesterol biosynthesis, saturated and *trans*-fatty acids. In addition, the diet lacks those components which increase fecal elimination of cholesterol and bile acids and reduce hepatic cholesterol biosynthesis, such as plant sterols, viscous dietary fibers, vegetable protein, and a range of other phytochemicals. These components and foods which contain them, such as nuts, are recognized to lower serum cholesterol (Jenkins et al., 1975; Anderson et al., 2000; Kay and Truswell, 1977; Jenkins et al., 1993a; Anderson et al., 1984; Sirtori et al., 1977; Carroll, 1991; Anderson et al., 1995; Lees et al., 1977; Miettinen et al., 1995; Jones et al., 1999; Sabate et al., 1993; Spiller et al., 1998; Kris-Etherton et al., 1999; Jenkins et al., 2002a), are recommended for use by the AHA (Krauss et al., 2000) and the Expert Panel III of NCEP (2001) and have FDA approval for CHD risk reduction health claims (United States Food and Drug Administration, 1998, 1999, 2000). We believe reintroduction of these food components in amounts similar to those consumed earlier in our evolution will go a considerable way to reduce premature cardiovascular disease and our progressive reliance on drug therapy to reduce the high rates of cardiovascular disease.

3. Reconstructed Simian and Neolithic diets

We, therefore, decided to reconstruct diets representing earlier phases in human evolution, feed them to contemporary humans for 2-week periods, and determine their physiological effects (Jenkins et al., 2001). We selected two dietary periods to study. One was a diet that might have been eaten in the Myocene 5–7 million years ago at a time when the diet of the human ancestor was probably not very different from the range of foods eaten by contemporary great apes and when the genetic make-up was possibly no more than 2–3% different from modern humans. It consisted of large amounts of leafy vegetables, nuts (almonds and hazelnuts), and fruit, some tropical, but all purchased in local grocery stores. Theoretically, all these foods could be eaten raw but the majority of vegetables were eaten cooked. The diet was effectively devoid of any significant amount of starch. The second diet was an early agricultural diet, possibly representing the food supply of 10 000 years ago (Neolithic) with a major focus on the introduction of starchy foods, especially cereals and legumes. Certainly with the use of fire, sporadically from 500 000 years ago onwards and more routinely in the last 100 000 years, consumption of starch from roots and tubers would be likely to be increasingly a part of the diet. However, the cultivation of cereals and legumes allowed starch consumption on a much larger scale.

These two diets, Myocene and Neolithic, were compared for effect on serum cholesterol with a modern therapeutic diet (NCEP Step 2 diet) very low in saturated fat and dietary cholesterol and with a similar macronutrient profile to the 'Simian'/Myocene diet. The menu plan and macronutrient profile for the three diets are given in Tables 1 and 2, respectively.

The major feature of the Simian diet was the large volume and the length of time spent eating. Considerable pressure had to be brought to bear on the subjects to ensure they ate all their food and did not lose weight. The foods were palatable but the volume (5.5 kg/d for a 70-kg man) was excessive. At the end of the 2-week diet periods of weight maintenance, LDL-cholesterol was reduced on the Simian diet by 33%, on the Neolithic diet by 23% and on the therapeutic diet by 7%. Perhaps more significantly the respective LDL:HDL cholesterol ratio reductions were 24, 12 and 5%, respectively (Fig. 1). The diets were of short duration but we have observed maximum reductions by 2 weeks in diets of this sort as demonstrated in the Portfolio diet study (Fig. 2).

The cholesterol reductions on the Simian diet were similar to the reductions achieved with the first generation statins. Bile acid losses reached 1 g/d in the men, a fourfold increase over the therapeutic diet. Analysis of the diet for components, which might alter cholesterol metabolism, showed that the Simian diet provided approximately 1 g of plant sterols daily, 145 g of fiber and 92 g of vegetable protein and on an average, over 70 g almonds or hazelnuts per day. The former two components would have reduced cholesterol and bile acid absorption and thus increased fecal ster-

Table 1
Repeating menus as eaten on the therapeutic and Neolithic diets and the 3-day repeating menu eaten on the Simian/Myocene diet

Therapeutic diet (NCEP Step 2)	Neolithic (starch-based)	Vegetable diet, day 1 (Simian/Myocene)	Vegetable diet, day 2 (Simian/Myocene)	Vegetable diet, day 3 (Simian/Myocene)
Breakfast				
205 g orange juice	65 g oats	32 g filberts*	202 g avocado	33 g almonds
72 g cream of wheat	43 g dates	302 g raspberries	184 g fresh figs	302 g blueberries
22 g safflower oil	26 g dried figs	302 g honeydew melon	332 g raspberries	333 g mango
26 g brown sugar	177 g yogurt	302 g banana	302 g banana	301 g banana
129 g skim milk	44 g raisins			
78 g banana	117 g banana			
154 g yogurt				
23 g jam				
Lunch				
159 g fat-free cheese	104 g whole wheat bread	503 g Brussels sprouts	503 g cabbage	503 g cabbage
96 g white bread	163 g 1% cottage cheese	302 g okra	302 g okra	100 g okra
153 g yogurt	127 g tomato	302 g green peas	256 g green peas	252 g green peas
23 g jam	172 g pears	322 g mushrooms	302 g snow peas	302 g red pepper
281 g apple with skin	147 g apple	32 g filberts	231 g onion	302 g snow peas
		322 g plum	704 g tangerine	33 g almonds
			302 g apple	322 g grapes
Dinner				
Cheese omelette	Bean casserole	503 g broccoli	503 g broccoli	503 g broccoli
103 g Lipton's Egg	31 g chickpeas	302 g eggplant	302 g asparagus	302 g eggplant
Beaters (egg	41 g lentils	302 g carrots	302 g eggplant	302 g carrot
substitute)	104 g brown rice	252 g snow peas	302 g carrots	302 g tomato
159 g fat-free cheese	65 g olives	32 g filberts	353 g honeydew melon	201 g onion
46 g olive oil*	64 g 7% mozzarella	302 g strawberries		33 g almonds
42 g mashed potato flakes	cheese	604 g tangerines		302 g pears
61 g white rice	38 g olive oil			100 g kiwi fruit
58 g broccoli	129 g broccoli			
132 g pears (modified from 38)	118 g banana			

* Cob or hazelnuts. Adapted from Jenkins et al. (2001).

oid loss (Kay and Truswell, 1977; Jenkins et al., 1993a; Lees et al., 1977), and the vegetable proteins would have reduced hepatic cholesterol synthesis (Kurowska and Carroll, 1992), and caused up-regulation of LDL-receptors (Lovati et al., 1987; Baum et al., 1998).

Table 2
Dietary profile of macronutrients, fatty acids, fiber and sterols in simulated evolutionary diets

	NCEP Step 2 therapeutic	Neolithic	Simian/Myocene
Energy (kcal/day)	2509	2415	2706
Total protein (% of energy)	19	15	18
Total fat (% of energy)	24	21	22
SFA (% of energy)	4	4	3
MUFA (% of energy)	13	9	12
PUFA (% of energy)	8	6	5
PUFA to SFA ratio	2	1.4	2
Available carbohydrate (% of energy)	57	63	60
Total dietary fiber (g/1000 kcal)	10	19	55
Dietary cholesterol (mg/1000 kcal)	17	8	0
Phytosterols (mg/1000 kcal)	101	169	385

Adapted from Jenkins et al. (2001). SFA, saturated fatty acids; MUFA, monounsaturated fatty acids; PUFA, polyunsaturated fatty acids.

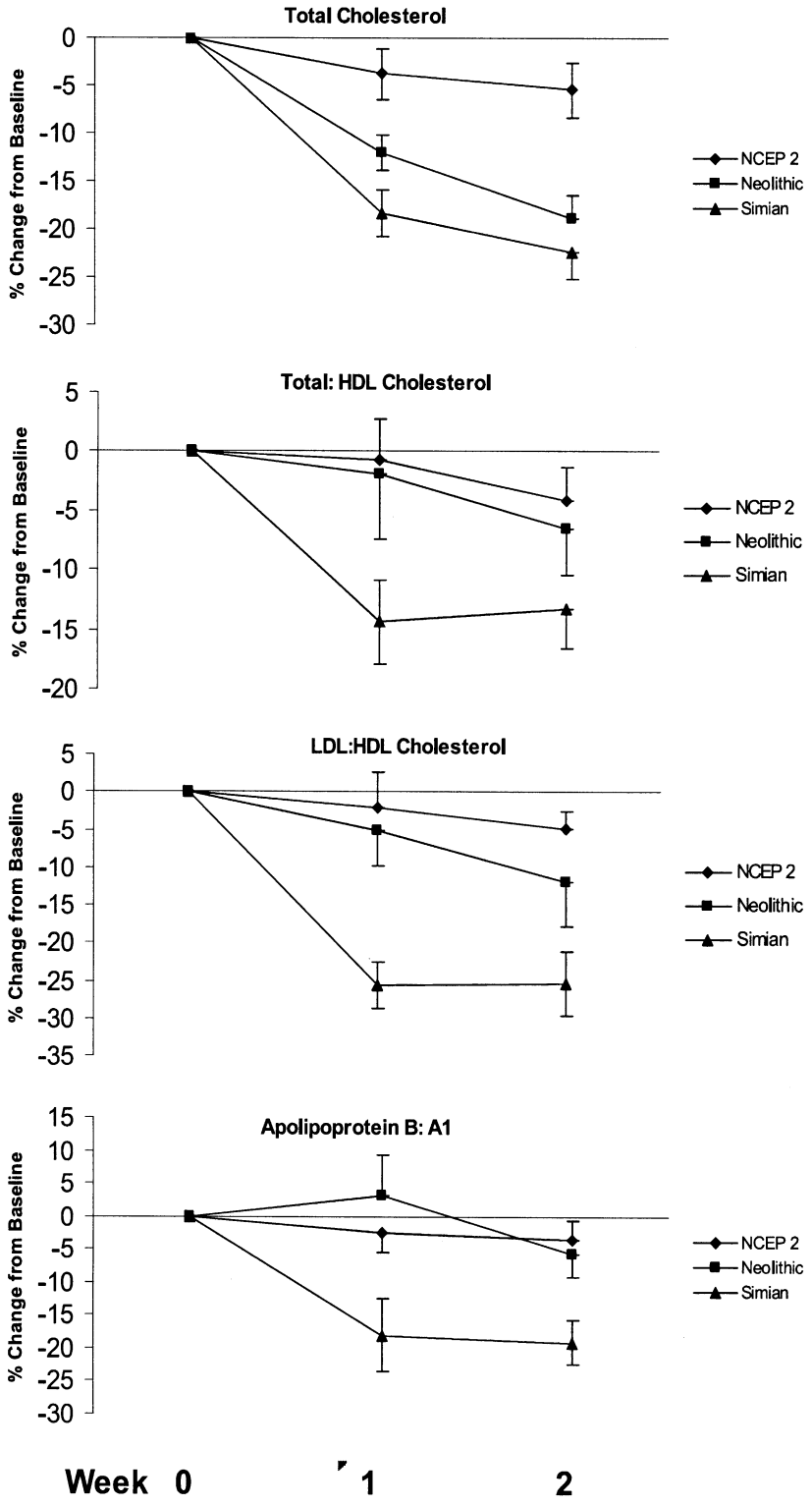

Fig. 1. Serum cholesterol and lipoprotein ratio percent changes after 1 and 2 weeks on low-fat modern therapeutic diet (NCEP step 2), Neolithic and Simian diets. Adapted from Jenkins et al. (2001).

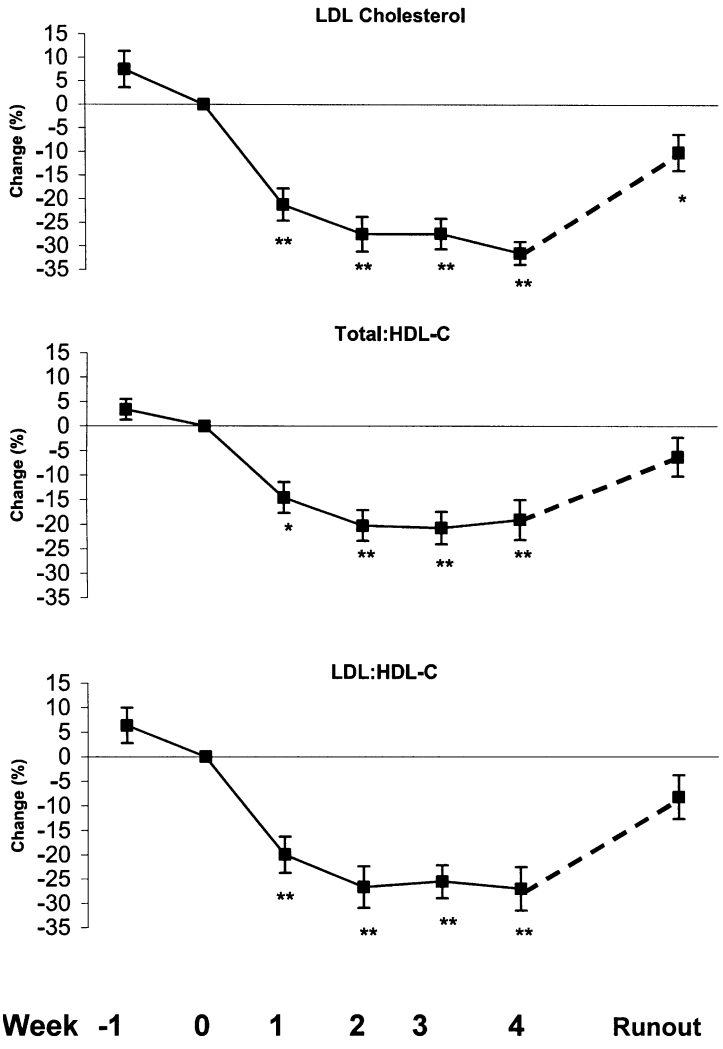

Fig. 2. Percent change from baseline in LDL-cholesterol and the ratios of total: HDL cholesterol and LDL: HDL cholesterol on the Portfolio Diet ($n=13$). Significantly different from baseline ($^{*}P<0.05$; $^{**}P\leq 0.001$). Adapted from Jenkins et al. (2002a).

This study suggested that serum cholesterol levels were likely to have been low throughout the course of human evolution and that reintroduction of foods containing cholesterol-lowering components might reduce the current apparent dependency on drugs for cholesterol control in the 21st century and beyond.

We could have studied diets closer to the chimpanzee (who also kill and eat rhesus monkeys) to which could be added molluscs (from the lacrustine environment) and insects (ants, locusts, etc.). Alternatively, a low saturated fat wild game diet of the Paleolithic, which has not been tested experimentally with the exception of Karen O'Dea's studies of the Australian Aborigine could have been investigated (O'Dea and Spargo, 1982). This latter diet, combined with exercise and weight loss showed major benefits in terms of blood lipids and glucose tolerance (O'Dea and Spargo, 1982). However, our argument has been that our genetic differences even from the orangutan and gibbon are not great. In this respect, we believe that diets high in fiber and vegetable proteins have shaped our metabolic processes over the greater (even if not the most significant) part of our evolution and the question, therefore, was what such diets would do to risk factors for our most prevalent chronic disease, coronary heart disease.

Table 3
Calculated macronutrient intakes (mean ± S.E.) before, during and after the Portfolio study

	Pre-study	Portfolio diet	Post-study
Energy (kcal/d)	1703 ± 120	1999 ± 118	1703 ± 104
Total protein (% of protein)	17 ± 1	22 ± 1	18 ± 1
Vegetable protein (% of protein)	49 ± 4	97 ± 0	39 ± 3
Available carbohydrate (% of energy)	53 ± 3	51 ± 1	58 ± 1
Total dietary fiber (g/1000 kcal)	17 ± 2	31 ± 1	18 ± 2
Total fat (% of energy)	28 ± 3	27 ± 1	23 ± 2
SFA (% of energy)	8 ± 1	4 ± 0	6 ± 1
MUFA (% of energy)	12 ± 2	12 ± 1	9 ± 1
PUFA (% of energy)	6 ± 0	10 ± 0	5 ± 1
Dietary cholesterol (mg/1000 kcal)	99 ± 13	10 ± 3	79 ± 9
Alcohol (% of energy)	2 ± 1	0 ± 0	1 ± 0
Satiety (−3 to +3)	1 ± 0	3 ± 0	1 ± 0

Adapted from Jenkins et al. (2002b). SFA, saturated fatty acids; MUFA, monounsaturated fatty acids; PUFA, polyunsaturated fatty acids.

4. Reintroduction of lost food components: the Portfolio diet

As the next step after the aforementioned study, our aim was to determine the effect on serum lipids of adding back into therapeutic diets those dietary elements which are likely to have been consumed in large quantities for the greater part of human evolution, namely, dietary fiber, vegetable proteins and plant sterols (Jenkins et al., 2002b). We added similar levels of vegetable proteins (93 g/d) and larger amounts of plant sterols (2 g/d) as used in the Simian diet, together with high levels of viscous dietary fiber, approximately 15 g/d and 28 g almonds per 2000-kcal diet, to the therapeutic low saturated fat diets of hyperlipidemic subjects (Table 3). In preliminarily studies the LDL-cholesterol and the LDL-C:HDL-C ratio reductions over the 1 month on the diets were approximately 29 and 23%, respectively (Fig. 2). These findings are almost the same as the data obtained on the Simian diet. Again the lipid reductions were similar to the starting dose of the older statins, the drugs which have changed contemporary thinking on the need for drug therapy for the middle aged general public.

5. Genetic evidence

It seems reasonable to suppose, for the 15 million years of evolution between the time when the gibbon and gorilla split from the common clade which gave rise to modern humans, that the diet would be heavily plant based (Kay, 1977; Milton, 1987), and therefore very high in fiber, vegetable proteins, plant sterols and associated phytochemicals. At the same time, substrates for cholesterol synthesis and cholesterol itself would be notably absent from the diet. The organism would, therefore, be under considerable evolutionary pressure to synthesize and conserve cholesterol in order to serve bodily functions, especially bile acid synthesis to absorb fat-soluble nutrients on a low fat diet. These pressures in the long-term would cause significant genetic differences and in the shorter term, the conservation of polymorphisms which favor retention of the cholesterol molecule for functions such as bile acid synthesis. The pressure may not have ended 5 million years ago but may have continued until relatively recent times. Certainly dental wear on the teeth of early hominoids suggests a very high fiber diet (Kay, 1977). It should not, therefore, come as a surprise if many polymorphisms and genetic traits were to be conserved in the human genome which favor increased cholesterol and bile acid absorption or synthesis (Table 4). For example, these could include the ABC genes (ABCG5 and ABCG8) for sterol absorption (Berge et al., 2000), the CETP gene for cholesterol ester transfer protein activity (Ordovas et al., 2000), the fatty acid binding protein, FABP2 gene for fatty acid absorption (Galluzzi et al., 2001), Apo B (Berg, 1986) and E gene (Davignon et al., 1988) for low density lipoprotein synthesis and the LDL-receptor gene for cholesterol uptake (Goldstein and Brown, 1987). Singly, none of the many common genetic variants which influence serum cholesterol levels

Table 4
Some common genetic variants explaining fasting blood lipids and demonstrating preponderence of traits favoring raised serum cholesterol levels and increased bile acid synthesis

Gene	Genotype	Frequency (%)	Outcome (% change from wild type)	Notes	Ref. #
CETP polymorphism-Taq1B	B1B1 (wild type)	56	HDL, 1.07		Ordovas et al. (2000)
	B2B2	44	HDL, 1.53 (−43%)	Favors cholesterol transfer to the liver for bile acid synthesis	
IFABP	A54 of FABP2 GG (wild type)	86	LDL, 3.36 Apo B, 1.01		Galluzzi et al. (2001)
	T54 GA/AA	14	LDL, 3.47 (−3%) Apo B, 1.04 (−3%)	Favors fatty acid absorption for cholesterol synthesis	
Apo E	Apo E2	13	LDL, 2.81 (23%) Apo B, 0.8 (23%)	Reduces cholesterol availability for bile acid synthesis	Jenkins et al. (1993b)
	Apo E3 (wild type)	72	LDL, 3.67 Apo B, 1.04		
	Apo E4	15	LDL, 3.98 (−8%) Apo B, 1.17 (−12%)	Favors cholesterol availability for bile acid synthesis	

have a major effect on the serum cholesterol level (Davignon et al., 1988). The Apo E polymorphism accounts for approximately 8–10% of the variation in the population and has the largest effect of any of the known polymorphisms (Davignon et al., 1988; Ye and Kwiterovich, 2000). However, their major effects are likely to be seen when a number of polymorphisms occur together and it is their combined effect which may result in the physiologically and pathologically significant differences commonly seen in the general population between individuals (Hegele, 1997). In a study of the evolution of the Apo B gene, it was noted in Chinese in Singapore who have very low levels of coronary artery disease (CAD), that of the 12 haplotypes identified in this group, 9 out of 12 were more common in CAD sufferers and three were found exclusively in those with CAD (Heng et al., 1999). The study numbers, however, were small (253 healthy and 211 with CAD). Larger numbers are required to allow firm conclusions to be drawn. Furthermore, if there was no natural selection in favor of high cholesterol levels, then it would be expected that SNPs promoting high and low cholesterol levels would occur with equal frequency in the population. This does not appear to be the case. A case can be made that common SNPs which influence serum cholesterol levels favor higher cholesterol levels. Thus, in the Apo E polymorphisms, Apo E4 which is associated with higher LDL-cholesterol levels than Apo E3 (the wild type) has a frequency of 16–21% in the general population compared to Apo E2 at 13–14% which favors lower cholesterol levels in the heterozygous form (Ordovas et al., 1987; Jenkins et al., 1993b), but nevertheless, prolong postprandial hypertriglyceridemia (Wolever et al., 1997). The subjects' higher LDL-cholesterol concentrations are associated with delayed clearance (Welty et al., 2000). We believe that the ability of the liver to synthesize bile acids is a function of primary importance. In diets low in fat, genetic traits would be conserved, which tend to increase fatty acid and cholesterol absorption, and increase cholesterol retention.

It is also possible that small genetic changes and the appearance of haplotypes for genes controlling lipid metabolism have occurred in the period after the divergence of man from other primates. Some of these haplotypes may have been able to develop in an environment where cholesterol availability for bile acid synthesis was not a primary restriction, e.g. after the development of the Acheulian hand axe. The subsequent availability of carrion brains and marrow increased dietary lipid and cholesterol availability. This thinking may be used to interpret the Apo E polymorphism in contemporary man. The predominant (wild type) Apo E haplotype in the other primates is Apo E4 (Hanlon and Rubinsztein, 1995). It can be hypothesized that in a relatively cholesterol-free environment, the primate cousins retained E4 as their form of apolipoprotein E while man acquired Apo E3 and E2 (Mahley and Rall, 1999). Nevertheless, the argument still remains that by retaining E4 at an approximate 20% frequency, a significant genetic determinant of higher cholesterol availability for bile acid synthesis is still present in the human genome.

6. Sustainable diets

The history of the evolution of the human diet indicates the tremendous war-chest of genetic flexibility possessed by humans resulting from the many different diets consumed at different stages of human evolution, from the time of our rodent-like ancestor 50 million years ago. Today the success of our species, related to dietary flexibility, poses a major environmental threat. However, our dietary flexibility could be an environmental asset. We can well live as the Eskimos in the arctic on a diet of fish, seal and whale blubber or we can thrive on vegetables, rice and curried lentils in the Indian tropics. Both of these extremes represent different stages in human dietary evolution. In the future our requirement for w-3 fats may have to be obtained directly from algal sources since cod and salmon are already part of a threatened ecology. High protein intakes from meat, fowl or dairy pose problems in terms of land use with the necessity to create more arable land through clearing forestland in the tropics and wooded areas in more temperate zones. Accelerated deforestation with further climate change is unacceptable, and therefore, intensive husbandry is required with problems of antibiotic use, manure disposal and disposal of slaughterhouse waste (blood, intestines, etc.).

Furthermore environmentalists can no longer be classed as individuals whose science is conflicted by their concerns for the well being of other species (Heaney, 2002). In an age of fixation on politically correct speech, equal opportunity and

affirmative action, these concepts will be counterproductive if restricted to the human species and not applied broadly to the rest of creation.

Continued studies of our dietary evolution to help define our requirements and our flexibility will in turn allow us to be guided by ecologists in our choice of foods. Together, we can then define broad possibilities for sustainable diets for man's future.

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