Endothelial Biomedicine

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Behav’orally modern humans evolved in Africa perhaps as early as 100 thousand years ago (kyr) (1) and, by 50 kyr, they began spreading throughout Eurasia and Australia. Since that evolutionary watershed, the human genome has changed little. For millions of years, human ancestors, like other organisms, had responded to altered environmental circumstances (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 ancient 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/mismatch between our genes and our modern lives is a likely contributor to many common chronic diseases and probably 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 endothe- lium.

Reconstructing the biomedical circumstances of Stone Age humans is 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 radiocarbon analysis. Archaeological 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) 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 kyr. We will never have electron micrographs of their endothelium. Nevertheless, by dint of ongoing multidisciplinary efforts, a definable and in-retrospect-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 that influenced their function.

ANCESTRAL HUMAN BIOLOGY

Blood Pressure

Numerous studies in varied geographic settings have established that the blood pressure of hunter-gatherer populations averages 100 to 110 systolic/70 to 75 diastolic, some well below the long accepted “normal” values for Americans.

1 Hunter-gatherers (myopposite 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 modifications that surround and adhere to protein-coding DNA. By modifying or mirroring genetic expression in response to environmental circumstances (e.g., nutritional changes), the epigenome provides rapid response capability - genetic flexibility independent of DNA evolution as classically understood.
Million years ago (Paleolithic)
8-6
Human and chimpanzee ancestral lines split. (Orrorin, Sahelanthropus). Beginnings of upright posture and bipedalism
6-4
Australopiths
4.5-2
Australopithecines (including *Lucy*?)
2-2.5
H. habilis (or A. habilis - genus disputed); initial appearance of stone tools
1.75
H. erectus/E. ergaster: achievement of modern human height and body proportions.
1.75-1.5
H. erectus migrates to southern Asian present until 30 kya or later
Presumably ancestral to H. floresiens
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
Behavially modern H. sapiens appears in Africa (improved linguistic capacity is thought to be the key evolutionary change)
Rapid technological innovation begins
60-50
H. sapiens spreads worldwide
20-10
Epipaleolithic; incipient agriculture

Thousand years ago (Neolithic)
10-2
Ice Age ends; agriculture becomes widespread
Sedentary being 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 pastoralists3 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 In stark contrast, the foods consumed by Americans yield more sodium than potassium, a nutritional electrolyte 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 a net acid-producing (5). Over a lifespan, the corrective metabolic measures required to maintain bone mineral density, preserve calcium and phosphorus, 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 than 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 (8). Many Westerners with "normal" BMIs are nonetheless overweight 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 acrobatically fit with VO2 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, swimming, 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
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 125 mg/dl (3.2 mmol/L), and none of the groups had an average value exceeding 150 mg/dl (3.9 mmol/L) (1). We have no data on the MDL(LOW, paroxysm). The hunter-gatherer mean falls within the range observed for serum cholesterol levels in five-living higher primates: 190 to 135 mg/dl (2.3 to 3.3 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 to 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 biocultural factors are even more so for determining a population’s blood lipid values.

Although foragers, horticulturalists, traditional rural agriculturists, and pastoralists all have low serum cholesterol levels, their intakes of dietary lipids vary substantially. Hunter-gatherers and most pastoralists (e.g., Masai) consume a considerable amount of fat and cholesterol, whereas the diets of horticulturists and rural agriculturists typically provide relatively little of either. The composite nutritional features are low levels 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 consumptive 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 Ages 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), fat probably contributed about 35% of daily energy intake (60). However, uncorrected fat consumption was obviously high for this African (7), because, during most of the year, animal fat from game is predominant and not measured with a fair low proportion of saturated fat that is found in commercial meat (27). Harmful trans fat intake was essentially negligible (versus ~2% of total energy in the United States). Wild ruminant flesh contains 1% to 5% trans-unsaturated acid, but this is converted, into two conjugated linoleic acid (CLA) isomers for which limited evidence indicates anticancerogenic and antiatherosclerotic activity (7). Polyunsaturated fat consumption for Paleolithic humans was nearly double that of the present day, and the overall pattern was much different, approximately 2:1 (oleic:linoleic) for ancestral humans (28); at least 10:1 currently (29).
Microinertial Intake

Typical Stone Agers were more physically active than are aver-
age Westerners: estimates of 5.2 MJ (1,240 kcal) per person per day versus 2.3 MJ (555 kcal) per person per day during their leisure time (19,101). Contrary to popular miscon-
ception, our "remote ancestors" (after the appearance of Homo erectus 1.7 million years ago) were about as tall as are aver-
age Americans (30). Consequently, preagricultural humans required considerable dietary energy each day — perhaps 12.1 MJ (2,900 kcal) for adult males (31). Uncolonized plants and wild game tend to provide high levels of microinertial relative to their energy content, unlike today's often calorisi-
cally concentrated foods. Hence, reticulated ancestral intake of vitamins, minerals (including antioxidants), and — proba-
ably — 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 antraced ancestral consumption is estimated at just over 500 mg (25).

The exception, previous, noted, is sodium. Preagricul-
tural intake is thought to have been less than 1 gram per day (25), whereas contemporary Westerners typically consume over 4 g/d because of added sodium in food processing, meat preparation, and as the table (4). The key factor's commercial-
cially available salt — not latitude. Tropical Venerexan Yana-
mans consume extremely little sodium, less than 50 mg/d. Conversely, the pattern for potassium follows the general rule — much less intake now than for Stone Agers (less than 3 g/d cur-
rently 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 ka because they were Africans, whereas the genus Nicotiana is indigenous to the Americas, Australia, and certain Pacific Islands (2). By about 50 ka (or even slightly before) humans had spread as far as Australia, whereas it is probably more recent, the ancestors of Native Americans, were not in the New World by 12,000 ypa (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 under-
lying, basal cause for atherosclerosis (32). He and numerous other investigators suggest that chronic vascular wall infec-
tion by such intracellular organisms produces the initial mural damage, either directly or by triggering an immunological inflammatory response. In either event, these authors main-
tain, such primary injury triggers the complex pathological pro-
cess leading to atherosclerosis. Absent this chronic infec-
tion, atheroembolic 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 normal existence minimized the sani-
tation problems that became critical after fixed settlements appeared about 10,000 years ago, and because several impor-
tant microbial illnesses are thought to have been spread from ani-
imals to humans after domestication, again beginning about 10,000 years ago (33).

Conversely, endemic infectious disorders are thought to have been major killers of prehistoric humans (34), and both C. pneumoniae and P. gingivalis are endemic conditions, at least in the contemporary Western world. If they were identi-

cally prevalent during the Stone age (and among those cur-

cent populations largely free from atherosclerosis), their role in vascular pathogenesis would have to be considered, necessary, but not sufficient. The modern epidemic of coronary, cere-
bral, 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 endothermal health, is shown in Table 16-2.

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

- Other factors being equal, how does the endothermal res-
pend 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 endothermal affected when a typical American sodium-potassium intake pattern is changed to one in which sodium is reduced to <1,000 mg/day and potas-
mium increased to 5,000 mg/day (36,37)?
- What is the endothermal impact of prolonged magnesium supphetation (to match reticulated Stone Age intake) (38)?
- Does a diet rich in long-chain (C20 and above) polyunsatur-
ated fatty acids with a Δ6-9omega ratio of about 2:1 protect the endotherm against some or all known harmful influ-
ences (39,40)?
- How does an elevated intake of antioxidants (to ancestral levels) affect the endothermal (41-43)?


Table 16-2. Ancestral versus Modern Humans

<table>
<thead>
<tr>
<th>Differences</th>
<th>Contributing Factors</th>
<th>Palaeolithic</th>
<th>Contemporary</th>
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<tr>
<td>Blood Pressure</td>
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<tr>
<td>Normotension through life cycle</td>
<td>Dietary intake &lt;100, BP lower</td>
<td>Lower</td>
<td>Higher</td>
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<tr>
<td>Contemporaneous</td>
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<tr>
<td>Blood Pressure</td>
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<td></td>
<td></td>
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<tr>
<td>Normotension with age many hypersensitivities</td>
<td>Body composition Less fat</td>
<td>Lower</td>
<td>Higher</td>
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<tr>
<td>Insulin Responsiveness</td>
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<tr>
<td>Palaeolithic</td>
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<tr>
<td>Nearly all insulin sensitive</td>
<td>BMI lower</td>
<td>Lower</td>
<td>Higher</td>
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<td>Contemporary</td>
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<td>Many insulin resistant</td>
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<td>Glycemic load fiber</td>
<td>Less muscle</td>
<td>Lower</td>
<td>Higher</td>
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<td>Lipid homeostasis</td>
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<td>Palaeolithic</td>
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<tr>
<td>Low saturated cholesterol</td>
<td>Saturated fat intake</td>
<td>Lower</td>
<td>Higher</td>
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<tr>
<td>Contemporary</td>
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<td>Higher saturated cholesderol</td>
<td>PUFAs Max</td>
<td>Lower</td>
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<td>REFERENCES</td>
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KEY POINTS

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

REFERENCES


