Endothelial Biomedicine

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The Ancestral Biomedical Environment

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Behaviorally modern humans evolved in Africa perhaps as early as 100 thousand years ago (kya) (1) and, by 50 kya, they began spreading throughout Eurasia and Australia. Since that evolutionary watershed, the human genome has changed little. For millions of years, human ancestors, like all other organisms, had responded to altered environmental circumstances solely through biological evolution (Table 16-1). However, during the past 50 millennia, humans have increasingly been able to adapt to new ambient circumstances through cultural innovation, in addition to the underlying (and slower) genetic change. Since agriculture and animal husbandry first appeared, perhaps 10,000 years ago, hemoglobinopathies and adult lactose tolerance are almost the only generally acknowledged genetic modifications. On the other hand, our lifestyle has changed radically: Nutrition, physical activity, reproductive experience, psychosocial relations, microbial interactions, and toxin/allergen exposure are all vastly different now from what they were for ancestral humans and prehumans during the period when our primary genetic makeup, including those factors relevant to endothelial health and disease, was selected.

The resulting discordance or mismatch between our genes and our modern lives is a likely contributor to many common chronic diseases and probably to various forms of endothelial dysfunction, so an appreciation of its potentially pertinent elements may further our understanding of pathophysiology. Also, awareness of the ancestral human lifestyle may suggest new avenues of prevention research applicable to the endothelium.

Reconstructing the biomedical circumstances of Stone Age humans is a fascinating, if sometimes frustrating endeavor. Several categories of data exist. Human skeletal remains are amenable to gross anatomical, microscopic, and biomechanical evaluation, as well as to radioisotopic analysis. Archeological finds, mainly at living sites, include the bones of animals consumed as food, botanical remains, artifacts (such as hearths, tools, weapons), and cave or rock wall paintings. Hunter-gatherer (forager)[1] groups studied in the last century (no true hunter-gatherers have survived into the twenty-first century) were the best, if imperfect, surrogates for Paleolithic humans. Their subsistence patterns, obligatory physical activity, reproductive experience, biomarkers (serum cholesterol levels, blood pressure, glucose responsiveness, etc.), and microbial interactions can be considered representative of patterns for the humans of 50 to 25 thousand years ago. Proximate analyses of the game animals and uncultivated plant foods consumed by recent hunter-gatherers provide further information regarding our ancestors' nutrient intake.

Most available evidence is thus indirect. We cannot take blood samples from, biopsy, observe, or interrogate our behaviorally modern ancestors of 25 kya. We will never have electron micrographs of their endothelium. Nevertheless, by dint of ongoing multidisciplinary efforts, a defensible and increasingly detailed picture of their life and health is emerging. It affords a view of the lifestyle for which our genes were originally selected, and it provides further understanding of the epigenetic milieu[2] that influenced their function.

ANCESTRAL HUMAN BIOLOGY

Blood Pressure

Numerous studies in varied geographic settings have established that the blood pressure of hunter-gather populations averages 100 to 110 systolic/70 to 75 diastolic (2), somewhat below the long-accepted "normal" values for Americans

1 Hunter-gatherers (synonymous with foragers) subsist on hunted wild animals, gathered wild plant foods, and aquatic resources. They have no domesticated plants or animals except the dog.

2 The epigenome consists of proteins and chemical molecules that surround and adhere to protein-encoding DNA. By amplifying or muting genetic expression in response to bioenvironmental circumstances (e.g., nutritional changes), the epigenome provides rapid response capability – genetic flexibility independent of DNA evolution as classically understood.

Table 16-1: The Time Scale of Human Evolution

Million years ago (Paleolithic)	
8–6	Human and chimpanzee ancestral lines split. (*Orrorin, Sahelanthropus*). Beginnings of upright posture and bipedalism
6–4	*Ardipithecines*
4.5–2	*Australopithecines* (including "Lucy")
~2.5	*H. habilis* (or *A. habilis* – genus disputed); initial appearance of stone tools
1.75	*H. erectus/H. ergaster*; achievement of modern human height and body proportions.
1.75–1.5	*H. erectus* migrates to southern Asia; present until 30 kya or later
	Presumably ancestral to *H. florensis*
1.75–0.2	Brain enlargement with little technological innovation
Thousand years ago (Paleolithic)	
750–500	*H. heidelbergensis*; ancestral (in Europe) to *H. neanderthalensis* and (in Africa) to *H. sapiens*
200–150	Anatomically modern *H. sapiens* appears in Africa with little or no technological advance
100–50	Behaviorally modern *H. sapiens* appears in Africa (improved linguistic capability is thought to be the key evolutionary change)
	Rapid technological innovation begins
60–5	*H. sapiens* spreads worldwide
20–10	*Epipaleolithic*; incipient agriculture
Thousand years ago (Neolithic)	
10–2	Ice Age ends, agriculture becomes widespread
	Sedentary living with towns and states; "civilization"

and other Westerners. Furthermore, the same studies have invariably found that forager blood pressure remains low as they age. Conversely, for inhabitants of developed nations, blood pressure typically rises as the population grows older. For hunter-gatherers, hypertension is almost nonexistent (2), whereas over 25% of American adults have elevated blood pressure (3).

Several factors appear to underlie these repeatedly confirmed observations. An obvious contributor is the availability of commercial salt. Hunter-gatherers are not the only low blood pressure societies. Traditional horticulturists, agriculturists, and pastoralists[3] whose economies lack commercial salt are also normotensive throughout their lives (2). As for all other free-living terrestrial mammals (both carnivores and herbivores), forager diets provide far more potassium than sodium (five to ten times as much) (4).[4] In stark contrast, the foods consumed by Americans yield more sodium than potassium, a nutritional electrolytic inversion with manifold pathophysiological implications (4). Of these, acid–base balance may be most important. As for recent hunter-gatherers, a high Stone-Ager intake of fruits and vegetables (twice the present consumption) tended to drive systemic pH toward alkalinity, whereas modern consumption of cereal grain products and dairy foods is net acid-producing (5). Over a lifespan, the corrective metabolic measures required to maintain homeostasis produce urinary calcium loss and accelerated skeletal mineral depletion while increasing the risk of urolithiasis (4). Effects on endothelial function have been little investigated.

Another significant influence is body size; greater body weight increases the risk of hypertension. The body mass indices (BMI) of recently studied hunter-gatherers average 21.5 (6), whereas the American mean is 26.5 (7). It is not clear that body mass independently influences blood pressure. Probably BMI is a marker for body composition, and it may be that excess fat relative to lean tissue is the pertinent biological variable. Forager skinfold thickness measurements, which are typically half or less those of age-matched North Americans, show that their fat content, as a percentage of total body weight, is typically below 15% for men and 25% for women (2). Many Westerners with "normal" BMIs are nonetheless overfat and/or undermuscled (8). When a convenient, inexpensive, and accurate method of determining body composition becomes available, this biomarker is likely to supplant BMI as a health status indicator.

Recently studied foragers have been aerobically fit with VO_2 max values placing them in the good to superior range, well above the poor to average values more characteristic of age-matched Americans (9,10). This difference clearly reflects the circumstances of hunter-gatherer life: travel, subsistence activities, and recreation all entail physical work.

Walking, running, carrying, digging, and dancing are prominent features of a lifestyle without motorized equipment or draft animals. Increasing one's aerobic power through a program of endurance exercise usually results in lower blood pressure (and a lower resting heart rate) (see Chapter 56) (11). For Stone Agers, such a program was obligatory, not elective.

Carbohydrate Metabolism

The insulin responsiveness of five different hunter-gatherer groups, on three continents, was evaluated in the last century (12). All showed remarkable insulin sensitivity, and it seems reasonable to assume that preagricultural human ancestors shared this desirable metabolic characteristic. Insulin resistance, an increasingly common finding in Americans and other Westerners, seems rare to nonexistent among foragers (12). However, migrant studies and serial determinations among societies undergoing acculturation to Western ways in their own homelands indicate that a population with initially favorable insulin responsiveness may become transformed within a generation or two into one with highly prevalent

3 Pastoralists practice animal herding as their primary economic activity (e.g., the Samburu and Maasai of East Africa).

4 The homeostatic response to chronic diet-derived net acid load includes release from bone of alkaline calcium salts (phosphates, carbonates) to buffer hydrogen (H^+). The liberated calcium and phosphorus are lost in the urine without compensatory gastrointestinal absorption; thus bone mineral content gradually declines.

insulin resistance (13,14). This shows that genetic makeup, while important, is not the main driving force regarding carbohydrate metabolism.

The chief behavioral changes associated with secular increases in insulin resistance have to do with diet and body habitus. The common nutritional elements that characterize populations with desirable insulin responsiveness include a limited intake of simple carbohydrate such as sugars and goods made from refined flour. Carbohydrate consumption itself may be substantial for insulin-sensitive groups, but is derived from whole grain (for many agriculturists) or from uncultivated fruits and vegetables (for hunter-gatherers). Such foods typically exhibit low glycemic indices and, especially, low glycemic loads (15). In addition, dietary fiber intake for normoglycemic populations tends to be considerable (16). The fiber may be predominantly insoluble (nonfermentable), as from wheat and rice, or it may be largely soluble (fermentable), as from wild fruits and vegetables. Uncultivated plant foods tend to be much more fibrous (three to four times as much fiber/100 g) than are the fruits and vegetables popular in Western nations (16). Groups tending to have a low prevalence of insulin resistance generally consume much more fiber (of all sorts) than do Americans, sometimes 70 to 100 g/day (16,17). Added sugar (i.e., extraneous to basic food items themselves) contributes up to 25% of American food energy each day (18). Foragers loved honey, an equivalent foodstuff, but it was difficult to obtain and usually available only on a seasonal basis. The best current estimate is that, over the course of a year, honey generally contributed about 2% to 3% of dietary energy for hunter-gatherers (4).

As discussed earlier, recently studied foragers have been lean, with BMIs in the low-normal range; corpulence is essentially unknown. On the other hand, Venus statuettes dating from 25,000 years ago prove that at least some ancestral humans were obese. However, the mere fact that such statuettes were made suggests they represented special, high-status individuals such as religious figures (shamans) or political leaders (19). Given the exertional requirements of hunter-gatherer existence, obesity would have been impossible for rank-and-file group members. Skeletal remains from the Late Paleolithic (50 to 10 kya) indicate average muscularity similar to that of today's superior athletes (10). This finding tends to confirm that strenuous physical activity was a hallmark of the ancestral lifestyle. Although depictions of humans are uncommon elements of cave and rock wall paintings from the Paleolithic, those available show lean and muscular individuals. No painted or etched figures matching the Venus statuettes have been found.

Higher BMIs are strongly correlated with a risk for insulin resistance, and individuals whose BMI is within normal limits also have increased risk if their body composition includes excessive adipose tissue. Both these circumstances were most uncommon among Stone Agers, and it seems likely that the metabolic milieu within which the human endothelium was designed to function was one in which hyperinsulinemia was rare.

Lipid Metabolism

During the twentieth century, the serum cholesterol values of six different hunter-gatherer groups living on four continents were determined. The mean was 123 mg/dL (3.2 mmol/L), and none of the groups had an average value exceeding 150 mg/dL (3.9 mmol/L) (2). (We have no data on the HDL:LDL partition.) The hunter-gatherer mean falls within the range observed for serum cholesterol levels in free-living higher primates –90 to 135 mg/dL (2.3 to 3.5 mmol/L) – much below those of average Americans (~200 mg/dL [5.2 mmol/L]) (2,20).

The cholesterol levels of hunter-gatherers (and other traditional peoples with originally low serum values) rise strikingly when they adopt a more Western lifestyle, whether by migration or by the introduction of new ways within their own region (21,22). This again indicates that, although genes are important, nutrition and other modifiable bioenvironmental factors are even more so for determining a population's blood lipid values.

Although foragers, horticulturists, traditional rural agriculturists, and pastoralists all have low serum cholesterol levels, their intake of dietary lipids varies substantially. Hunter-gatherers and most pastoralists (e.g., Maasai) consume a considerable amount of fat and cholesterol, whereas the diets of horticulturists and rural agriculturists typically provide relatively little of either. The common nutritional features are a low level of saturated fat and almost no harmful trans fatty acids (4), while dietary intake of cholesterol and total fat appears to be of limited importance regarding serum cholesterol levels (23).

During the Late Paleolithic (50,000 to 15,000 B.P.) our ancestors were consummate hunters, obtaining about 50% of their dietary energy from animal sources (24). Although game animals are much leaner than the commercial animals from which our supermarket meat is obtained, their cholesterol content is quite similar, so cholesterol consumption for Stone Agers averaged about 500 mg/day (versus <300 mg/day for contemporary Americans) (25). In Northeast Africa, the region where behaviorally modern humans are thought to have evolved (1), fats probably contributed about 35% of daily energy intake (26). However saturated fat consumption was only about half that of Americans (~7% versus 12% to 15%) because, during most of the year, animal fat from game is predominantly monosaturated with a far lower proportion of saturated fat than is found in commercial meat (27). Harmful trans fat intake was essentially nil (versus ~2% of total energy in the United States). Wild ruminant flesh contains 3% to 5% trans-vaccenic acid, but this is converted, after absorption, into conjugated linoleic acid (CLA) isomers for which limited evidence indicates anticarcinogenic and antiatherosclerotic activity (7). Polyunsaturated fat consumption for Paleolithic humans was nearly double that of Americans, and the $\omega 6$:$\omega 3$ partition was much different, approximately 2:1 ($\omega 6$:$\omega 3$) for ancestral humans (28); at least 10:1 currently (29).

Micronutrient Intake

Typical Stone Agers were more physically active than are average Westerners: estimates of 5.2 MJ (1,240 kcal)/day versus 2.3 MJ (555 Kcal)/day as energy expenditure during physical activity have been proposed (9,10). Contrary to popular misconception, our remote ancestors (after the appearance of *Homo erectus* 1.7 million years ago) were about as tall as are average Americans (30). Consequently, preagricultural humans required considerable dietary energy each day – perhaps 12.1 MJ (2,900 kcal) for adult males (9,10). Uncultivated plants and wild game tend to provide high levels of micronutrients relative to their energy content, unlike today's often calorically concentrated foods. Hence, retrojected ancestral intake of vitamins, minerals (including antioxidants), and – probably – phytochemicals was high, ranging from 1.5 to 8 times current intake depending on the specific nutrient (25,31). For example, mean daily vitamin C intake for American adults is about 90 mg, whereas retrojected ancestral consumption is estimated at just over 500 mg (25).

The exception, previously noted, is sodium. Preagricultural intake is thought to have been less than 1 gram per day (25), whereas contemporary Westerners typically consume over 4 g/d because of salt added during food processing, meal preparation, and at the table (4). The key factor is commercially available salt – not latitude. Tropical Venezuelan Yanamamo consume extremely little sodium, less than 500 mg/d. Conversely, the pattern for potassium follows the general rule – much less intake now than for Stone Agers (less than 3 g/d currently versus up to 10 g/d in the past) (4).

Tobacco Abuse

Tobacco abuse was an impossibility for the earliest behaviorally modern humans of 60 to 50 kya because they were Africans, whereas the genus *Nicotiana* is indigenous to the Americas, Australia, and certain Pacific Islands (2). By about 50 kya (or even slightly before) humans had spread as far as Australia, while Paleoindians, the ancestors of Native Americans, were in the New World by 12,000 B.P (and perhaps earlier; this dating is contentious). However, contemporary human ancestors who came from Europe, Asia, or Africa had no experience with tobacco until the voyages of Columbus 500 years ago. This relatively brief exposure has been insufficient to develop any genetically based resistance to its adverse health effects. Indeed, Australian Aborigines and Native Americans appear similarly prone to tobacco-linked disorders, so even 50 millennia have failed to provide significant immunity.

Microbial Interactions

In his book, *Plague Time*, biologist Paul Ewald argues that microorganisms, especially *Chlamydia pneumoniae*, but also *Porphyromonas gingivalis*, and perhaps others are the underlying, basal cause for atherosclerosis (32). He and numerous other investigators suggest that chronic vascular wall infection by such intracellular organisms produces the initial mural damage, either directly or by triggering an immunological inflammatory response. In either event, these authors maintain, such primary injury triggers the complex pathological process leading to atherosclerosis. Absent this chronic infection, atherosclerotic vascular disease fails to develop, no matter what commonly accepted risk factors are present.

Epidemic infectious diseases are thought to have been rare to nonexistent among Stone Agers because of the small group size, because their nomadic existence minimized the sanitation problems that became critical after fixed settlements appeared about 10,000 years ago, and because several important microbial illnesses are thought to have spread from animals to humans after domestication, again beginning about 10,000 years ago (33).

Conversely, endemic infectious disorders are thought to have been major killers of Paleolithic humans (34), and both *C. pneumoniae* and *P. gingivalis* are endemic conditions, at least in the contemporary Western world. If they were similarly prevalent during the Stone Age (and among those current populations largely free from atherosclerosis), their role in vascular pathogenesis would have to be considered necessary, but not sufficient. The modern epidemic of coronary, cerebral, and peripheral vascular disease may have resulted from the superimposition of tobacco abuse, hypercholesterolemia, hypertension, and other factors on an underlying infectious or inflammatory predisposition that has existed perhaps as long as there have been humans.

POTENTIAL RESEARCH INITIATIVES

A recapitulation of selected biomedical differences between ancestral and contemporary humans, potentially pertinent to endothelial health, is shown in Table 16-2.

Their collective or individual influence on endothelial microanatomy and physiology provide many possibly rewarding opportunities, for example:

- Other factors being equal, how does the endothelium respond when total blood cholesterol is varied between 3.2 mmol/L (125 mg/dL) and 5.2 mmol/L (200 mg/dL) (35)?
- Is the endothelium affected when a typical American sodium–potassium intake pattern is changed to one in which sodium is restricted to <1,000 mg/day and potassium increased to >5,000 mg/day (36,37)?
- What is the endothelial impact of prolonged magnesium supplementation (to match retrojected Stone Age intake) (38)?
- Does a diet rich in long-chain (C20 and above) polyunsaturated fatty acids with an $\omega 6{:}\omega 3$ ratio of about 2:1 protect the endothelium against some or all known harmful influences (39,40)?
- How does an elevated intake of antioxidants (to ancestral levels) affect the endothelium (41–43)?

Table 16-2: Ancestral versus Modern Humans

Differences	*Contributing Factors*	*Paleolithic*	*Contemporary*
Blood Pressure			
Paleolithic:			
Normotensive through life cycle	Dietary intake of electrolytes	$Na^+ << K^+$	$Na^+ > K^+$
	BMI	Lower	Higher
Contemporary:			
Tends to rise with age; many hypertensives	Aerobic power	Higher	Lower
Insulin Responsiveness			
Paleolithic:			
Nearly all insulin sensitive	BMI	Lower	Higher
	Body composition	More muscle Less fat	Less muscle More fat
Contemporary:			
Many insulin resistant	Glycemic load	Lower	Higher
	Fiber	High intake	Low intake
Lipid Metabolism			
Paleolithic:			
Lower serum cholesterol	Saturated fat intake	Lower	Higher
	Trans fat	Almost nil	2% of energy intake
Contemporary:			
Higher serum cholesterol	PUFA	More	Less
	$\omega 6{:}\omega 3$	~2:1	10:1 (or more)
	Simple CHO	Lower	Higher
	Dietary fiber	Higher	Lower

- Over time, does a consistently low glycemic load diet affect the endothelium beneficially (44,45)?
- Does the endothelium respond differently to an alkalinizing dietary pattern compared with one that is acid-producing (46)?

More important than any single investigative lead is the integrative, theoretical framework provided by the concept that the human genome was selected through evolutionary experience for the biobehavioral circumstances of ancestral life and that contemporary chronic diseases arise, in large measure, from the discordance that has been created between our genes and our lives. Deviation from and reversion toward the original human pattern may underlie, respectively, both disease causation and prevention. Perhaps a program of research based on the evolutionary discordance paradigm could make a vital contribution to the understanding and ultimate conquest of chronic illnesses, including those involving the endothelium.

KEY POINTS

- We are genetic Stone Agers living in a Space Age biomedical milieu.
- Discordance between our Stone Age protein-encoding DNA and our contemporary (especially affluent) lifestyles promotes development of chronic degenerative diseases, including those affecting the endothelium.

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