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Nutritional Armor in Evolution: Docosahexaenoic Acid as a Determinant of Neural, Evolution and Hominid Brain Development

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ABSTRACT The aim of this article is to draw attention to the special significance of docosahexaenoic acid (DHA) in the brain, the potential relevance of its abundance to the evolution of the brain in past history, and now the relevance of paucity in the food supply to the rise in mental ill-health. Membrane lipids of photoreceptors, synapses, and neurons over the last 600 million years contained consistent and similarly high levels of DHA despite wide genomic change. The consistency is despite the DHA precursor differing only by 2 protons. This striking conservation is an example of Darwin's "Conditions of Existence," which he described as the higher force in evolution. A purpose of this article is to suggest that the present paradigm of food production currently based on protein requirements, should change to serve the specific lipid needs of the brain to address the rise in mental ill-health.[1]

INTRODUCTION

Role of the Fatty Acids

The Nobel Prize in Physiology and Medicine 1982 for Sune K. Bergström, Bengt I. Samuelsson, and John R. Vane was given for their discovery of oxidative derivatives of arachidonic acid (AA) as intimate regulators of cell function at a specific locality, especially in eicosanoid response to injury with thrombogenic and inflammatory responses. Samuelsson published evidence of oxidative products of AA causing thrombogenesis and inflammation. However, Samuelsson also published the first evidence of an elegant symmetry of coordinating immune cell action to clean the damage and bring about resolution of the injury through AA lipoxygenase products.[2]

The eicosanoids formed from AA play important roles in neural function including sleep induction (PGD2), long-term potentiation, spatial learning and synaptic plasticity (PGE2), and resolution of inflammation (lipoxins). Cyclooxygenase inhibitors have been shown to reduce oxidative stress and cognitive impairment. In addition, drugs that are used to treat depression have been shown to reduce the turnover of AA to PGE2 in the brain. Diets deficient in ω-3 polyunsaturated fatty acids (PUFAs) lead to reduced docosahexaenoic acid (DHA) in the brain and increased turnover of AA to eicosanoids, an effect which is overcome by restoring ω-3 PUFA to the diet. In neural trauma and neurodegenerative diseases, there is a dramatic rise in levels of AA-derived eicosanoids.[3]

In addition to the cyclic and oxidative products of AA, there are also oxidative and anti-inflammatory products of DHA with neuroprotective bioactivity (dihydroxy-docosatriene, neuroprotectin D1), which are strongly neuroprotective[4,5] including the ω-3 resolvins.[6] Moreover, the highly unsaturated fatty acids in the membrane phospholipids can act on their own. They can be released and act as ligands of nuclear receptors, controlling certain genes.[7] AA itself is a ligand for the peroxisome proliferator-activated receptors (PPARs) and DHA for the retinoid X receptors[8] and will switch on over 100 genes involved with brain development.[9]

Neuronal migration and neurogenesis are impaired in fetal rats whose mothers have been deprived of ω-3 fatty acid.[10] DHA has also been shown to promote neurite growth and synaptogenesis in embryonic hippocampal neurons.[11] Moreover, the molecular species of the membrane phosphoglycerides are distinct physiological membrane constituents.[12] Stearoyl-arachidonyl-di-acyl glycerol is specifically released in cell activation and is responsible for the activation of protein kinase C.[13,14] Such evidence offers a new explanation for the mechanism of action of the chlorpromazine type antipsychotic drugs acting on the lipid domain rather than the protein.[15,16] The prime target for this psychotropic drug is the serine phosphoglycerides. These phosphoglycerides are rich in DHA. This evidence provides a possible explanation as to how nutrition could influence the function of these drugs.[13,14] Hence here is another dimension to the function of the lipids in which the lipids can be seen to contribute specifically to cellular information, gene expression and functional regulation very much in response to the environment and local events with surgical precision.

DHA (all-cis-docosa-4,7,10,13,16,19-hexaenoic acid—C22:6 ω-3, DHA) is a major constituent of the brain membrane

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phosphoglycerides and together with AA is essential for brain growth and function.[17] The richest sources of DHA are in marine and some fresh water foods. It can be made from its parent precursor α-linolenic acid. However, there is an order of magnitude difference in the preferential incorporation of DHA preformed into the developing rat pup brain, as opposed to its synthesis from α-linolenic acid.[18,19] There is a paucity of DHA in the land food chain and these sources also contain competing fats such as linoleic acid of the ω-6 family. The purpose of this article is to draw attention to the fact that the brain first evolved in the sea 500 million years ago using DHA for its signaling structures and our brains today still depend on the same chemistry. In the marine food chain, DHA coexists with the iodine and other trace elements vital for the development and function of the brain, whereas there is a paucity of iodine in the land food web. Because of diet, some 2 billion people are currently at risk of iodine deficiency and the consequent risk of mental retardation in the young. On the other hand, AA being a second major component of the brain is largely of land origin but it is also available preformed in warm water sea and fresh water foods. However, of the two fatty acids DHA is the most difficult to synthesize and hence limiting.

It is our contention that the movement in the 19th to 21st centuries away from traditional use of sea foods and increased emphasis on land based food supply is a likely cause in the rise in brain disorders including mental ill-health, stress, and other psychiatric disorders. With brain disorders having overtaken all other burdens of ill-health in the West,[20] a better understanding of DHA and its function could help motivate the required food policy changes. Although much research needs to be done on how to meet the demand from a rising population, much can be done with existing knowledge to meet this grand challenge.

Darwin on Conditions of Existence: The Higher Force

During the writing of the "Driving Force," David Marsh pointed out that in all 6 editions of Darwin's treatise on evolution he identified two forces in evolution, "Natural Selection" and the "Conditions of Existence" (The Driving Force: Food, evolution, and the Future Crawford MA and Marsh DE, 1989, Heinemann). Of the two, he considered the latter was "the higher force."[21] After finishing the 6th edition Darwin spent much of his time looking for what he called "pangenes." These he thought would be the interface between the environment and the genes. The proof he was correct can now be found in epigenetics,[22] which, like his concept of pangenes is an apparent, heritable change in gene expression independent of an alteration in the sequence of DNA and usually induced by an environmental or nutritional influence. The epigenetic change can be stably maintained[23] and operate over several generations before the appearance of a genetic shift.

After Darwin, August Weismann considered the "Conditions of Existence" was too close to Lamarck's theory of the "inheritance of acquired characteristics." So he conducted an experiment where he cut the tails off unfortunate rodents and watched generation after generation of cutting that they still grew tails. From this experiment, he concluded that "the Conditions of Existence" had no role in evolution. In 1893, he published an article under the title of the "All Sufficiency of Natural Selection." From then on, evolutionary biologists—with but few exceptions—believed only in the force of "Natural Selection" or Neo-Darwinism.

Weismann should have known better that his experiment was one of "mutilation" not "Conditions of Existence." After all, the Welsh sheep farmers had been cutting off the tails of their sheep for centuries. Moreover, Professor Ephraim Yavin of the Weizmann Institute of Science, in Israel, pointed out to us that it was even more surprising for Weismann to indulge in such mutilation when Jews had been cutting off foreskins for 3,000 years! The Egyptians before that had been doing the same so the practice dates back for perhaps 7,000 years! Needless to say, both Egyptian and Jewish newborns still produce foreskins.

It is important to recognize that Darwin frequently comments on the "modification" of a species by Natural Selection. Even within that framework, random mutation is now seen as an inadequate explanation for evolution, never mind the origin of species. To explain origin, T. H. Huxley invited his readers to imagine monkeys randomly typing. He claimed they would eventually produce the works of Shakespeare. If a monkey types 3 or 4 keys every second one can calculate that with 45 keys available and with the log of 45 = 1.65 the number of permutations is greater than a 50 figure number to produce 1 line of a Shakespeare sonnet! Even if the monkey started at the big bang he would struggle to get through the permutations within the life of the universe. This *reductio ad absurdum* is not an argument for intelligent design but an argument for the dominant role of the laws of physics and chemistry. The origin of life and evolution was not a random process. Hydrogen, the first and commonest element, does not react with gold but does with oxygen to produce water. Even then it will not do it at the temperature of a star. At very high temperatures, however, oxygen obviously reacted with silicon to produce rocks and then at lower temperatures with hydrogen to produce water. Making the chemicals of life is simply a more sophisticated business of the same principle. In other words, the origin of life and evolution obeyed the natural laws in response to the "Conditions of Existence."

There are numerous examples that the "Conditions of Existence" is the higher law. For example, in the early part of last century, the average height of adult humans increased by about 0.4 inches/decade. Likewise, cardiovascular disease rose from being a rare event, to the number 1 cause of death by the 1970s. Moreover, the complications accompanying obesity have made obesity the major health concern of this

new century. None of these changes can be explained by changes in the genome or Natural Selection.

Conditions of Existence

There are four other stunning examples of the higher power of the Conditions of Existence.

(1) The first is of course the origin of the Solar System if not the Big Bang itself and its consequences. The Fermi Lab and the Large Hadron Collider are examples of the seriousness with which physicists consider the Conditions of Existence.
(2) The origin of life itself: this was followed by anaerobic prokaryotes that display little or no change in composition despite 2.5 million years of existence.
(3) Change occurred when oxygen tension, excreted by photosynthesis and the photolysis of water breached the Pasteur point at which oxidative metabolism becomes thermodynamically possible. When that happened about 600 million years ago, multicellular, air breathing systems evolved and all the 32 phyla we know today came into existence in a very short geological time span. No new phyla have been formed since.
(4) The rapid collapse of the Dinosaurs after ruling the earth for 135 million years and the equally rapid rise of flowering plants and mammals. A meteorite catastrophe is a fundamental change in conditions which resulted in a new class of primary producers, the angiosperms.

These episodes are just a few of many cited by Rattray Taylor[24] and by Gould and Eldridge[25] and described as "punctuated evolution." The stalemate in Conditions of Existence over the 2.5 billion years of prokaryotes proves that DNA clearly could not change life itself no matter how "selfish" the gene may have been! DNA is remarkably stable. People even try to extract it from reptiles that lived over 60 million years ago! Nor is DNA changed in response to the small changes in temperature and pressures around the planet. The key to its success is the robustness of its stable reproduction. As the DNA ultimately dictates the proteins, the proteins themselves could not be responsible for change in response to different conditions. Hence something other than DNA must have responded to external change to explain the sudden explosion of cellular organization, cell and phyla diversity in the Cambrian and the sudden change in size, shape, and disease pattern in our own species in one century.

Traditionally, it is considered that the birth of the 32 phyla was triggered by the advent of oxidative metabolism which is 8 times more efficient than anaerobic metabolism. This view is indisputable. As discussed above, within physiological temperature ranges, it is unlikely that a change in temperature or pressure would alter the DNA. However, there is a feature in the biology of the cell that does respond to the environment, i.e., to temperature and pressure. It does not show the robustness of DNA but is responsive to both the physics and chemistry of the environment. This cell feature is presented by the lipids that make up the cell membranes, which provide the basis for the organization of eukaryotic cells.

LIPIDS AND THE ORIGIN OF MULTICELLULAR LIFE

The life forms of the first 2.5 billion after the origin of life were anaerobic, single celled systems with no intracellular detail recorded in the fossil record. The Cambrian explosion, however, was associated with the appearance of intracellular compartmentalization provided by cell membranes which constitute of lipids. This compartmentalization is seen in every electron micrograph of eukaryotic cells (Fig. 1). The lipids formed the membranes that housed the transporters, ion channels, signaling, and cell recognition systems. As such, lipids made intracellular specialization possible, and have been integral to specialization and multicellular evolution.

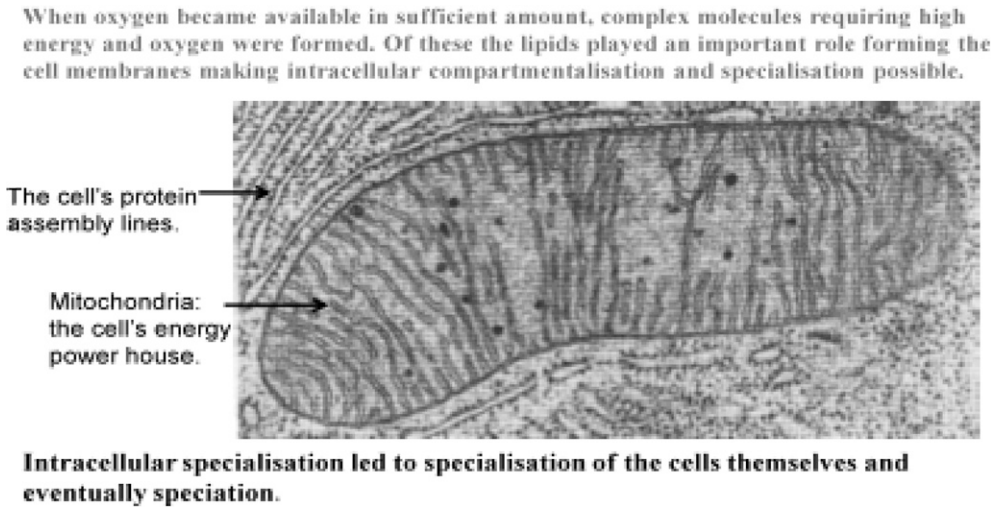

FIGURE 1. Lipid provided the intra and inter cell structure to create compartments and specialization. They thus played a pivotal role in cell specialization and speciation.

Thus, we propose the thesis that lipids were key drivers in the Cambrian explosion.

The next section will discuss the plausibility that the lipids played their part in the sequence of events that followed the emergence of oxidative metabolism and indeed the Cambrian explosion. The logical conclusion and importance of this insight is that the lipids are still modifying our species today. This conclusion has implications for the future as we shall see later in this text.

MISCONCEPTION OF THE CELL MEMBRANE LIPID

For some time, people have given little thought to membrane lipids considering them mainly as a barrier to water and water-soluble substances. Text books and many research articles depicted membrane lipids as a uniform, double row of match sticks with the heads facing the outside with the wooden sticks inside the bilayer. They are drawn to look like a symmetrical railway track.

This view cannot be correct. Acyl groups that correspond to the sticks, vary in chain length mainly from 16 to 24 carbons (Fig. 1). They may be saturated and adopt a preferred straight line, indeed like the match stick. They may have a double bond that introduces a kink so the carbon chain is no longer a match stick. They may have multiple double bonds that tend to impart a helical or coiled structure. Commonly, there are fatty acids with 2 to 6 methylene interrupted double bonds in 18 to 22 or more carbon atoms in the chain. The length, the space filling volume, electrical, physical, and van der Waals properties of the molecule are dependent on the number of carbon atoms in the chain and number of double bonds.

The polar head groups that are represented by the heads of the match sticks are not only of different shapes but range in charge strength from, for example, positively charged, primary amines to the powerful, quaternary amines associated with negatively charged phosphate groups. The choline phosphoglycerides have a quaternary amine and sits on the external face of the cell membrane. By contrast, the internal side is mainly filled with a primary amine—ethanolamine phosphoglycerides. A strongly basic quaternary amine on the outside and a weak primary amine on the inner face immediately presents a dipole moment adding electrical potential to the membrane. In addition, different lipophilic membrane proteins like to preferentially dock with individual molecular species which in turn will influence the nature of surrounding lipids.

How the misconception of the lipid membrane has been repeated from research papers to textbooks is difficult to understand as it so easily seen as false. Any one of these molecular arrangements completely destroys the regular match stick image of membrane lipids. The bilayer seen in the electron microscope is a dead system not a live one. Unfortunately, this misconception has stymied the understanding of the specific properties of the individual molecular species of the lipids and the properties of the membrane as a functional unit with diverse electrochemical and physical properties.

With regard to the physical properties, the melting points and hence the liquidity of the lipids varies from a saturated fat that is solid at room temperatures, as in the beef fat people turned into candles before electricity, to a liquid with the introduction of one cis double bond in the $\Delta 9$ position, as in olive oil. Hence in the lipids, Nature had building blocks for cells that could be used at different ambient temperatures—from the North Atlantic to the Equator! The space filling and liquidity characteristics also enabled a response to pressure contrasts as on land compared to the Mariana Trench 10,911 m deep. The Panthalassic Ocean of the late pre-Cambrian 600 million years ago had 85% more water than today and any barren land above water was below the equator, down where the Antarctic is today. Hence the evolutionary process was taking place in sea water with varying conditions which likely included much volcanic activity adding local spice in terms of both chemistry and temperature.

LIPID COMPLEXITY ADVANCES SOPHISTICATED CELLULAR ORGANIZATION

The study of the anaerobic systems of the rumen and gut flora shows that in the absence of oxygen, the double bonds of unsaturated fatty acids are used as hydrogen acceptors resulting in saturated fatty acids and trans-isomers. Therefore, it is unlikely that highly unsaturated fatty acids, such as DHA with six double bonds, would have been in abundance before the Cambrian explosion, when during the 2.5-billion-year prokaryote period anaerobic metabolism was prevalent. It requires 6 oxygen atoms to make the 6 double bonds of DHA alone. Also, the synthesis of phosphoglycerides themselves is energy intensive. Hence the emergence of oxidative metabolism made possible the synthesis of many types of highly unsaturated fatty acids and different phosphoglyceride molecular species.

Cell specialization in the Vendian and early Cambrian led to differentiation with the expression of a variety of proteins which in turn led to a requirement for varying types of lipids to fit with the cell specific proteins. We now find that the membrane and in particular the lipid domains around the receptors, signaling systems, transporters, and ion channels are strongly conserved. This conservation is seen especially well in the fatty acid composition of the lipids associated with the rod outer segment of the photoreceptor and synapses as the membrane lipid in the cephalopod photoreceptor is virtually identical in all vertebrate species that evolved and diversified since some 440 to 490 million years ago.[26]

It is known that different cells have different global lipid compositions which mean that the differentially expressed proteins are taking advantage of this wealth of lipid diversity. For example, brain lipids are different from the heart lipids and mitochondrial lipids are different from those in the nuclear envelope. There are differences even within the mitochondria. And when you look deeper, you find even parts of the same membrane are different as in the rafts and caveolae

compared with the region of lipophilic proteins with micro domains in evidence.[15]

However, lipid–lipid interactions will also have played a role in cell diversification, e.g., the formation of myelin in the nervous system. The influence of the protein on lipid structure decays logarithmically, with distance from the protein. However, in parts of the nervous system, there is so little protein that lipid–lipid interaction must be a major determinant of composition. As in crystallization, it would be expected that like would form preferentially with like, hence the uniformity of myelin where there is a lipid–lipid dominance. In the photoreceptor, where the number of polar head groups between rhodopsins is small, the van der Waals and electrochemical influence of the protein stretches throughout the interprotein space leading to a DHA-rich, uniformity of composition for >50% of the acyl groups. There is virtually no species difference among the vertebrates and even some invertebrates.

The conclusion for this part of the thesis is that the infusion of oxygen was not just responsible for facilitating the higher energy efficiency of aerobic metabolism as is commonly thought. Oxygen availability was also responsible for the growth in diversity of both protein and lipid structures, and these were at the root of the emergence of cellular and subcellular structures and intracellular specialization, rapidly followed by cell specialization and the 32 phyla (Fig. 2).

There is a large variety of fatty acids constituting essential building blocks for membrane lipids. There are saturated, monounsaturated, and PUFAs in the sn-1 and sn-2 positions of the phosphoglycerides that give rise to a large number of possible fatty acid combinations within the membrane phopsholipids. For example, there are choline, serine, inositol, and ethanolamine phosphoglycerides, plasmalogens, cardiolipin, sphingolipid, and glycosphingolipid species, which include the many galactocerebrosides found in neural tissue, and glucocerebrosides present in muscle and other tissues contributing to a considerable number of words in the lipid dictionary.

TABLE I. Fatty Acid Species in sn-1 and sn-2 Positions[22]

	sn-2 Position		
sn-1 Position	Monounsaturated	Di- and Triunsaturated	≥ = Tetra unsaturated
C14:0	C16:1n-7	C18:2n-6	C20:4n-6
C16:0	C18:1n-7	C18:3n-6	C22:4n-6
C18:0	C18:1n-9	C20:2n-6	C22:5n-6
C22:0	C20:1n-9	C20:3n-6	C20:5n-3
C24:0	C24:1n-9	C18:3n-3	C22:5n-3
C16ald			C22:6n-3
C18:0ald			
C18:1ald			
C18:2ald			

In addition to the sn-1 and sn-2 positions, the sn-3 position (polar head group) can be substituted with either choline, ethanolamine, serine, inositol, or glycerol giving rise to approximately 720 molecular species.

The variety of lipids is vast, with about 340 of the most common molecular species, 720 common, and several 1,000 altogether if the rarer and sometimes trace amounts are counted. This variety is possible because the system appears to be operating in 6 dimensions with the 4th dimension being the electrochemical profile, the 5th dimension the van der Waals forces, and the 6th dimension temperature. This high degree of structural sophistication provides for the multidimensional requirements for the physical and electrochemical environment for protein, physical and electrical function (Table I).

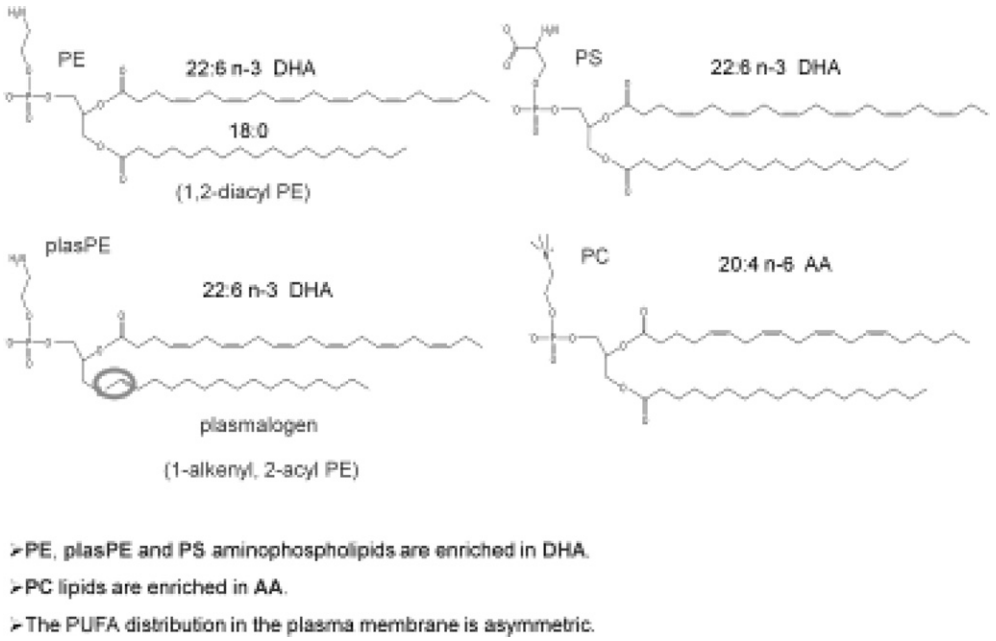

FIGURE 2. Some key brain phosphoglyceride molecular species.

It is now known that alteration of the lipid composition in the protein domains will affect protein function. Because the first point of contact between the environment and the cell is the plasma membrane, we have here the explanation for the response of the cell and the genome to the environment. At the beginning of animal evolution, life was poikilothermic. Hence the lipids would have responded to the temperature differences in contrasting habitats where there would likely also be contrasts in pressure. That would certainly have meant that the very most primitive life would have spread and found itself in widely contrasting environments with requiring different plasma protein domains and setting the stage for different evolutionary directions.

ON GENOMIC CONSERVATION AND STABILITY

The function of DNA has dominated recent biology and evidence indicates that the DNA, unlike the lipids, is remarkably stable. The genome of the Puffer Fish (*Fugu rubripes*[27]) was sequenced in 2001 (http://fugu.hgmp.mrc.ac.uk/PFW/Other/consortium.html). The Puffer Fish genome dates back 450 million years, but the regulatory elements of some genes such as the Hox genes[28] and coagulation factors are strikingly conserved. Indeed, three-quarters of predicted human proteins have a strong match to Fugu although approximately a quarter of the human proteins had highly diverged from or had no Puffer Fish homologs.[27] That and much other similar genomic evidence implies a high degree of genomic conservation and stability. When the data on the human genome was published, Craig Venter, the leader of the U.S. Human Genome project declared that there was not enough diversity to explain biological behavior.

With the evidence today that the lipids do indeed influence gene expression, it may well be that they had a greater influence on these evolutionary events than they have been given credit for. Remarkably, DNA can be extracted from long dead animals. However, that is not true of the highly unsaturated lipids that die rapidly with the death of the host. Thus, controversial as it may sound, lipids may be more of a life force than DNA.

DHA IN EXTREME LIPID CONSERVATION OVER 500 MILLION YEARS

For the first 2.5 billion years of life, photosynthesis converted sunlight into proteins and carbohydrates. At the beginning of animal evolution, DHA provided the basic membrane backbone of new photoreceptors that converted photons into electricity. The electrical and ionic consequences would have laid the foundation for the evolution of the nervous system and the brain.

If we date the conservation of DHA in signaling back to the dynoflagellate photoreceptor, we are talking about 600 million years of conservation. Bloom et al[29] pointed out that this conservation occurred despite the fact that the close precursor of DHA, the ω-3 docosapentaenoic acid (ω-3 DPA), which differs from DHA only by 2H, is less susceptible to peroxidation and requires less energy to synthesize. Despite genomic changes taking place from worms to humans, multicellular organisms did not (perhaps could not) swap docosapentaenoic for DHA and the conservation of DHA in the vision and the brain dates across the known range of the present genomic representatives of vertebrate evolution. It is as though DHA is the master of DNA.

THE IRREPLACEABLE DHA

The fatty acid composition of the brain lipids is essentially the same for 42 mammalian species studied. The major difference in the brains between species is not brain chemistry but the extent or size of the brain.[30] In land mammals, the size of the brain relates to the availability of DHA. The marine mammals have abundant DHA but difficulty in accessing AA which they nonetheless need for reproduction and brain function despite many millions of years of inhabiting the sea.[31,32] Hence, while on land DHA would be limiting, in the sea, AA appears to be limiting (Fig. 3).

DHA is clearly unique. Liquidity is often cited as the reason for DHA's special function, but this property is little different from the ω-3 DPA. The liquidity differences between DHA and the ω-3 DPA do not explain the uniqueness of DHA over 600 million years of evolution, but unambiguous biophysical evidence suggests that DHA has special mechanical properties because of curvature and springiness that make it irreplaceable.[33–35]

In addition to its characteristic mechanical properties, we speculate that the 6 methylene interrupted doubles bonds in DHA uniquely contribute π-electrons to signal transmission. Extended Huckel calculations based on the least occupied orbitals for DHA show that the bonds have a + and a – lobe and that the + and – signs of orbitals of the two different hydrogens on the CH2 groups also have + and – signs related

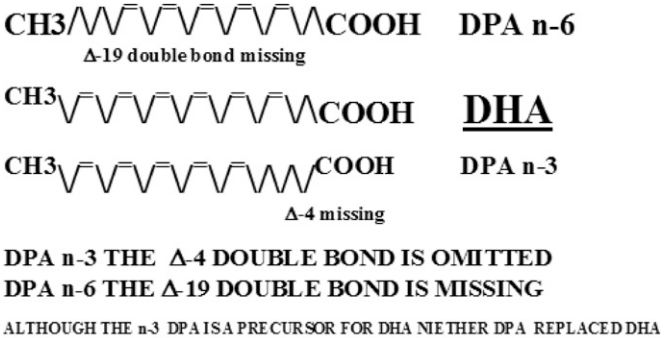

FIGURE 3. What is special about DHA? The optimum physical hypothesis (OPH) (DHA—a 600 million year track record).

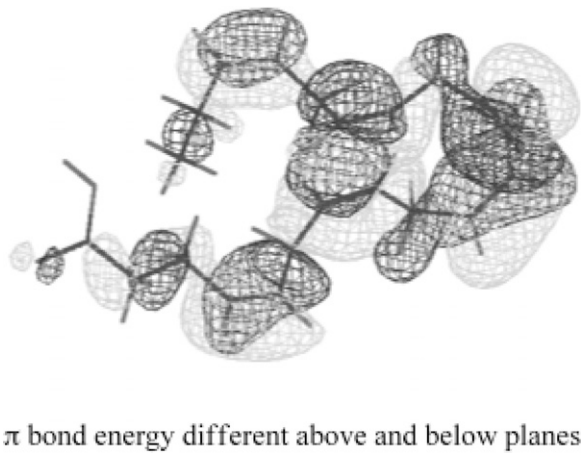

FIGURE 4. Least unoccupied molecular orbitals—LUMO in DHA (π bond energy different above and below planes; green lower, mauve higher energy).

to (typically opposite to) the signs of the adjacent π bonds (Fig. 4).

This simple mechanism can explain electron coherence over a large distance, even though the double bonds are not extended resonance structures across a sequence of carbons with only single hydrogens. ω-3 DPA, which has five methylene groups following the double bond sequence, lacks these electrophysical properties. This idea offers a quantum mechanical electron transfer explaining precision of function unique to DHA, which becomes dysfunctional if a double bond is missing at either end of the molecule.[35,36] This is an operational example of Darwin's "Conditions of Existence."

THE CRETACEOUS AND AA

The next obvious lipid involvement in the Conditions of Existence occurred during the Cretaceous period as flowering plants evolved their protected seeds. The fish and reptilian era might well be expected to have been based on green foods. Fish depend on ω-3 fatty acids for reproduction, however, the introduction of the flowering plants brought ω-6 fatty acids into the picture with their protected seeds being rich in linoleic acid. Coincidentally, mammals evolved depending on ω-6 fatty acids for reproduction. With the brain utilizing ω-6 and ω-3 fatty acids in a ratio of about 1 to 1 or 2 to 1, the injection of the ω-6 to an already ω-3-rich food web would have played a critical role in the advance of brain evolution leading to the larger relative brain capacity of the mammals and ultimately, cerebral expansion in human evolution. There is good evidence describing the competition between fatty acids especially between the ω-6 and ω-3 families as they both use the same enzymatic systems for synthesis and metabolism.[37,38] Hence, the emergence of abundant flowering plants with protected seeds can be viewed as another example of the changing biochemical conditions leading to an evolutionary novelty; again an example of Darwin's "Conditions of Existence."

THE TISSUE IS THE ISSUE

In modern time, the increasing reliance on food made from soya, corn, and sunflower seed oils has greatly increased dietary ω-6 fatty acid, and more specifically, linoleic acid intake resulting in a high linoleic acid to DHA ratio in the modern Western diet (Fig. 5).[38]

As linoleic acid can compete with DHA for incorporation into cellular lipids, the tissue ratio of linoleic acid to DHA varies across species depending on fatty acid availability in the diet. The marine Dolphin comes the closest to *Homo sapiens* with regard to brain/body size ratio. In a dolphin brain of about 1.8 kg, with the dolphin having ready access to dietary DHA, the ratio of all ω-6 to ω-3 fatty acids is close to 1 to 1 and the linoleic acid to DHA ratio is 0.067 (Fig. 6).[31]

In a typical large, savannah mammal, the linoleic acid to DHA ratio is about 30 to 1 whereas the average brain size is only 350 g. This ratio makes the point that where tissue levels of linoleic acid are high and DHA low as in the case of the large land mammals, the brain size relative to the body diminishes: a form of degenerative brain evolution. By contrast,

FIGURE 5. The rhinoceros gets all the protein it needs for a prodigious velocity of body growth reaching a 1 ton body weight in 4 years from birth.

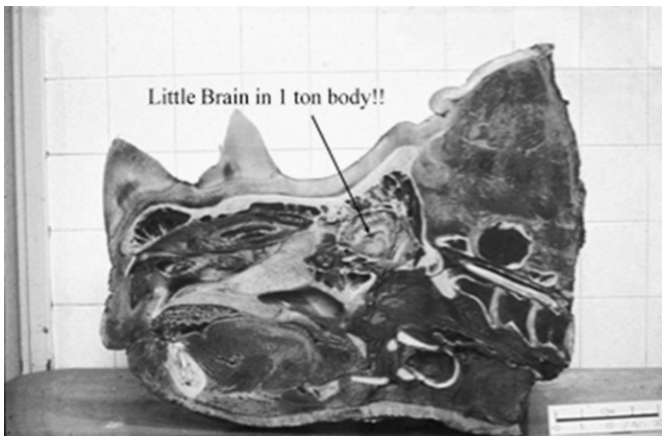

FIGURE 6. Despite such body growth and eating grass, a primary source of α-linolenic acid, it makes little DHA and has a very small brain.

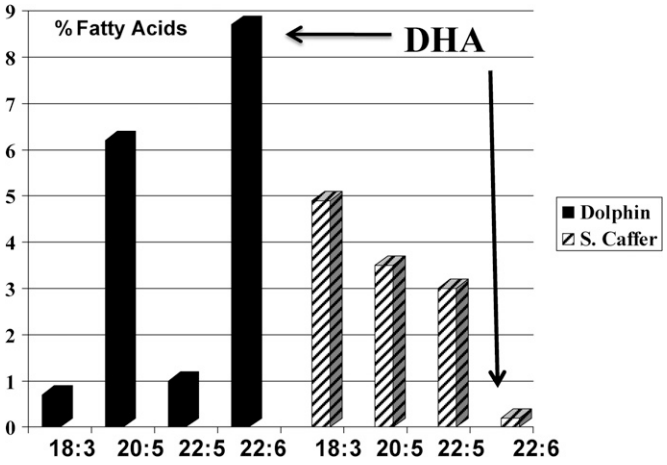

FIGURE 7. Liver ethanolamine phophogyceride from *Syncerus caffer* (Cape buffalo) and *Tursiops truncatus* (dolphin).

when the linoleic acid is low and DHA is high, you have cerebral expansion as in the case of the Dolphin.

We suggest that the evolving hominid that became *H. sapiens* would have been in a biochemical situation more like the Dolphin than the land-based mammals.[30,31] Note that buffalo liver lipid is quite rich in α-linolenic acid, EPA, and even the ω-3 DPA but despite this wealth of precursor, fails to synthesize significant DHA (Fig. 7). The contrast with the Dolphin lipids in this respect is striking.

COASTAL EVOLUTION OF *H. SAPIENS*

With clear evidence of the involvement of DHA in brain development, gene expression and function, DHA must have played a role in the evolution of the human brain. The biological science supports the view that a powerful evolutionary advantage for cerebral expansion would have come from a regular, food-rich source of DHA and associated trace elements. As the marine food web is by far the richest source, the evolutionary advantage of coastal evolution is obvious. Evolution of the big brain could not have happened inland. On land, relative brain size degenerates as body size and growth velocity increases, from the >2% of small mammals (e.g., squirrels and capuchins) to <0.1% diminishing even within the primates from a cebus monkey to the chimpanzee, gorilla, and rhinoceros (Fig. 8).

Consistent with the role of lipids in evolution, the Dolphin and the Gray Whale still retain their requirement for AA assumedly for the mammalian reproductive process.[31,32] Hence, although the marine mammals had an abundant supply of ω-3 fatty acids, they were hard put to get their ω-6 AA. The Gray Whale migrates 9,000 to 11,000 km from the Bering Sea in the Arctic to the warm waters of the lagoons of Baja, Mexico where it breeds. A likely explanation for this huge effort is to seek out the AA -rich foods present in warm waters.[32] None the less it is clear from the comparative evidence that both arachidonic and DHAs are required for the brain.

H. sapiens enjoyed coastal habitats rather than savannah environments. Savannah environments favor poikilothermic animals. In the coastal niche, evolving hominids would have had the best of both worlds. At just under 2%, *H. sapiens* has a brain body weight ratio which would be totally exceptional if considered as a land-based mammal but not if there was a rich supply of preformed DHA in the diet. Thus, the ease of obtaining both foods containing DHA and AA likely facilitated the harmony between body and brain growth during human evolution.

Logarithmic plots have commonly been used to obtain straight lines and explore the relationship between body size and brain size. The relationship is a straight line for most land mammals, but with the brain size diminishing logarithmically as the body size increases. Humans stand out as outliers with exceptionally large brains when compared to all other land mammals. The conclusion is that in land animals eating

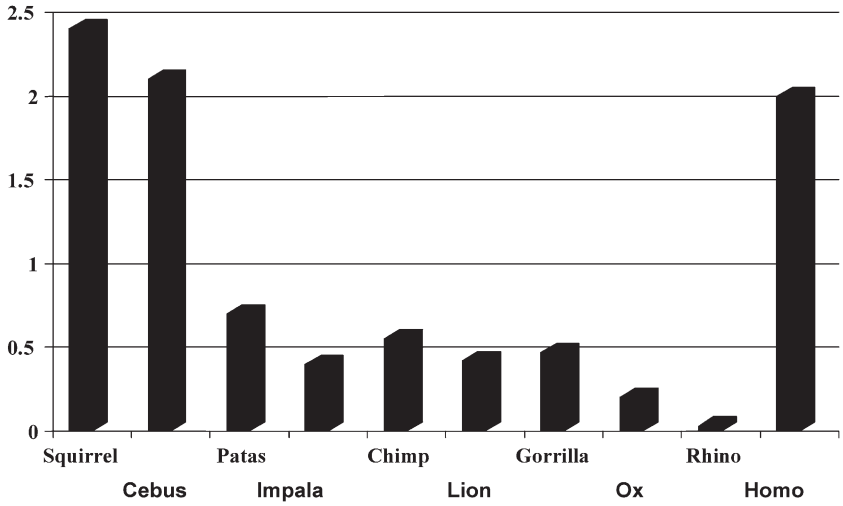

FIGURE 8. Land-based mammals compared to *H. Sapiens*. They have lost relative brain capacity as they evolved larger bodies.

land-based foods, the rate limited synthesis from α-linolenic acid to DHA was outstripped by the velocity of protein accretion and body growth with a consequent universal shrinking of relative brain size among all land mammals without exception. Again, this evidence puts the evolution of *H. sapiens* at the marine and lacustrine coastlines with access to preformed DHA from the aquatic resources.[39]

Fossil evidence for incontrovertible exploitation of the sea foods has been described by Marean et al.[40] "We have identified the earliest appearance of a dietary, technological, and cultural package that included coastal occupation, bladelet technology, pigment use and dietary expansion to marine shellfish, and is dated to a time close to the biological emergence of modern humans (160-180kya)."[41]

Further, the earliest identification of jewelry, a definitive example of cultural behavior, is in the form of shell beads as necklaces.[42] Indeed, most anthropologists accept that population of the planet after migration out of Africa occurred primarily by moving along coastlines and major rivers or by moving from lake to lake across North Africa.[43]

Physiological Evidence

Added to the biochemical evidence is the physiological basis first articulated by Sir Alistair Hardy in 1960[43] and followed up by Elaine Morgan.[44,45] Their writings formed the basis of the Aquatic Ape Theory. Simply put they claimed that the physiology of *H. sapiens* was more akin to that of marine mammals than those of the savannahs. For example, we have a diving reflex, children are born knowing how to swim but have to learn to walk, bipedal locomotion would have come naturally from wading, swimming, and diving, we are hairless, we lose water by perspiration to keep cool and therefore "wherever we were evolving we had to have water to drink" (A comment made by Professor Philip Tobias at a McCarrison Society conference on "Human Origins," held at the Zoological Society 2006). All the savannah animals have hair and various physiological tricks to conserve water, which is sparsely available on the savannahs. In 1961, Neil Casperd and MAC found they were losing 1.5 L an hour on foot safari on the savannah in Uganda. Newspaper reports contend that the Israeli army found they needed to drink 20 L of water a day to remain fighting fit in the heat of the North African desert, which would be very similar to our condition in the savannahs of East Africa.

Iodine and Selenium Deficiency in Inland Populations Strengthens the Case of a Coastal Origin for the Line Leading to H. sapiens

If DHA and trace elements in the marine food web, including iodine, zinc, and selenium, were required for cerebral expansion, then in areas where these nutrients are sparse, such as inland, there would be greater incident of brain malformation. This is indeed the case.[46–50]

Keshan disease, which is considered to be caused by selenium deficiency, is most prevalent in inland in China. Likewise, iodine deficiency that causes a spectrum of defects on the fetus ranging from retarded fetal development and brain damage to fetal death and stillbirths[48–50] is most common in inland regions where 2 billion are currently at risk, but seldom seen in the fishing villages. Correction of deficiency produces a "coming to life" writes Prof Basil Hetzel who coined the term iodine deficiency disorders many years ago. In view of the coexistence of iodine and DHA in the marine food web, it is highly likely that iodine deficiency is associated with an ω-3 fatty acid deficiency, especially DHA deficiency! Therefore, it is not surprising that Nyuar et al[51] report the lowest levels of DHA in the milk of mothers from Sudan, a nation with a high prevalence of iodine deficiency.[52]

The Rift Valley: Geological and Paleontological Evidence from the African Rift Valley and Nile Basin

The East African Rift Valley is a unique tectonic province in both type and extent, unmatched anywhere else on Earth. The Red Sea, Gulf of Aden, and the East African Rift Valley are the only current examples of what is geologically termed a "failed ocean." Rifting began about 30 Ma, thinning and stretching the continental crust, but significant uplift did not begin until 15 Ma. The Red Sea axis has thin longitudinal strips of oceanic crust that are only about 5 Ma.[53,54] In East Africa, faulting related to this crustal extension and uplift formed a series of half-graben basins, which link together to form the Rift Valley. Large lakes formed in these basins, with inputs from both interior drainage and river systems. On the border fault side of the lakes, cliffs can rise to more than 2 km above the lake level.

Some lakes were so extensive during Cenozoic (65 Ma to present) that they are correctly termed proto-oceans. Lakes Malawi and Tanganyika presently have water depths of up to 1,500 and 600 m, respectively. Many of the deep water channels are similar in form and scale to those observed in the deep ocean.[55–57] Lake Victoria is presently 69,000 km^2 and is the world's largest tropical lake.[57]

East Africa has provided littoral environments on a massive scale throughout the evolution of *Homo*. *Homo* fossil and archaeological sites located within the East African Rift Valley[58,59] as well as other parts of the world are consistently and unarguably waterside areas replete with potential aquatic food resources.[39,60,61] Most or all *Homo* apparently entered Europe and Asia by moving northward along the Nile Basin into the Levantine and onwards.[62] Although African *H. sapiens* dates to about 200 ka, the earliest known anatomically modern *H. sapiens* remains recovered outside Africa (93 ka) from Qafzeh, Israel,[63,64] are associated with coastal habitation and consistent with migrations up and down the Nile corridor (Fig. 9).

Recently, is has become evident that *Homo* made water crossings of the Bab El-Mandeb Straight from Eritrea to the Arabian peninsula[65–67] (Fig. 9). Evidence for Middle Stone Age human occupation of the Red Sea coast of Eritrea dates to 125 ka, during the last interglacial.[68,69] Interestingly,

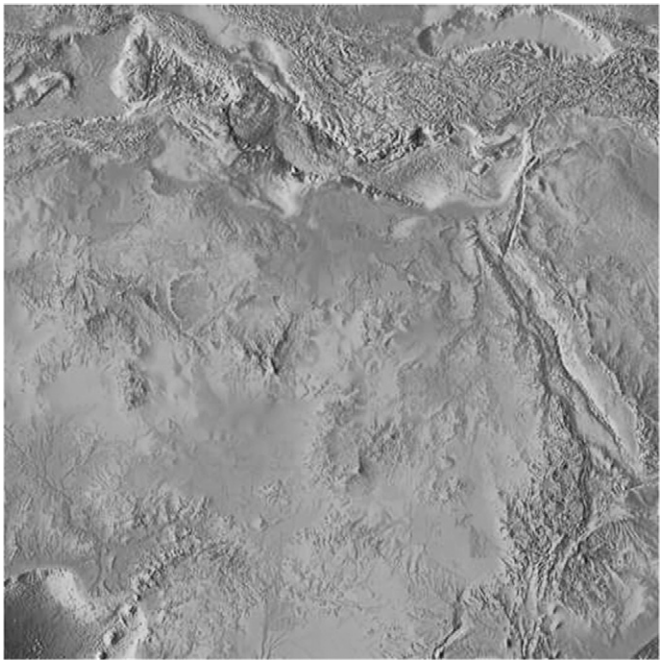

FIGURE 9. Relief map of Afar Triangle East Africa, showing the Red Sea basin and initiation of the Rift Valley. Note also Nile Corridor to the Mediterranean region and Eurasia.

Walter et al[70] conclude that "the eventual dispersal of humans out of Africa was due to increased human competition for marine resources, possibly during hyper-arid conditions." This is diametrically opposed to previous savannah hypotheses, because littoral foods are now the driving force for a population migration, not an accidental or incidental food source. Eastwards, *H. sapiens* made extensive water crossings to reach the Philippines by 67 ka (Fig. 10).[71]

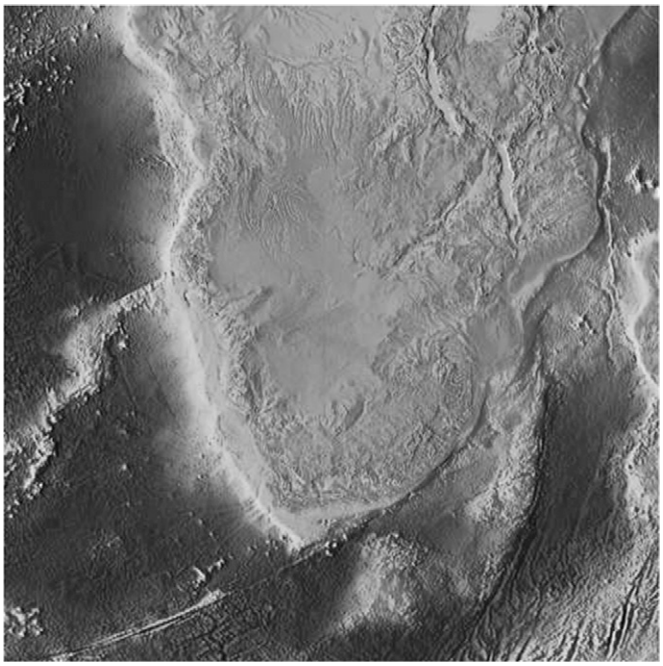

FIGURE 10. Southern Africa, showing Cape of Good Hope and continuation of Rift Valley with its proto-oceanic lakes. Lake Victoria is on the northern border of the map. Note continental shelf on the southern border—this area was exposed during glaciation periods.

African Coastal Environments Provide Concrete Evidence for Modern Human Behavior

There is virtually unanimous agreement that anatomically and behaviorally modern humans left Africa to populate the entire world about 50 ka.[72–75] The number of individuals responsible for this migration is staggeringly small—perhaps only few hundred or thousand. Numerous genetic markers in modern humans point to a recent African origin.[76,77] At least some and perhaps all of our ancestral *H. sapiens* survived in coastal refugia and thus were highly adapted to exploiting coastal/littoral environments and evidently benefitted tremendously from exploiting this niche.

Tattersall[75] notes that becoming human took place in 2 separate stages: first the distinctive human morphology became established in Africa about 200 ka, followed by symbolic behavior 75 to 100 ka later in Africa, but at 40 ka in Europe. The complex human neural substrate existed as part of modern anatomy, but was not fully exploited until symbolic behavior developed. The earliest evidence for human symbolic behavior—the hallmark of modernity—comes from archaeological investigations of African Middle Stone Age humans. These sites are South African coastal caves filled with shell middens, fish bones, and the remains of marine birds and mammals, including cormorants, Cape penguins, fur seals, and whales (Die Kelders, Klasies River, Blombos, Pinnacle Point, Ysterfontein). Associated with these assemblages are some of the oldest fossils accepted as modern human.[78–82]

Recovered from Blombos cave (~75 ka) are decoratively engraved ochers and a precocious bone industry (including engraving) not seen in Europe until 40 ka.[83–86] At Pinnacle point (~164 ka), Marean et al[87] found ochers and numerous examples of bladelet technology normally seen only in the Late Stone Age. At the same time, humans at Pinnacle Point used fire treatment to improve materials use in stone work,[88] demonstrating a significant engineering capability was present. Not to be overlooked are the precocious bone harpoon and fish remains in the Katanda lakeshore locality dating to 100 ka.[89]

The oldest known example of personal ornamentation consists of marine mollusk shells either drilled or carefully selected to be strung as a necklace. Some shells also have evidence for coloration with ochre. "Explicitly symbolic objects" such as shell necklaces are found at Blombos Cave,[90] Grotte des Pigeons, Morrocco,[91] Qafzeh and Skhul, Israel, and at other locations in Morrocco and Algeria.[92] Clearly these shells held value and humans either visited the shoreline or traded with others who had.

Numerous triggers may have played a role in the development of modern logical and symbolic reasoning and the shift to a primary reliance on cultural rather than biological

evolution. Leading candidates include the development of language,[75] rapidly changing climate, and local increases in population that allowed ready transfer of cultural and technological concepts to peers and offspring.[86,91,93] However, the outcome we observe around us today requires as both a necessary and sufficient condition that abundant long-chain PUFA, as well as complete protein, trace elements, and vitamin sources be available to all members of a prehistoric society for generation after generation. The most parsimonious means to do this is to assume that *Homo* palaeoenvironments were consistently littoral marine, riverine, or lacustrine. Interestingly, shoreline environments provide for the population increases that are indeed vital to keep cultural and technological innovations alive.[86,87,94] These various aspects are not contradictory and indeed are interconnected.

Before the recognition that modern behavior originated early in Africa as opposed to after 50 ka in Europe, most researchers looked to genetic mutation(s) that may have allowed the symbolic mind to appear. Fortunately, it is now recognized that aspects of nutrition are a condition of existence.[35,87,95–100] demographics,[94,101] and language,[75] and were a driving force in evolution. A remaining question is why modern behavior apparently died out in Africa, then reappeared 30 to 60 ka later in Europe but not in many places in Asia.[40,73,79,93,101–103]

The fossil record is only what people find where conditions allow preservation. The "mosaic" appearance of modern human behavior as reported is both easily understood and predicted by a model in which environmental factors strongly influence gene expression. Epigenetic changes in gene expression occur in only a few generations, and can result in (semi-)permanent changes in the organism that are passed on to offspring. Although it may take several million years to evolve a complex primate brain, the "switch" that turns it on to human cultural overdrive could happen in a hundred years. The influence of long chain PUFA alone on gene expression is fundamental, dramatic, and profound.[6–8] Thus, if an entire local population has abundant DHA, I, Zn, Cu, and Se in the food supply year-round and generation after generation, then the impact on gene expression would be predicted to quickly affect brain structure and function. Time after time, it is noted that cultures consuming diets rich in DHA have displayed greater range of tool technologies. We suggest that this development has been the effect of diet and environmental conditions on gene expression and epigenetics which in turn led to greater brain development and cultural advancement.[35,36,104,105]

A REASON FOR CONCERN

In the above discussion, we have tried to develop an understanding of why DHA is the only ω-3 fatty acid used in neural signaling processes over 600 million years of evolution, despite the large scale change in genomics over that same time period. John F. Kennedy said "we celebrate the past to awaken the future." We now understand that maternal nutrition before and during pregnancy is an independent risk factor for low birth weight and poor pregnancy outcome.[106–110] Postnatal nutrition is also a priority to ensure good maternal nutrition for herself and for milk.[111,112] Hence, poor maternal health and nutrition before and during pregnancy disadvantages fetal development resulting in low birth weight, and permanent mental and cognitive deficits,[113] with risk of heart disease, diabetes, and stroke in later life.[114] Disadvantaged or disordered brain development during this period is lifelong.

Poor neurodevelopment restricts the individual's capacity to acquire numeracy and technical skills.[115] In addition, in clinical trials, ω-3 fatty acids may protect against sudden death from heart disease.[116] There is also evidence that a high linoleic acid diet will compete with the ω-3 fatty acids and induce behavioral pathology.[28,117] Deficits of marine fats during pregnancy have been linked to an adverse verbal IQ and behavioral outcomes in the children at 8 years of age[118] and to bipolar disorder.[119,120] Low ω-3 status has also been associated epidemiologically with Alzheimer's disease (AD).[121,122] It is one matter to identify the risk of AD and a completely different affair to attempt to correct such a process. Although many are trying to treat AD in late life with ω-3 fatty acids, it is a tall order to attempt to reverse a process so long in the making, possibly even before birth.[123,124]

The abundance of the oceans was so taken for granted that people are still hunting and gathering its products despite the fact that Food and Agricultural Organization informs us that the total world catch reached a limit 20 or more years ago. Just over a century ago, oysters were gathered and presented on the bar table in the East end of London free for those who bought beer. In Maryland, 616,000 tons of oysters were harvested in 1889 as opposed to only 12,000 tons in 2002. This loss of ocean food has additional consequences, as the calcium carbonate shell from the quantity of oysters harvested in Maryland in 1889 removed 270,000 tons of CO_2 from the atmosphere.

THE CHALLENGE OF THE RISE IN BRAIN DISORDERS

In the beginning of the last century, candles were made from beef fat, a hard, saturated type fat. Then came electricity and we now "eat the candles." Added to this dietary novelty of beef fat was the hydrogenation of fish and plant oils to make cooking fats and margarines. Even worse, the selection of livestock animals for weight gain led to the use of high-energy foods, intensification, growth promoters, and denial of exercise to promote growth and fatty meat. A wild bovid relative of a modern intensified animal provides more protein energy than beef fat as would have been the condition throughout the adaptation of human physiology. The conventional, intensively reared carcass with 30% fat has 50% lean meat, which translates into 9 times the calorific value coming from hard, beef fat compared to protein. All of this ends up in our stomachs together with added trans-isomers from animal

fats and hydrogenation of fish and vegetable oils. These were major changes in the nutritional conditions which featured in the rise of heart disease and its rise from a rarity at the beginning of the 20th century to the leading cause of death today. A report by Food and Agriculture Organization–World Health Organisation in 1978[125] recommended a correction of this abuse of the animal but little has been done. Since World War II, there has been an added nutritional change, as there has been an explosion of linoleic acid from soya, cereals, and grains. In all of this the ω-3 fatty acids were swamped.[38]

Cardiovascular disease became the no. 1 killer in the West and the rise in death from heart disease by the beginning of the 1970s was considered to be because of "bad fats." Having found that the brain is largely made of good fats,[17] it followed that unless something was done, the brain would be next: a prediction published in 1972.[125] The significance of lipid nutrition for brain health was acknowledged at the Food and Agriculture Organization–World Health Organisation first consultation on the role of dietary fats in human nutrition.[126] It identified essential fatty acid requirements for the brain and early human development and recommended the correction of the fatty food system. Nothing was done and if anything matters have got worse. In a sense, parallel with the rise in bad fats came the rise in sugar consumption and fructose use in foods and drinks, that has led concern over diabetes and metabolic syndrome.[1,127]

The 1972 prediction has been proved correct. Brain disorders now account for the highest cost in the burden of ill-health in Europe at a cost of €386 billion for the 25 member states at 2004 prices.[5] A reassessment in 2010 put the EU cost at €789 billion. In the United Kingdom, Dr. Jo Nurse for the Department of Health estimated the cost of mental ill-health in 2007 to be £77 billion, a cost greater than heart disease and cancer combined. The cost was reassessed for 2010 at £105 billion. (Dr. Jo Nurse, Mental Health Division of the Department of Health, United Kingdom). The Wellcome Trust Web site put the cost of mental ill-health at £113 billion for 2013. This matter needs urgent attention. Evolution does not stand still. We have the knowledge to shape our own present and future destiny. As Admiral Carmona said at the outset of this conference, "we do not have time."

CONCLUSION

The biological priority of *H. sapiens* is the brain. The brain is largely made of lipid with its origin in the sea 500 to 600 million years ago. Brain development is the province of the mother with 70% of the adult brain cells dividing before birth. Last century, the nutrition paradigm for food, agriculture, and human nutrition was based on protein and growth. This century, a new and more appropriate paradigm is needed for *H. sapiens*.

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