A new era for science in nutrition$^{1,2}$

Alexander Leaf, MD, and Peter C Weber, MD

Humanity has existed as a genus for about 2 million years. During this period food has been a limiting factor in population growth. Man has not always been so successful in conquering the earth's resources for his own uses as he appears to be today. It took until 1850 for the population on earth to grow to one billion persons. In 1930 the population had increased to two billion. By 1960 the population had risen to 3 billion and in 1976 there were four billion people on earth (1). In July, 1986 the news gave very little notice to the fact that the 5 billionth individual had been added to the world's population. This population growth is depicted dramatically in Figure 1. Yet this exponential growth, which is a measure of the success of our genus, may also portend problems for our kind in food supplies and other essential resources.

The good news today, however, is that we are producing sufficient food to feed the world's population, the New York Times has reported (2), citing figures for grain production from the Food and Agriculture Organization (3). That there is still famine in Africa and some 4 or 5 hundred millions of children suffer from protein-calorie malnutrition (4), is because of poor distribution of food products not because of any absolute shortage of food. The distribution problems are not caused by technical problems in transportation but rather by ignorance and by economic and political systems which foster or at least condone such distribution inequalities—another example of the disparity between our technological and social evolutions.

The remarkable success in keeping the food supply in step with the expanding population is a triumph of modern technology. In both the developed and developing countries the crop yield per hectare of cultivated land has increased. This results from genetic improvements in the grains planted, fertilizers, pesticides, and energy subsidies that drive the farm machinery. These developments have for the moment created a situation of abundance, if such a self-congratulatory note is justified while millions suffer the consequences of the distribution problems. The quantitative aspects of the supply of food seem for the moment solved though I think every person must have serious concerns for the future.

What can be said regarding the qualitative aspects of our foods? Much was learned through the 1930's and '40's about essential amino acids, vitamins, and minerals but still there is much more to be known to define requirements of these essential constituents of our diets. Studies continue to define these requirements for the several stages of the life cycle and for special conditions of pregnancy and various diseases that may alter the requirements for specific nutrients. These important developments constitute the classic era of nutrition but not its golden period, on the threshold of which, I believe, we are now poised. The beginnings of the present period commenced gradually with the realization that nutrition and optimal health are inextricably interdependent, that there is more to nutrition than simply providing sufficient amounts of the known essential ingredients in our diets.

Eaton and Konner (5) in their provocative discussion of paleolithic nutrition ascribe the period during which our genetic adaptation to diet occurred to the 4 million years spanning...
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our prehuman hominid ancestors, the australopithecines, and the 2 million years of existence of humanity as a genus. The last 40,000 years of existence of truly modern human beings, Homo sapiens sapiens, has been too brief a period for our drastically changing dietary habits to have affected our genetic makeup, they assert. The foods available to evolving hominids varied widely according to the paleontological period, geographical location, and seasonal conditions so that our ancestral line maintained the versatility of the omnivore that typifies most primates. Natural selection, they state, has provided us with nutritional adaptability.

Human beings today, however, are confronted with diet-related health problems that were previously of minor importance and for which prior genetic adaptation has poorly prepared us. Chronic illness, affecting the older postreproductive persons primarily, could have had little selective influence during evolution, yet such conditions are now the major cause of morbidity and mortality in Western nations. As physicians and nutritionists we are increasingly convinced that the dietary habits adopted by Western societies over the past 100 years make an important etiologic contribution to coronary heart disease, hypertension, diabetes, and some types of cancer. These conditions have emerged as dominant health problems only in the past century and, as Eaton and Konner (5) point out, are virtually unknown among the few surviving hunter-gatherer populations whose way of life and eating habits most closely resemble those of preagricultural human beings (6). The longer life expectancy of people in industrialized countries is not the only reason that the chronic illnesses have assumed importance. The members of technologically primitive cultures who survive to the age of 60 years or more remain relatively free from these disorders, unlike their civilized counterparts (7–9). Eaton and Konner (5) have estimated a proposed average daily macronutrient intake for late paleolithic human beings consuming a 3000 kcal diet containing 35% meat (788 g of game) and 65% vegetable (1464 g) foods with the composition shown in Table 1. Note that despite the very high animal protein intake, fat intake is low by our standards and contains a high proportion of polyunsaturated fatty acids. This important situation arises because game animals were lean and since they foraged for their food rather than being fattened with grains, as are present domesticated meat sources, little of the fat they contained was saturated and the plants they ate provided a relatively high proportion of polyunsaturated fatty acids. Furthermore—and probably highly significant—the fat of wild animals contains appreciable amounts of eicosapentaenoic acid (C20:5n-3), ~4% (5). Because the vegetable portion of the diet must also have contained appreciable amounts of n-3 polyunsaturated fatty acids including eicosapentaenoic acid (C20:5n-3), it becomes apparent that paleolithic man was ingesting an appreciable amount of these interesting n-3 fatty acids. In
TABLE 1
Proposed average daily macronutrient intake for late paleolithic humans consuming a 3000 kcal diet containing 35% meat and 65% vegetable foods as compared with current US diet (1983)*

<table>
<thead>
<tr>
<th></th>
<th>Paleolithic</th>
<th>Current US</th>
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<tbody>
<tr>
<td>Protein Animal</td>
<td>251</td>
<td>90</td>
</tr>
<tr>
<td>Vegetable</td>
<td>60</td>
<td>28</td>
</tr>
<tr>
<td>Fat Animal</td>
<td>71</td>
<td>142</td>
</tr>
<tr>
<td>Vegetable</td>
<td>30</td>
<td>82</td>
</tr>
<tr>
<td>(P:S ratio = 1.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cholesterol</td>
<td>591</td>
<td>600</td>
</tr>
<tr>
<td>Carbohydrate</td>
<td>334</td>
<td>335</td>
</tr>
<tr>
<td>Fiber</td>
<td>46</td>
<td>20</td>
</tr>
</tbody>
</table>

(P:S ratio = 1.4) (P:S ratio = 0.44)

* Modified from references 5 and 10.

contemporary nutrition such quantities of n-3 fatty acids are present only in the diets of Eskimos and Japanese fishermen in whom the incidence of atherosclerosis and its most serious manifestation, coronary artery disease, is very much lower than among Western affluent societies (11, 12). It was the epidemiologic studies by Dyerberg and Bang (13) on the Greenland Eskimos that stimulated so much interest today in the preventive role of n-3 polyunsaturated fatty acids on the development of coronary artery disease. Table 2 shows the relatively low incidence of coronary artery disease among the Greenland Eskimos compared with Danes and North Americans, despite equally high total dietary-fat intakes shown in Table 3 (14). The striking difference in the fatty acid composition of the dietary fats is seen in Table 3 (14) in which the high n-3 and low n-6 fatty acids of the Eskimo diet are contrasted to the inverse ratio of these fats in the Danish diet.

TABLE 2
Age-standardized death rates in percent of all deaths from ischemic heart disease*

<table>
<thead>
<tr>
<th></th>
<th>Males age 45-64</th>
<th>HHD deaths</th>
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<tbody>
<tr>
<td>United States</td>
<td>40.4</td>
<td></td>
</tr>
<tr>
<td>Denmark*</td>
<td>34.7</td>
<td></td>
</tr>
<tr>
<td>Greenland*</td>
<td>5.3</td>
<td></td>
</tr>
</tbody>
</table>

* From Dyerberg, 1982 (14); for years 1974–1976.

As an example of one current new scientific development in nutrition, the biochemical and physiological evidence suggesting that these two classes of polyunsaturated fatty acids (n-3 and n-6) in our diets may play important roles in the occurrence or prevention of coronary heart disease, will be summarized. When n-3 fatty acids are contained in our diet, eicosapentaenoic acid (C20:5n-3) enters membrane phospholipids competing with arachidonic acid (C20:4n-6) for the 2-position in these phospholipids. But it is from these polyunsaturated fatty acids, when liberated by a specific phospholipase A2, that eicosanoids are formed. Two eicosanoids, namely prostacyclin (synthesized by endothelial cells that line the inside of blood vessels) and thromboxane (made by platelets), the circulating particles that play a fundamental role in blood clot formation, are most pertinent to the development of atherosclerotic disease. Prostacyclin acts to dilate blood vessels and to prevent platelets from aggregating whereas thromboxane is a potent vasoconstrictor and causes platelets to aggregate. Platelet adhesion and aggregation at sites of endothelial injury are important initiating factors in the development of atherosclerosis. Prostacyclin opposes these atherogenic actions of thromboxane.

Eicosapentaenoic acid (EPA) when present in the diet not only competes with and reduces the content of arachidonic acid (AA) in membrane phospholipids, but it also competes with AA as substrate for the cyclooxygenase enzyme that converts these polyunsaturated fatty acids to prostacyclin or thromboxane. The result of this substrate competition is that there is a
TABLE 4
Potential antiatheromatous effects of n-3 polyunsaturated fatty acids

1. Reduce platelet aggregatory thromboxane and increase antiaggregatory prostacyclin.
2. Decrease platelet aggregation and reduce platelet thrombi at sites of endothelial injury blocking early stages of atherosclerosis.
3. Leukotriene production is modified to reduce the inflammatory reaction at the site of vascular injury.
4. Fibrinolytic activity of plasma is increased.
5. Vasospastic response to catecholamines is reduced.
6. Blood viscosity is reduced and blood pressure slightly lowered.
7. Blood lipid profile is favorably affected.
8. Counteract the proliferative vascular response to atherogenic stimuli at the lesion level.

sharp inhibition of thromboxane A₂ produced by platelets from AA and only small amounts of a physiologically inactive thromboxane A₃ synthesized from EPA, whereas there is little or no decrease in the amount of prostacyclin I₂ made by endothelial cells from AA and an additional amount of physiologically active prostacyclin I₃ synthesized from EPA (15). The net result is strongly antiaggregatory and vasodilatory—conditions which should prevent the development of atherosclerosis. The EPA also competes with AA as substrate for the lipoxygenase enzyme in the synthesis of leukotrienes in a manner that reduces inflammatory reactions. This latter effect diminishes the inflammatory component of atherosclerotic lesions. There are other potentially antiatherosclerotic effects of n-3 fatty acids and there are summarized in Table 4. Taken together with the modern hypothesis regarding the pathogenesis of atherosclerosis, as formulated by Ross (16) and by Steinberg (17), these effects of n-3 fatty acids in preventing atherosclerosis are understandable.

Figure 2 presents our oversimplified depiction of the pathogenesis of atherosclerosis. It makes the point that in most cases of atherosclerotic disease as it afflicts our society, platelet aggregation at sites of endothelial injury is an important early event in the initiation of atherosclerosis. Probably only in the very rare genetic condition of homozygous familial hy-
percholesterolemia in man are the very high plasma levels of cholesterol alone sufficient to initiate and sustain the atherosclerotic process (18). This schematic also indicates that in the usual cases of coronary artery disease with only moderate elevation of LDL cholesterol, a number of events must occur to prepare the vessel wall before cholesterol can be deposited to form the atheromatous lesions; in fact the deposition of cholesterol in the smooth muscle cells and monocyte/macrophages in the vessel walls is almost a secondary event. It seems that there will be multiple sites at which the atherosclerotic process may be aborted or inhibited, as shown in Figure 3, prior to any role for cholesterol, although almost our entire dietary and pharmaceutical approach to preventing coronary heart disease today is directed to lowering the plasma cholesterol levels.

In conclusion, the dietary events that have led to the current epidemic of coronary heart disease may be depicted hypothetically in

Figure 4. According to this view the paleolithic diet, during the period when our genetic patterns were established, was high in protein and cholesterol but was low in total fat with a high P:S ratio and much of the polyunsaturated fatty acids were the n-3α-linolenic, eicosapentaenoic and docosahexaenoic acids. In more recent times the introduction of agriculture with dependence of diets on grains led to an increase in total saturated fatty acids and in the n-6 polyunsaturated fatty acids, linoleic and arachidonic acids. In the past century the industrial revolution, the emergence of agribusiness with processed foods, grain fattened livestock, and hydrogenation of vegetable fats have all further reduced the content of n-3 fatty acids and increased n-6 fatty acids and saturated fats in our Western diets. These changes in diet together with smoking, hypertension, obesity, some forms of stress, and indolence have conspired to create the present epidemic of cardiovascular diseases which account for approximately half of all deaths and huge
FIG 4. Hypothetical scheme of the relative percentages of fat and different fatty acid families in human nutrition as extrapolated from cross-sectional analyses of contemporary hunter-gatherer populations and from longitudinal observations and their putative changes during the preceding 100 yr in relation to the recent increase in the frequency of coronary artery disease (CAD). From data of Eaton and Konner (5) and Kinsella (19).

health costs in affluent Western countries. Scientific research will surely clarify further our understanding of the role of nutrition in these diseases in which dietary maladaptation plays such a major role. These are again exciting times for great progress in the science of nutrition!

References