

The Role of Docosaehxaenoic and the Marine Food Web as Determinants of Evolution and Hominid Brain Development: The Challenge for Human Sustainability

Michael A Crawford, PhD, FSB, FRCPath
Imperial College, London, United Kingdom
michael.crawford@imperial.ac.uk
www.mother-and-child.org



**Partnerships in Environmental Management
for the Seas of East Asia**

The Role of Docosahexaenoic and the
Marine Food Web as Determinants of
Evolution and Hominid Brain Development:

THE CHALLENGE FOR HUMAN SUSTAINABILITY

Michael A Crawford, PhD, FSB, FRCPath
Imperial College, London, United Kingdom
michael.crawford@imperial.ac.uk
www.mother-and-child.org

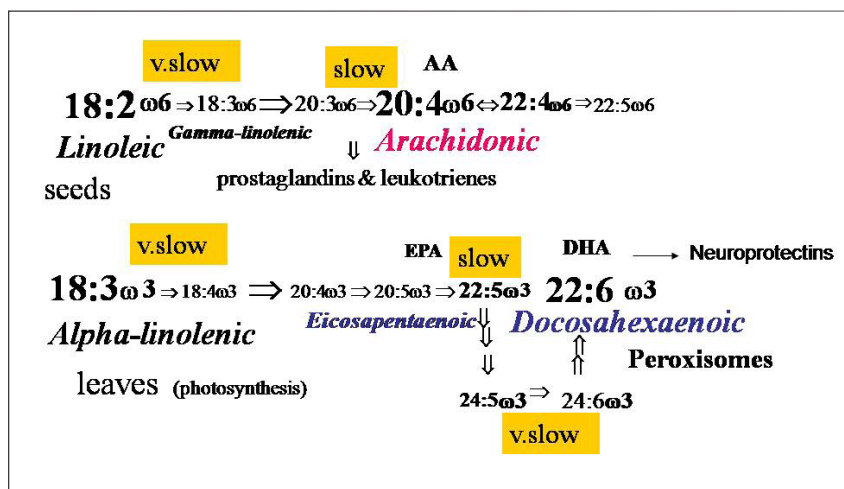
Introduction: The challenge of the rise in brain disorders

The brain is 60 percent fat which specifically requires Omega-3 docosahexaenoic acid (DHA) for growth, and function (Crawford and Sinclair, 1972). In the 1970s, "bad fats" were already considered to cause arterial and heart disease and were responsible for the rise in cardio-vascular death from a rarity to becoming the No. 1 killer in that one century. I recognized that if bad fats caused arterial disease in the heart, it was also likely to affect the arteries in the brain. More importantly "bad fats" would be expected to adversely affect the brain itself. Consequently, I published the prediction that unless the food system

changed to serve the arteries and brain, then a rise in brain disorders would be the next (Crawford and Crawford, 1972). Graham Rose reviewing the book for the *Sunday Times*, wrote that unless there was a response then we would become a "race of Morons"!

Unfortunately, in the 1970s and even the 1980s, there was little or no interest other than hostility shown in the idea that there were special essential fats required for the brain and hence important to maternal and infant nutrition. The evidence that there was a major fallacy in the paradigm of human nutrition food policy was not welcomed by those who held to the paradigm that protein was of paramount importance: many still do. The problem

Figure 1. Synthesis of Arachidonic (AA) and Docosahexaenoic (DHA) from Linoleic and α -linolenic Acids, the same enzyme systems are used for both, resulting in competition.



of the fish catch reaching a plateau was seen of little importance as protein could be obtained from other sources. The value of fish and seafood is not protein but the cluster of brain-specific lipids and trace elements.

This fallacy is amply illustrated by the illustration of the rhinoceros. This animal reaches a one ton body weight four years after birth. The rhinoceros obtains all the protein it needs for this prodigious rate of body growth from the simplest food resource, namely grass. What it does not do is to obtain the essential fats needed for brain growth. It can only build a tiny brain weighing no more than 350 g. Clearly different principles are involved in brain growth compared to body growth. The priority of the body may well be protein but that of the brain is brain-specific fat.

Docosahexaenoic acid (DHA) in the brain

Of special relevance to the brain fats, DHA is found in high concentration in signalling systems where it has a specific functional role. Neural cells have a particularly high membrane content of DHA. In different mammalian species, brain size varies but the DHA content does not (Crawford, et al., 1976; Crawford, et al., 1993) suggesting a high degree of evolutionary conservation. DHA is rapidly and selectively incorporated in neural membranes and is concentrated at synaptic signalling sites (Sinclair and Crawford, 1972; Suzuki, et al., 1997). It is the most unsaturated of cell membrane fatty acids (Jump, 2002). DHA is synthesized from α -linolenic acid which occurs as a by product of photosynthesis and thus in green foods. However, the process is strongly rate limited (Sinclair, 1975; Sprecher, 1993; Sprecher, et al., 1999).

The desaturase reactions are rate limiting, being the slowest in the sequence of chain elongation and the insertion of double bonds into the molecules. Hence, if you examine the fatty acid composition of tissues other than the brain, you will see for example, quantities of linoleic acid

present with arachidonic acid (ArA). If the conversions were fast, all the linoleic acid would be converted to arachidonate. Moreover this high proportion of linoleic acid in for example human red cells or plasma lecithins or in plasma cholesterol esters or even triglycerides is in evidence despite the fact that the 18 carbon fatty acids are oxidized at a rapid rate some four times faster than the long chain derivatives (Leyton, et al., 1987). This rate limitation means that there is an *order of magnitude advantage* to the provision of preformed DHA in the diet as opposed to its synthesis from α -linolenic acid for incorporation into the developing rat brain (Sinclair and Crawford, 1972). The human metabolic process is slower than in rats so one can expect a lower value of α -linolenic acid as a precursor of DHA for the human brain. Conversely, provision of preformed ArA or especially DHA would be advantageous (Brenna, et al., 2009).

An additional factor in the utilization of DHA for the brain, arteries and heart is that other fatty acids will compete with utilization. Last century, the rise in saturated, and trans isomer fats derived from animal intensification and technology, was a major concern. However, the rise in soya oil production has led to a greater than 1,000-fold increase in linoleic acid. Linoleic acid being an ω 6 fatty acid competes with the ω 3 and is thought to be one of the causes of the rise in mental ill health (Blasbalg, et al., 2011).

Some of the evidence — base for selective advantage from a coastal habitat

The land-food chain is poor in preformed DHA which as can be seen from **Figure 1** is the most limited in its biosynthesis. It is restricted to the eating of very small mammals, birds and bird and reptile eggs. The marine food web by contrast is very rich in DHA. Its origin is photosynthetic unlike the Omega-6 fatty acids which dominate plant energy storage for reproduction in the seed oils on land. The history of early hominids on land would have represented

a relative deficiency state compared to the coastal habitat where hominids would have had access to both land and aquatic resources. This habitat would have provided a significant advantage over hominids reliant on inland produce.

Experimental evidence on the requirement for the Omega-3 fatty acids for the brain supports this view of evolution. It starts with deficiency studies in rodents demonstrating loss of learning ability (Lamprey and Walker, 1978), encephalomalacia in chickens (Budowski, et al., 1987), visual loss, hair loss, skin lesions and behavioural pathology in primates (Fiennes, et al., 1973; Neuringer, et al., 1986) and visual and cognitive trials in human infants (Birch, et al., 2000; Carlson and Werkman, 1996; Martinez and Vazquez, 1998; Birch, et al., 2010). Suzuki, et al., (1997) demonstrated the selective uptake by the synapse for DHA a key to neural transmission and the establishment of neuronal pathways and hence learning. It has been suggested that this process of uptake during activity would re-inforce the synapse and is a potential explanation for the establishment of neuronal pathways and hence the learning process through repetition (Crawford, et al., 2008). This idea is consistent with the fact that a key characteristic of $\omega 3$ deficiency is reduced learning capacity.

Dr. Joseph Hibbeln's work at the NIH USA is now pointing to the link between major depression and low fish and seafood consumption (Hibbeln, 1998) and importantly, adverse behaviours and a low consumption of fish and seafood during pregnancy with a study on the follow up of children to eight years of age from over 14,000 pregnancies. These studies demonstrate a clear link between seafood and fish consumption by the mother during the pregnancy on verbal IQ and social behaviour (Hibbeln, et al., 2007).

In the human species, most brain cells divide pre-natally and the studies in pre-term infants have all been positive. Hence it was unsurprising that a systematic

review on term infants described conflicting results on cognition (Simmer, 2000). However, in collaboration with the Hebrew University of Jerusalem, we described competition existing between $\omega 6/\omega 3$ fatty acids and showed that their balance is critical for brain development and structural integrity (Budowski and Crawford, 1985). Unfortunately, the Simmer review did not take into account the differences in dose level of the different fatty acids, or amounts of competing fatty acids such as linoleic acid in the different formula, nor the biochemical form of delivery. More recently, Uauy and Dangour (2009) have presented a critical and comprehensive review of the evidence for the essentiality of DHA for brain development in the human infant with Brenna and Lapillonne (2009) discussing the requirements in pregnancy (FAO-WHO, 2010).

History is an important part of our knowledge base which helps inform the present and the future. Concepts of evolution claim to tell us about the history before the written record. The most celebrated concept of evolution is that of Charles Darwin who identified how small advantages repeated over many generations could lead to the survival of the fittest. However, he also wrote in each of his additions that there were two forces in evolution, natural selection and conditions of existence. Of the two, he writes the latter is the most powerful. However, this latter aspect of his philosophy has been sidelined. None the less both the selective advantage of the marine food chain in providing elements missing on land for neurogenesis together with the conditions of existence at a shoreline habitat is now obvious from the science.

The function of DHA is becoming clearer today with evidence it is involved in neuronal migration and neurogenesis (Yavin, et al., 2009; Brand, et al., 2010), vision (Benolken, et al., 1973; Neuringer, et al., 1986), electrical signalling (Crawford, et al., 2008) and as a precursor for

neuroprotectin D1, a powerful antioxidant (Niemoller, et al., 2009). It has also been shown that DHA acts as a ligand for nuclear receptors and stimulates the expression of over 107 genes associated with energy use and brain development (Kitajka, et al., 2002; 2004; Barcelo Coblijn, et al., 2003a; 2003b). These studies have indicated that DHA is essential to brain development and function. They add an important new dimension to the evolution of the brain in the sense that it would not only be an advantage in the classical Darwinian sense but also act as a biochemical driver of brain evolution. Hence natural selection would have operated side by side with the environmental stimulus of the marine food web forcing brain development.

The advantage of preformed DHA in the diet to brain development would have been its contribution to the nourishment of the mother, the embryo, fetus and infant brain development being enhanced generation after generation. DHA is poorly available from the land food chain but is abundant in the marine food web. Hence the likelihood is that the evolution of *H. sapiens* was coastal with access to aquatic resources rich in DHA and trace elements similarly required such as iodine and selenium (Crawford, et al., 1999; Broadhurst, et al., 2002). There would be a significant survival gain associated with enhanced brain development and cognition associated with a rich source of DHA. With extinction of several thousand species over the last century and our closest relatives, the great apes, on the brink of extinction, there can be no doubt about which species is surviving today.

My interpretation of the evidence is that it would have been impossible for a hominid to evolve into *H. sapiens* as an inland hunter and gatherer. Some argue that hominids could have obtained their DHA from the brains and marrow of animals they killed. It is clear that they have never hunted and tried to extract the brains from the large herbivores which would have been the food source. Even with modern bone saws, it is a formidable task.

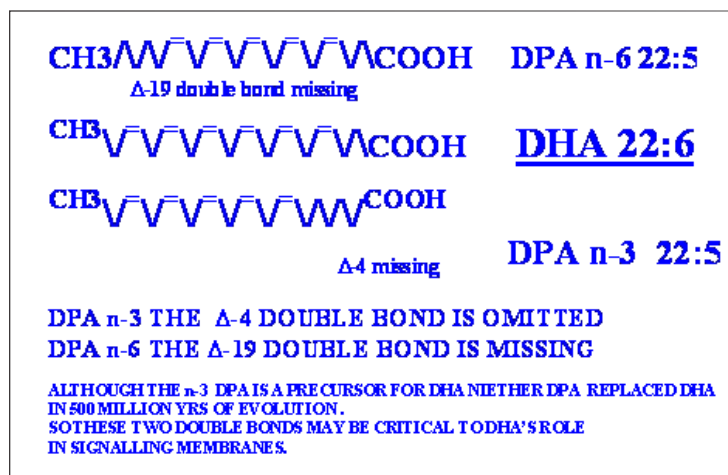
Unless you have dry ice or some form of refrigeration, the brain would rapidly deteriorate. Indeed there would only be about 300-400g brain beside some several kilograms of protein-rich meat. Moreover, it is not so much as the men but the pregnant women and young girls who most need the DHA and trace elements to ensure the continued epigenetic, upward pressure on cognitive development of the embryo, fetus and new born. Regardless of whether or not the men were successful in their killing, the women could walk along the shoreline gathering seafood in abundance, even when heavily pregnant or breast feeding, with little or no effort and doubtless accompanied by their children. As for obtaining the DHA from bone marrow, well there is precious little there.

The significance of iodine and trace elements

But this is not all. The land-based food chain is also poor in iodine and trace elements. There are 2 billion people at risk of iodine deficiency, which is well established to be the commonest cause of mental retardation in children. In 1990-1993, I was invited by Dr. Darwin Karyadi to help the Department of Health of the Indonesian Government with the World Health Organization (WHO) to solve the problems of anaemia in pregnancy and iodine deficiency disease. They had 1 million severely mentally retarded children and 800,000 cretins, the severe form of iodine deficiency in the mother causing facial distortions as a consequence of the restriction of brain development before birth. Some 60 percent of the school children had goitre (goiter) — a sign of iodine deficiency. However, these school children were all inland. There was no goitre in the fishing villages! At a conference on Nutrition and the Brain, hosted by Dr. Gopalan of the Indian Nutrition Foundation in New Dehli, I was to learn that an almost identical situation applied in Kerala, India.

Although iodized salt was in use, the high humidity and cooking methods

Figure 2. The Uniqueness of DHA. A million-year track record in neural signalling structure and function.



tended to volatilize the iodine. I therefore recommended the development of kelp forests. Indonesia had solved the problem of malnutrition and infection with a remarkably worthwhile Posyandu organization across the country which cared for pregnant and lactating women and mothers with young children, providing for vaccinations, nutrition advice, the monitoring of infant growth and strong community support for the mothers and children. Protein-calorie malnutrition, vitamin A deficiency were no longer a problem: however, both iodine deficiency and anaemia in pregnancy was. They are now developing kelp farming in waters around Bali. The kelp is very rich in iodine and other trace elements as well as providing some Omega-3 fatty acids.

It is a common fact that for millions of years, it has been raining on the land and the elements have been washed from the land into the sea. In previous history, this meant that the coastal resources were extremely rich and would have provided evolving humans with a wealth of brain foods. So when people talk about the importance of fish oils, it is clear that seafood have a much greater significance in the provision of these trace elements as well. This fact represents a problem of genetic engineering of plants to make DHA. The loss of trace elements from soils in recent millennia has been exacerbated

by intensive agriculture (Thomas, 2007). Besides, there is no need for genetic engineering of plants as marine algae can make DHA and also contain trace elements.

The Uniqueness of Docosahexaenoic acid

Since the evolution of the cephalopods and possibly as far back as before the Cambrian explosion in the dinoflagellates with their eye spot, DHA is found as the principle structural component of the visual system, synapse and neurones. It is present at greater than 50 percent of the photoreceptor membrane lipids which includes di-docosahexaenoic acid molecular species of the phosphoglycerides in the cephalopods, fish, amphibia, reptiles, birds, mammals and ourselves. This richness of DHA in the photoreceptor is shared with the synapse and neurones.

There are two molecules which differ from DHA by only two hydrogen atoms (the Omega 6 and 3 docosapentaenoic acids DPA, see **Figure 2**), one of these is a precursor for DHA. Yet neither was used throughout this 500–600 million year period of evolution. Biology thus seems highly sensitive to the slight difference of the one double bond between DHA and the DPA molecules. The presence of DHA's full complement of six double bonds is for

some reason an important priority in neural membranes and from the evolutionary record would seem to have been conserved in this capacity for 500 million years or more. This to me is the most compelling evidence for the absolute essentiality for DHA in the brain. It is a far superior order than any randomized clinical trial which cannot hope to test the significance of 500 million years of conservation which was tested by natural selection and genomic change over the whole stretch of vertebrate, animal evolution. This evidence combined with the experimental evidence, especially in gene instruction, adds to the case for a coastal origin of hominid cerebral expansion.

Is DHA the ultimate in liquidity for cell membranes

The significance of DHA to brain function is now recognized. However, there is still debate on its mechanism of action which is largely considered to be its high degree of liquidity. We have speculated that its unique, six methylene interrupted cis-double bond sequence (all-cis-docosa-4,7,10,13,16,19-hexaenoic acid, C22:6 ω 3) may be responsible for its mechanism of action and its extreme conservation in neural tissues (Bloom, et al., 1999).

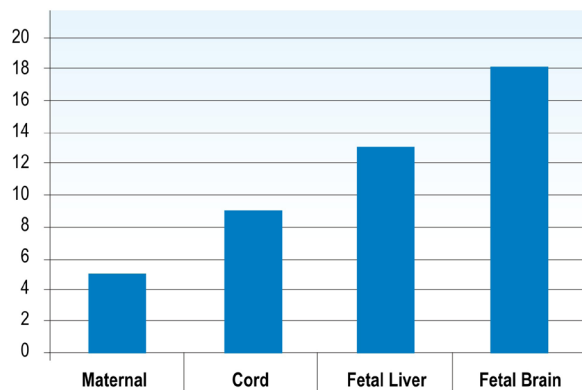
The conventional view that DHA is "needed" for liquidity is teleological and Lamarkian. More scientifically, Bloom, et al., (1999) discarded the idea of liquidity as an explanation for its striking conservation in neural systems for over 500 million years of evolution. The difference in liquidity between the ω 3-docosapentaenoic acid (all-cis-docosa-7,10,13,16,19-pentaenoic acid C22:5 ω 3, ω 3DPA) with only one double bond different) and DHA is marginal. Yet the ω 3DPA being en route to DHA, is more readily synthesized, less difficult to obtain from the food chain and less vulnerable to oxidative damage, yet it has not replaced DHA in the visual and neural systems in the teleosts, elasmobranchs, cephalopods, fish, amphibia, reptiles, birds or mammals. The ω 6 DPA, which also differs from DHA again by the absence of one double bond

(between carbons 19-20) does not replace DHA except under extreme, artificial deficiency conditions in the laboratory and infant feeding with formula deficient of omega 3 fatty acids. Even so, the replacement is only partial and function is depressed. Infants fed without DHA in the formula effectively lost visual acuity to the equivalent of failing 1.5 lines on the eye chart (Birch, et al., 2010).

Nature's preference for DHA in the brain is strikingly demonstrated in large, vegetarian land mammals, in which DPA is the dominant ω 3 metabolite found in non-neural tissues and thus abundantly available (Crawford, et al., 1969). Yet neural membranes even in these mammals still conserved the DHA-rich composition. During the evolution of the land mammals, this retention of composition in land mammals was associated with economy in brain size. There was a logarithmic decline in relative brain size as they evolved larger, protein-rich, bodies based on food structure with only the precursors, linoleic and α -linolenic acids found in plants (Crawford, et al., 1993).

The slow rate of desaturation of the fatty acids especially in the insertion of the last double bond (**Figure 1**) explains the difficulty of accumulating DHA from land food. In the marine food chain, the photosynthetic systems produce a profile of the simpler Omega-3 fatty acids with some producing DHA itself. The animals which browse these substrates are eaten by small sea animals which are then eaten by bigger animals which themselves get eaten. At each step the DHA proportion is stepped up but that of the 18 and 20 carbon chain lengths diminished. This principle of bio-magnification is the same as we reported on biomagnifications in human fetal development: the placental, figuratively speaking, eats the maternal blood, the fetus then eats the placental product which is deposited in the liver and then eaten by the developing brain (Crawford, et al., 1976, see **Figure 3**). A study of the human placenta indicated that the process was Nature's preferential

Figure 3. Biomagnification of DHA: Mid term data (Crawford et al Lancet 1976).



is highly conserved. The brain is built to a tight specification according to the availability of the essential fats.

Certain mammals left the land to radiate into the marine habitat starting about 50 million years ago. With unlimited access to the DHA food web, the marine mammals retained a far better brain body weight harmony. The dolphin for example has 1.8 kg brain which compares to little more than 350 g in a zebra which has a similar body weight.

selection for the DHA and not its synthesis from precursor. There is very little precursor in the fetal circulation and beyond: biosynthetic conversion would be academic (Crawford, 2000).

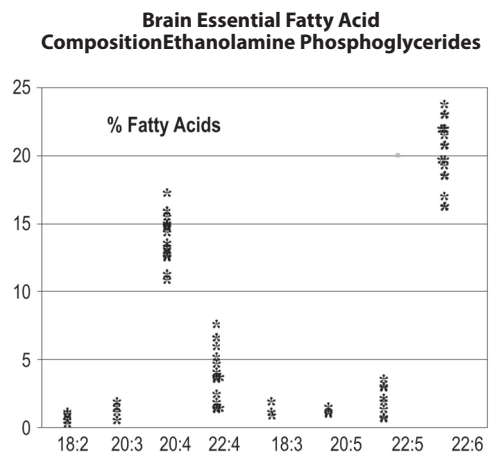
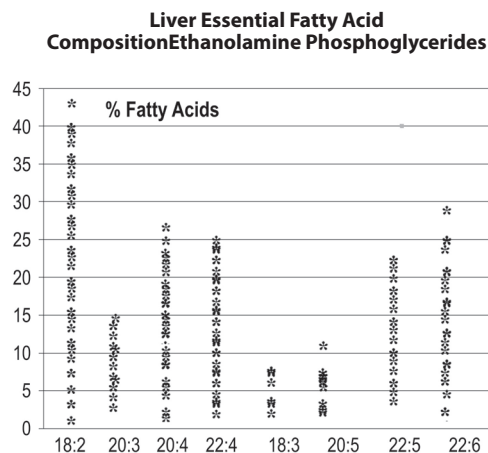
Conservation of brain chemistry in land and marine mammals

The comparative evidence shows that while the fats may vary in the cell membranes from species to species depending diet and genes, brain chemistry

This loss of brain capacity is universal in large land mammals.

The migration from land to sea occurred over approximately a 50-million year period with wave after wave of land mammals occupying the land-water interface and becoming increasingly committed to a marine habitat. There must have been a very strong mental force for them to become so irrevocably committed to a marine habitat. One can only guess that the brain specific nutrients of the marine system was that driving force.

Figure 4. Essential fatty acid content of the inner membrane lipids in liver and brains of 42 species. Note variability in the liver and the uniformity on the brain. It is not the chemistry of the brain that differs between species it is the extent to which it evolved.



Source: Crawford M, Casperd N, Sinclair AJ (1976) The long chain metabolites of linoleic and linolenic acids in liver and brain in herbivores and carnivores. *Comp. Biochem. Physiol.* 54B: 395-401.

Source: Crawford M, Casperd N, Sinclair AJ (1976) The long chain metabolites of linoleic and linolenic acids in liver and brain in herbivores and carnivores. *Comp. Biochem. Physiol.* 54B: 395-401.

Figure 5. Zebra and Dolphin livers: A comparison of the evolution of the brain on land and in the sea in relation to the availability of DHA in the food web.

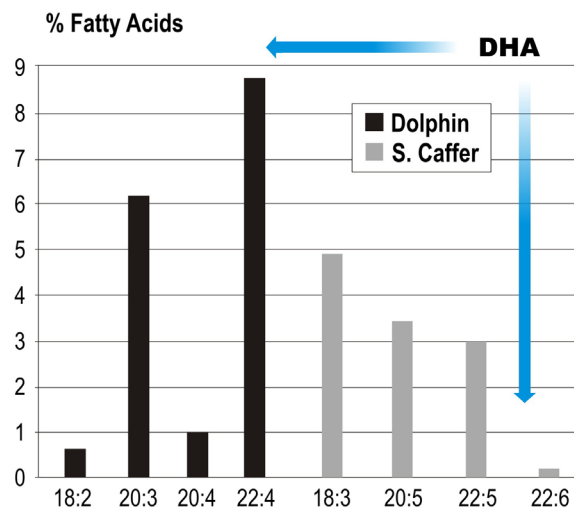
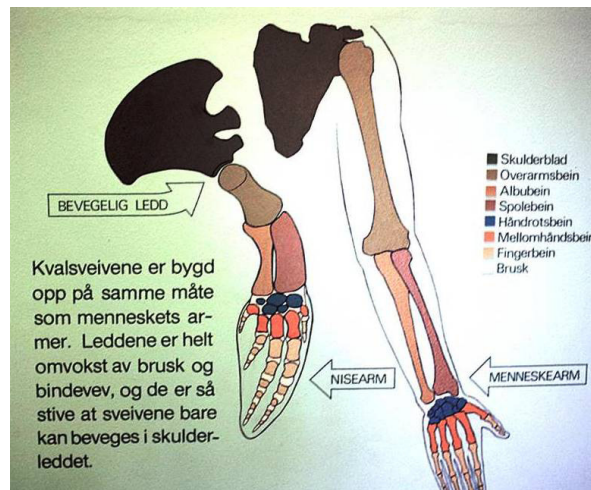


Figure 6. The arms and hands of the Dolphin.



It is difficult to imagine there was a sudden genetic change that one day led to that excursion from land to sea. The evidence of vestigial legs in a dolphin embryo and the presence of all the anatomically identical arm bones and the bones of the hand and fingers in the flipper of the dolphin strongly argue the case of gradual epigenetic changes leading to the total commitment to the marine habitat (**Figure 5 and 6**). They evidently still have the genes for arms, hands and legs. Just as the economy expressed in land mammals with the shrinking brain in response to the poor availability of DHA so similarly, the

epigenetic response to a high phosphorus/low calcium diet might have led to economy with calcium and shrinking long bones with the hand becoming covered in skin to make the paddle. The seafood and DHA-rich diet would have favoured intelligence, greater sensory perception and happiness acting to drive these land mammals into the sea.

A human example of the transition from land to sea

The El Molo whom we visited in the 1960s, lived on the shores of Lake Turkana, often

Figure 7. El Molo Fish eaters: Bent tibia (photo from Dr. Roy Shaffer).



referred to as the Jade Sea. They relied on food and fish from the lake as Mount Loiengalani had created a lava desert down to the lakeshore. Their fishing methods meant that they only caught largish fish and in consequence had little calcium in their high phosphorous diet. Their shin bones were bent and they complained of pain in their legs (**Figure 7**) which was relieved when they waded in water to catch the fish. Quite plausibly, they were on their way to becoming freshwater dolphins! This evidence is important as it sheds light on the transitional epigenetic changes that might have participated in driving land mammals into the sea, wave after wave, over a 50-million year period.

The last translocation in the migration of mammals from land to sea took place with the Dolphins. They finally cut ties to the land about 7 million years ago. This timeframe coincides with the separation from the great apes of the line that came down to humans. This gene separation meant that the pre-human ape was separate, i.e., distant from the other apes. The forest fringes and savannah edges would leave the pre-humans with the possibility of intermingling and breeding.

A likely scenario is that exploration of rivers down stream would have eventually led

them to an estuary where they would have seen the seabirds opening oysters, mussels and eating other aquatic life. They would have been led by the seabirds to empty beaches, rocky outcrops and pools, laden with food, indeed the richest food resource on the planet: the Dolphins had gone!

H. sapiens does not have a large brain

Of the large mammals, the Dolphin, with about 1.8 kg of brain at one percent of its body size, comes the closest to Homo sapiens with two percent of its body size as brain. At just under two percent, H. sapiens has a brain body weight ratio which would be totally exceptional if considered as a land-based mammal. Interestingly, H. sapiens has a smaller brain body weight ratio than a squirrel which at nearly 2.5 percent is greater than H. sapiens.

The conclusion from this fact is that without exception, evolution on land from the small beginnings, resulted in diminishing relative brain size, a feature readily explained by the lack of DHA in the land food web together with the rate limited synthesis being outstripped by the velocity of protein accretion and body growth as referred to earlier in the rhinoceros. Note in **Figure 5**, the buffalo

liver lipid is quite rich in the land plant precursor α -linolenic acid. There is also significant amounts of EPA and even the ω 3 DPA (C22:5 ω 3) but despite this wealth of precursor, it fails to synthesize much DHA. The contrast with the Dolphin lipids in this respect is striking.

If we compare the relative size of the brain with small mammals and *H. sapiens*, it is clear we have not really won a big brain at all. What happened was that we must have found an ecological niche which enabled brain growth to keep pace with body growth. From the evidence base that ecological niche could not have been on land: it had to be at the water's edge. The richness in DHA and trace elements of this niche enabled the evolving primate to maintain a harmony of growth that was denied the large land mammals.

A role for the land-based lipid — arachidonic acid

Both arachidonic and DHA are needed for the growth and development of the brain and its function (see **Figure 2**, Crawford and Sinclair, 1972). Prior to the collapse of the giant reptiles, flowering plants had been evolving. By the end of the Cretaceous period, the flowering plants and those with protected seeds developed in abundance. Green plants

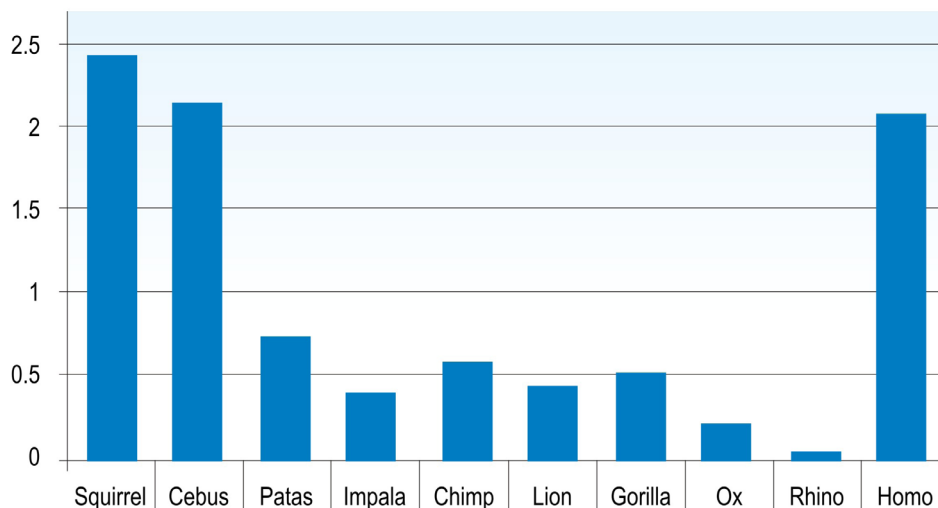
provided alpha-linolenic acid. However, the oils stored in the protected seeds was and still is, largely the Omega-6 linoleic acid, the precursor for arachidonic acid. The synthesis of arachidonic acid is more readily achieved compared to DHA. Data we obtained over the years on 42 mammalian species showed that the ratio of arachidonic acid and its chain elongation product (C22:4 ω 6) to DHA is between 1 and 2 to 1. The marine mammals like the Dolphin, with their large brain to body weight ratios, are none the less lower than *Homo*. They are constrained not by DHA but by the paucity of arachidonic acid in the marine food web (Caraveo-Patin, et al., 2009). *Homo* by contrast would have obtained arachidonic acid from birds, eggs and small mammals.

Arachidonic acid is the precursor for adhesion-type prostaglandins as well as the prostacyclin which is important in vasodilation and anti-thrombus formation (Min and Crawford, 2004). It is plausible that arachidonic acid, in this way, contributed to the physiological changes which led to the egg adhering to the placental wall, angiogenesis and the vascularisation of the placenta which then led to the evolution of the mammals.

Whatever happened, it is clear that the advance to placental mammals resulted in

Figure 8. Land-based mammals compared to *H. sapiens*.

Homo sapiens does not have a big brain, large land mammals have small brains!



a leap in relative brain capacity compared to the previous egg-laying systems. Arachidonic acid is the major fatty acid in the inner cell membrane of the vascular endothelium. Hence the availability of Omega-6 fatty acids in abundance after the emergence of the flowering plants and protected seeds, would have facilitated the development of the vascularization of the region of adhering egg leading to the vascular development that became the placenta.

A littoral ecosystem would therefore have provided an evolving primate with access to both arachidonic acid and DHA and hence would have had the best of both worlds. This harmony of brain-specific fatty acids would have been accentuated by the fact that warm water fish in the rivers, lakes and sea are also a significant source of arachidonic acid (Broadhurst, et al., 1998). This double advantage would have been important to a small evolving primate, long before it was sufficiently large to take on hunting game animals as is a common perception.

Sea and lacustrine food and fish would have been incredibly abundant and simple to catch. The museum in Heavenly on the Nevada-California border describes the Indians who lived around Lake Tahoe as never bothering to make boats as all they had to do was to wade into the water to catch the fish by hand.

Another simple reason for the coastal origin lies in our teeth and the discovery of how to use fire which was quite late in human evolution. Our teeth lack the skin-tearing capability of the carnivores and even omnivorous species such as baboons. At its simplest level, to evolve a large brain, in addition to what has already been discussed requires a high energy input. During fetal development, the brain uses 70 percent of all the energy supplied to it from the mother for brain growth and after birth it is still at 60 percent. Until fire and cooking became a part of the system, food was eaten raw. We eat vegetables but these have a low energy density. However, seafood are still eaten raw as in oysters and sushi. Seafood and fish would have been a simple solution to providing energy, micronutrient and brain specific lipids simultaneously. If this is doubted, just think of how fat a walrus or elephant seal is, which become enormously fat eating this type of food.

The sum of this evidence puts the evolution of *H. sapiens* firmly at the marine and lacustrine coastlines with access to preformed DHA from the aquatic resources. And freshwater to drink from the estuary. Support for this conclusion comes from incontrovertible evidence of extensive exploitation of the marine food chain by our ancestors was dated to some 180,000 years ago. The evidence contains culturally

Table 1. Arachidonic acid content of Rift Valley Lake fish compared to Salmon.

Fish and habitat	Fat (gy100 g meat)	AA (mg100 g meat)	DHA (mg100 g meat)
Tropics			
Indian Halibut	1.7	102	168
<i>Rift Valley Lake Nyasa, Tanzania</i>			
Mbebelele (catfish)	10.3	421	842
Njenu (carp)	4.9	270	363
Mfui (local sp.)	1.1	84	200
Kambale (local sp.)	1.8	99	227
<i>Lake Turkana, Kenya</i>			
Tilapia species	2.3	184	343Perc
Perch	2.6	190	447
<i>North Atlantic</i>			
Salmon	9.8	112	1601

significant ochres and decoration of tools, at a time coincident with the emergence of modern humans (Trapani, 2008; Klein, et al., 2004; Marean, 2010). In that sense human evolution would have had the best of both worlds.

The real and present challenge with escalation of disorders of the brain

The paucity of the marine nutrient cluster on land meant that land based mammals lost relative brain capacity as they evolved larger and larger bodies.

Sadly in western countries, fish and seafood, once a mainstay of the food system, has been lost through pollution of the estuaries and coastlines in not much more than one century following the industrial revolution. In Maryland, USA, 616,000 tons/year of oysters were being harvested in the late 1880s. In 2004, it was only 12,000 tons. The oyster shell is mainly solid calcium carbonate. In 1889, this meant they sank 270,000 tons of solid CO_2 on land. In 2002, the loss of the carbon sink was only 7,000 tons. The difference of 263,000 tons of CO_2 not sunk is from just this one estuary.

In London around 1900, the bar men in the East-end would go down to the Thames and collect oysters to put on the bar for free for those who bought beer. Today, there are no oysters to gather. The Rhine, the Ganges, Yangtze, and Jakarta Bay to name but a few, have been destroyed. The pollution has been worldwide in its destruction of the ecological niche where the marine food chain should take off in earnest. The Firth of Forth where I grew up in Scotland enjoying fresh seafood gathered from the shore now has notices warning that seafood is not fit for human consumption. An estuarine destruction in the first half of my life time is illustrated in **Figure 10**. The Firth of Forth used to be



Figure 10. A sign posted in Firth of Fort, Scotland. Photo: Crawford.

renowned for its seafood.

The warm shallow waters of the coasts and especially the estuaries, allow the penetration of sunlight to foster photosynthetic systems of many sorts. In addition to the phyto-plankton which provide food for filter feeders and fish, the weeds offer the sanctuaries and feed for the seafood and fish. Added to this mix is the mineral wealth that was washed from the land by the rain into the rivers and estuaries. The tragedy of the Maryland loss of the massive oyster harvest will have been repeated worldwide with but a few exceptions. This loss of carbon fixation by the photosynthetic life of the estuaries is likely to be equivalent to the loss of several rainforests yet there is little comment on this matter.

Fortunately in 2009 at a meeting in Manila, the Ministerial Forum at the Third East Asian Seas Congress adopted the Manila Declaration entitled "Strengthening the Implementation of Integrated Coastal Management for Sustainable Development

and Climate Change Adaptation in the Seas of East Asia Region.” Key issue No. 2 was the agreement by all nations present to respond “to common threats posed by uncontrolled development of coastal areas, poverty, resource degradation and marine pollution from land- and sea-based sources”.

The Declaration of Manila along with the preceding Declaration of Muscat, Oman, were presented to the Climate Conference in Copenhagen, on 6–18 December 2009. However, awareness of this issue still seems missing in the North Western countries where the pollution of the estuaries is almost total with few exceptions in sparsely populated northern regions.

The significance of this evidence is important to the future of humanity

Brain disorders now account for the highest cost in the burden of ill health in Europe with a price of €386 Billion Euros at 2004 prices (Andlin-Sobocki, et al., 2005). A question by Lord Morris at that time in the UK Upper House of Parliament revealed that no estimate had been made of the national cost of brain disorders in the UK. Subsequently, Dr. Jo Nurse, head of the Mental Health Division of the Department of Health did the assessment which was that the cost in 2007 had reached £77 billion, a cost greater than heart disease and cancer combined. The estimate by Dr. Jo Nurse is now £105 billion.

Moreover, the rise in brain disorders is being globalized. It is predicted by the Global Forum of Health to be in the top three burdens of ill health worldwide by 2020. The first three are heart disease, perinatal conditions (adverse pregnancy outcomes) and mental ill health. All three have a nutritional background.

There is compelling evidence that the reasons for all three to be related to the loss of ‘sea food’ and their replacement by ‘land food’ (Hibbeln, et al., 2002, 2004, 2007). The risk of this loss and hence seafood to

the human brain, exposes the mistake in food policy last century which was based on increasing physical growth of plants, animals and humans instead of considering the requirements for the brain. The primary concern was and still is protein. Protein is important for body growth. However, the evidence clearly tells us that there are different principles involved in body growth on the one hand and brain growth on the other. It is vital that in this century the focus must be on the requirements of the brain.

The fish provision is currently based on the Stone Age principle of hunting and gathering. The total wild catch plateaued about 20 years ago. Aquaculture has advanced remarkably. However, culture of carnivorous fish depends on the wild catch which means it too will reach a limit. Already, signs are there in adulteration of the fish with vegetable oils. This adulteration will have two impacts. First it will deplete the nutritional value for Omega-3 fatty acids. Secondly, it runs the risk of introducing a BSE like problem as happened with cows when the nutritional principles of the species was abandoned to save costs. A further problem of using land-based food is that the fish and seafood are not just of value for their oils but as mentioned above, also for the trace elements such as iodine, selenium, zinc, manganese and copper, all of which are essential for the brain and specifically for the anti-oxidant enzyme defences. Unfortunately, the land has been washed over millions and millions of years. Iodine deficiency is a problem for inland people and affects 2 billion people today. The solution needs the agriculturalizing of the oceans and enhancing the development, use and consumption of seafood worldwide.

In conclusion, DHA appears to have been conserved in neural signalling systems during animal evolution. The brain evolved in the sea 500 million years ago using DHA for its signalling structures. Despite evolution from dynoflagellates to ammonites, to trilobites to fish, amphibia,

to the reptiles, to dinosaurs, giant mammals, primates and humans it is still the major functional and only Omega-3 component responsible for vision, all sensory and motor functions and cognition as well as participating in the control of blood flow and neural gene expression. Its availability from land systems is very poor. With brain disorders having overtaken all other burdens of ill health in Western countries and being globalized (Global Forum of Health) solutions are urgently needed to arrest and reverse this rise in brain disorders and mental ill health. In addition, the marine food chain is not just about fish oils but it is also vital for other nutrients including iodine and trace

elements. This rise in brain disorders threatens the very essence of what makes us human. That threatens the sustainability of our own species. It is the brain which makes humans different from other animals. This fact focuses on the need this century to redefine food policy so that it specifically serves the nutrition of the brain, especially during fetal and early neonatal development. To meet that requirement there is a need also to develop the marine food web this century and that means addressing estuarine and coastal pollution which has been killing the forests of the oceans. With the wild catch having reached its limit some 20 years ago, the solution has to involve the development of marine agriculture.

ACKNOWLEDGEMENTS

We wish to express my appreciation to the many colleagues who have helped formulate these ideas, including Myer Bloom Physics Vancouver; Leigh Broadhurst and Walt Schmidt at the USDA, Beltsville USA; Javier Caraveo-Patiño, Mexico; Stephen Cunnane Sherbrooke, Canada; Keb Gebremeskel, IBCHN London; Laurance Harbige, Greenwich; Holm Holmsen Bergen, Norway; Ivan Golfetto, Caracas, Venezuela; Lucilla Poston St Thomas, London; Patrick Drury, King's Fund; Glynn Williams at the Nuffield Institute of Comparative Medicine; Zoological Society of London; John Parkington, Anthropology, Capetown; Hiramitsu Suzuki, NFRI, Japan; Ephraim Yavin and Ram Reifen Rehovot, Israel; Yiqun Wang, IBCHN London; Ole Mouritsen, MEMPHYS, Denmark; and Professor Letten F. Saugstad for her encouragement and support through the Letten F Saugstad Foundation, Norway. We thank David Marsh for drawing to attention to Darwin's notion of pangenesis linking environment and the genome and his views on "conditions of existence." We are also grateful to Catherine Lehane for reading the manuscript and commenting. The photograph of the Dolphin arms and hands was taken at the Museum in Tromsø, Norway. The author has no conflicts of interest to declare.

REFERENCES

- Andlin-Sobocki, P, J. Jonsson, H-U. Wittchen, and J. Olesen. 2005. "Cost of disorders of the brain in Europe." *European Journal of Neurology* 2005, 12 (Suppl. 1): 1–27.
- Anderle, P, P. Farmer, A. Berger, and M.A. Roberts. 2004. "Nutrigenomic approach to understanding the mechanisms by which dietary long chain fatty acids induce gene signals and control mechanisms involved in carcinogenesis." *Nutrition*. 20, 103–108.
- Barcelo Coblijn, G., K. Kitajka, L.G. Puskas, E. Hogyes, A. Zvara, L. Hackler Jr., and T. Farkas. 2003a. "Gene expression and molecular composition of phospholipids in rat brain in relation to dietary n-6 to n-3 fatty acid ratio." *Biochim Biophys Acta*. 1632, 72–79.
- Barcelo Coblijn, G., E. Hogyes, K. Kitajka, L.G. Puskas, A. Zvara, L. Hackler Jr., C. Nyakas, Z. Penke, and T. Farkas. 2003b. "Modification by docosahexaenoic acid of age induced alterations in gene expression and molecular composition of rat brain phospholipids." *Proc. Natl. Acad. Sci. USA*. 100, 11321–11326.
- Barker, DJ. 2007. "The origins of the developmental origins theory." *J Intern Med*; 61(5):412-7.
- Bazan, N.G. 1989. "The metabolism of Omega-3 polyunsaturated fatty acids in the eye: The possible role of docosahexaenoic acid and docosanoids in retinal physiology and ocular pathology." *Prog. Clin. Biol. Res.* 312, 95–112.
- Benolken, R.M, R.E. Anderson, T.G. Wheeler. 1973 "Membrane fatty acids associated with the electrical response in visual excitation." *Science*. 182(118):1253-4.
- Beydoun, M.A, J. S. Kaufman, J.A. Satia, W. Rosamond, and A.R. Folsom. 2007. "Plasma in_3 fatty acids and the risk of cognitive decline in older adults: The Atherosclerosis Risk in Communities Study 1–3." *Am J Clin Nutr* ;85:1103–11. Birch HG & Gussow JD "Disadvantaged Children" 1970 Harcourt, Brace & World Inc. NY.
- Birch, E.E, S. Garfield, D.E. Hoffman, et al., 2000. "A randomised trial of early dietary supply of long chain polyunsaturated fatty acids and mental development in term infants." *Dev Med Child Neurol* 42: 174-181.
- Birch, E.E., Carlson, S.E., D.R. Hoffman, K.M. Fitzgerald-Gustafson, V.L. Fu, J.R. Drover, Y.S. Castañeda, L. Minns, D.K. Wheaton, D. Mundy, J. Marunycz, and D.A. Diersen-Schade. 2010. The DIAMOND (DHA Intake And Measurement Of Neural Development) Study: A double-masked, randomized controlled

- clinical trial of the maturation of infant visual acuity as a function of the dietary level of docosahexaenoic acid." *Am J Clin Nutr*; 91(4):848-59.
- Blasbalg, T.L., J.R. Hibbeln, C.E. Ramsden, S.F. Majchrzak, and R.R. Rawlings. 2011. "Changes in consumption of Omega-3 and Omega-6 fatty acids in the United States during the 20th century." *Am J Clin Nutr*. 2011 Mar 2. [Epub ahead of print].
- Bloom, M., F. Linseisen, J. Lloyd-Smith, and M.A. Crawford. 1999. "Insights from NMR on the Functional Role of Polyunsaturated Lipids in the Brain." In: "Magnetic Resonance and Brain Function - Approaches from Physics" Proceedings of the 1998 Enrico Fermi International School of Physics, Enrico Fermi Lecture, Course #139, Varenna, Italy, ed. B. Maraviglia.
- Bourre, J.-M., M. Francois, A. Youyou, O.S. Dumont, and G. Durand. 1989. *J. Nutr.* 119, 1880–1892.
- Bourre, J.M. 2005. "Dietary Omega-3 Fatty acids and psychiatry: Mood, behaviour, stress, depression, dementia and aging." *J. Nutr. Health Aging*. 9, 31–38.
- Brand, A., M.A. Crawford, and E. Yavin. 2010. "Retailing docosahexaenoic acid-containing phospholipid species during impaired neurogenesis following Omega-3 alpha-linolenic acid deprivation." *J Neurochem*. 114(5):1393-404.
- Brenna, J.T., and A. Lapillonne. 2009. "Background paper on fat and fatty acid requirements during pregnancy and lactation." *Ann Nutr Metab*; 55(1-3):97-122.
- Brenna, J.T., N. Salem Jr, A.J. Sinclair, and S.C. Cunnane. 2009. Alpha-Linolenic acid supplementation and conversion to n-3 long-chain polyunsaturated fatty acids in humans. *International Society for the Study of Fatty Acids and Lipids, ISSFAL. Prostaglandins Leukot Essent Fatty Acids*; 80(2-3):85-91
- Broadhurst, C.L., Y. Wang, M.A. Crawford, S. Cunnane, J. Parkinson, and W.F. Schmidt. 2002. "Brain-specific lipids from marine, lacustrine, or terrestrial food resources: Potential impact on early African Homo sapiens." *J. Comp Biochem Physiol. Part B: Biochemistry and Molecular Biology*. 131: 653-673
- Broadhurst C. L., S.C. Cunnane, and M.A. Crawford. 1998. "Rift Valley lake fish and shellfish provided brain specific nutrition for early Homo." *Br J. Nutr.* 79: 3-21.
- Brown, M.F. 1994. "Modulation of rhodopsin function by properties of the membrane bilayer." *Chem. Phys. Lipids* 73, 159-180.
- Brunaldi, K., M. A. Miranda, F. Abdulkader, R. Curi, and J. Procopio. 2005. "Fatty acid flip-flop and proton transport determined by short-circuit current in planar bilayers." *J. Lipid Res*. 46: 245–251.
- Budowski, P. and M.A. Crawford. 1985. "Alpha-linolenic acid as a regulator of the metabolism of arachidonic acid: dietary implications of the ratio n-6:n-3 fatty acids." *Proc. Nut. Soc.* 44: 221-229.
- Budowski, P., M.J. Leighfield, and M.A. Crawford. 1987 "Nutritional encephalomalacia in the chick: an exposure of the vulnerable period for cerebellar development and the possible need for both ω 6 and ω 3 fatty acids." *Br. J. Nutr.* 58: 511-520.
- Carlson, S.E., and M. Neuringer. 1999. "Polyunsaturated fatty acid status and neurodevelopment: a summary and critical analysis of the literature." *Lipids*. 34, 171–178.
- Carlson, S.E., and S.H. Werkman. 1996. "A randomized trial of visual attention in of preterm infants fed docosahexaenoic acid until two months." *Lipids*. 31: 85-90.
- Catalan, J., T. Moriguchi, B. Slotnick, M. Murthy, R.S. Greiner, and N. Salem Jr. 2002. "Cognitive deficits in docosahexaenoic acid deficient rats." *Behav. Neurosci.* 116, 1022–1031. 20785–20835.
- Corella, D., and J.M. Ordovas. 2005. "Single Nucleotide Polymorphisms that Influence Lipid Metabolism: Interaction with Dietary Factors." *Annu. Rev Nutr.* 25, 341–390.
- Caraveo-Patin, J., Y. Wang, L.A. Soto, K. Ghebremeskel, C. Lehane, and M.A. Crawford. 2009. "Eco-physiological repercussions of dietary arachidonic acid in cell membranes of active tissues of the Gray whale." *Marine Ecology, Marine Ecology* (2009) 1–11.
- Crawford, M.A. 2007. "A Role for Lipids as Determinants of Evolution and Hominid Brain Development." In *Poly-unsaturated Fatty Acids, Neural Function and Mental Health. Biologiske Skrifter 56, Det Kongelige Danske Videnskabernes Selskab, The Royal Danish Academy of Sciences and Letters*, ed O. G. Mouritsen and M.A. Crawford. 7-24 pp.
- Crawford, M.A. 2000. "The placental delivery of arachidonic and docosahexaenoic acids: implications for the lipid nutrition of the preterm infant." *Am J Clin Nutr*. 71:2755-2845.
- Crawford, M.A. 1992. "The role of dietary fatty acids in biology: their place in the evolution of the human brain." *Nutr. Rev.* 50: 3 – 11.
- Crawford, M.A., L.C. Broadhurst, C. Galli, K. Ghebremeskel, H. Holmsen, L.F. Saugstad, F. Schmidt, A.J. Sinclair, S.C. Cunnane. 2008. "The Role of Docosahexaenoic and Arachidonic Acids as Determinants of Evolution and Hominid Brain Development." In *Fisheries for Global Welfare and Environment: K. Tsukamoto, T. Kawamura, T. Takeuchi, T. D. Beard, Jr. and M. J. Kaiser, eds., 5th World Fisheries Congress 2008*, pp. 57–76, Terrapub, Tokyo.
- Crawford, M.A., M. Bloom, C.L. Broadhurst, W.F. Schmidt, S.C. Cunnane, C. Galli, K. Ghebremeskel, F. Linseisen, J. Lloyd-Smith and J. Parkinson. 1999. "Evidence for the unique function of DHA during the evolution of the modern hominid brain." *Lipids* 34, S39-S47.
- Crawford, M.A., S.C. Cunnane, and L.S. Harbige. 1993. "A new theory of evolution: Quantum theory." *Illrd International Congress on essential fatty acids and eicosanoids*, Am. Oil Chem. Soc., ed A.J. Sinclair, R. Gibson, Adelaide, 87-95.
- Crawford, M.A., N.M. Casperd, and A.J. Sinclair. 1976. "The long chain metabolites of linoleic and linolenic acids in liver and brain in herbivores and carnivores." *Comp. Biochem. Physiol.* 54B: 395-401.
- Crawford, M.A., and A.J. Sinclair. 1972. "Nutritional influences in the evolution of the mammalian brain." In: *Lipids, malnutrition and developing brain*. Eds. Elliot K, Knight J. A Ciba Foundation Symposium, Amsterdam, Elsevier. 267-292.
- Crawford, M.A. and S.M. Crawford. 1972. "What we eat today." Neville Searman, London.
- Crawford, M.A., M.M. Gale, and M.H. Woodford. 1969. "Linoleic acid and linolenic acid elongation products in muscle tissue of *Syncerus caffer* and other ruminant species." *Biochem. J.* 115: 25-27.
- Cunnane, S.C., V. Francescutti, J.T. Brenna, M.A. Crawford. 2000. "Breast fed infants achieve a higher rate of brain and whole body docosahexaenoate accumulation than formula fed infants not consuming dietary docosahexaenoate." *Lipids*. 35, 105–111.
- Dräger, U.C. 2006. "Retinoic Acid Signaling in the Functioning Brain." *Sci. STKE* Feb 2006.
- Ehringer, W., D. Belcher, S.R. Wassall and W. Stillwell. 1990. "A comparison of the effects of linoleic (18:3W3) and docosahexaenoic (22:6W3) acids on phospholipid bilayers." *Chem. Phys. Lipids*, 54: 79-88
- FAO-WHO. 2010. "Fats and Fatty Acids in Human Nutrition." Report of an Expert Consultation, no 91, FAO Rome.
- Fiennes, R.N.T. W., A.J. Sinclair, and M.A. Crawford. 1973. "Essential fatty acid studies in primates: Linolenic acid requirements of Capuchins." *J. Med. Prim.* 2: 155-169.
- Gawrisch, K., N.V. Eldho, and L.L. Holte. 2003. "The structure of DHA in phospholipid membranes." *Lipids*. 2003 Apr; 38(4):445-52.
- Global Forum of Health. www.globalforumhealth.org
- Hibbeln, J.R., L.R. Nieminen, and W.E. Lands. 2004. "Increasing homicide rates and linoleic acid consumption among five Western countries 1961-2000." *Lipids*; 39(12):1207-13.
- Hibbeln, J.R. 2002. "Seafood consumption, the DHA content of mothers' milk and prevalence rates of postpartum depression: a cross-national, ecological analysis." *J Affect Disord*; 69(1-3):15-29.
- Hibbeln JR. 1998. "Fish consumption and major depression." *Lancet*; 351(9110):1213.
- Hibbeln, J., J. Davis, C. Steer, P. Emmett, I. Rogers, C. Williams, and J. Golding. 2007. "Maternal seafood consumption in pregnancy and neurodevelopmental outcomes in childhood (ALSPAC study): An observational cohort

- study." *The Lancet*, Volume 369, Issue 9561, Pages 578-585.
- Hopfield, J. J. 1974. "Electron transfer between biological molecules by thermally activated tunnelling." *Proceedings of the National Academy of Sciences USA* 71, 3640-3644.
- Holte, LL, S.A. Peter, T.M. Sinnwell and K. Gawrisch. 1995. "2H Nuclear Magnetic Resonance Order Parameter Profiles Suggest a Change of Molecular Shape for Phosphatidylcholines Containing a Polyunsaturated Acyl Chain." *Biophys. J.* 68, 2396-2403.
- Jump, D. B. 2002. The Biochemistry of n-3 Polyunsaturated Fatty Acids." *J. Biol. Chem.*, 277(11), 8755-8758.
- Kitajka, K., L.G. Puskas, A. Zvara, L. Hackler, Jr., G. Barcelo Coblijn, Y.K. Yeo, and T. Farkas. 2002. "The role of n-3 polyunsaturated fatty acids in brain: Modulation of rat brain gene expression by dietary n-3 fatty acids." *Proc. Natl. Acad. Sci. USA.* 99, 2619-2624.
- Kitajka, K., A.J. Sinclair, R.S. Weisinger, H.S. Weisinger, M. Mathai, A.P. Jayasooriya, J.E. Halver, and L.G. Puskas. 2004. "Effects of dietary omega-3 polyunsaturated fatty acids on brain gene expression." *Proc. Natl. Acad. Sci. USA.* 101, 10931-10936.
- Klein, R.G., G. Avery, K. Cruz-Urbe, D. Halkett, J.E. Parkington, T. Steele, T.P. Volman, and R. Yates. 2004. "The Ysterfontein 1 Middle Stone Age site, South Africa, and early human exploitation of coastal resources." *Proc Natl Acad Sci U S A.* 101(16):5708-15
- Lamprey, M.S., and B.L. Walker. 1978. "Learning behavior and brain lipid composition in rats subjected to essential fatty acid deficiency during gestation, lactation and growth." *J. Nutr.* 108, 358-367.
- Leigh Broadhurst, C., Y. Wang, M.A. Crawford, S.C. Cunnane, J.E. Parkington, and W.E. Schmid. 2002. "Brain-specific lipids from marine, lacustrine, or terrestrial food resources: potential impact on early African Homo sapiens." *Comparative Biochemistry and Physiology Part B: Biochemistry and Molecular Biology*; 131 (4), 653-673.
- Leyton, J., P.J. Drury and M.A. Crawford. 1987. "Differential Oxidation of saturated and unsaturated fatty acids in vivo in the rat." *Br. J. Nutr.* 57: 383-393.
- Litt, J., H.G. Taylor, N. Klein, and M. Hack. 2005. "Learning disabilities in children with very low birthweight: prevalence, neuropsychological correlates, and educational interventions." *J Learn Disabil*;38(2):130-41.
- Marchioli, R., F. Barzi, E. Bomba, C. Chieffo, D. Di Gregorio, R. Di Mascio, M.G. Franzosi, E. Geraci, G. Levantesi, A.P. Maggioni, L. Mantini, R.M. Marfisi, G. Mastrogioseppe, N. Mininni, G.L. Nicolosi, M. Santini, C. Schweiger, L. Tavazzi, G. Tognoni, C. Tucci, F. Valagussa; GISSI-Prevenzione Investigators. 2002. "Early protection against sudden death by n-3 polyunsaturated fatty acids after myocardial infarction: Time-course analysis of the results of the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI)-Prevenzione." *Circulation*; 105(16):1897-903.
- Marean, C.W. 2010. "Pinnacle Point Cave 13B (Western Cape Province, South Africa) in context: The Cape Floral kingdom, shellfish, and modern human origins." *J Hum Evol.* 59(3-4):425-43.
- Martinez, M., and E. Vazquez. 1998. "MRI evidence that docosahexaenoic acid ethyl ester improves myelination in generalized peroxisomal disorders." *Neurology.* 51(1): 26-32.
- Mihailescu, M., and K. Gawrisch. 2006. "The structure of polyunsaturated lipid bilayers important for rhodopsin function: A neutron diffraction study." *Biophys J*;90(1):L04-6.
- Min, Y., and M.A. Crawford. 2004. "Essential Fatty Acids." In: *The Eicosanoids*, ed Peter Curtis Prior, John Wiley and Sons Ltd., West Sussex, England Chap 22: pp257-276.
- Moser, C.C., T.A. Farid, S.E. Chobot, and P.L. Dutton. 2006. "Electron tunnelling chains of mitochondria." *Biochim Biophys Acta*;1757(9-10):1096-109
- Neuringer, M., W.E. Connor, D.S. Lin, L. Barstad, and S. Luck. 1986. "Biochemical and functional effects of prenatal and postnatal omega 3 fatty acid deficiency on retina and brain in rhesus monkeys." *Proc Natl Acad Sci U S A.* 83(11): 4021-4025.
- Niemoller, T.D., D.T. Stark, and N.G. Bazan. 2009. "Omega-3 fatty acid docosahexaenoic acid is the precursor of neuroprotectin D1 in the nervous system." *World Rev Nutr Diet.* 2009; 99:46-54.
- Penrose, R. 2001. "Consciousness, the brain, and spacetime geometry: an addendum. Some new developments on the Orch OR model for consciousness." *Ann NY Acad Sci*; 929:105-10.
- Puskas, L.G., K. Kitajka, C. Nyakas, and T. Farkas. 2003. "Short term administration of omega-3 fatty acids from fish oil results in increased transthyretin transcription in old rat hippocampus." *Proc. Natl. Acad. Sci. USA.* 100, 1580-1585.
- Puskas, L.G., E. Bereczki, M. Santha, L. Vigh, G. Csanadi, F. Spener, P. Ferdinandy, A. Onody, and K. Kitajka. 2004. "Cholesterol and cholesterol plus DHA diet-induced gene expression and fatty acid changes in mouse eye and brain." *Biochimie.* 86, 817-824.
- Puskas, L.G., Z.B. Nagy, Z. Giricz, A. Onody, C. Csonka, K. Kitajka, L. Hackler Jr., A. Zvara, and P. Ferdinandy. 2004. "Cholesterol diet induced hyperlipidemia influences gene expression pattern of rat hearts: a DNA microarray study." *FEBS Lett.* 562, 99-104.
- Saugstad, L.F. 2001. "Manic depressive psychosis and schizophrenia are neurological disorders at the extremes of CNS maturation and nutritional disorders associated with a deficit in marine fat." *Med Hypotheses.* 57(6):679-92.
- Sinclair, A.J., and M.A. Crawford. 1972. "The incorporation of linolenic and docosahexaenoic acid into liver and brain lipids of developing rats." *FEBS Lett.* 26: 127-129.
- Sinclair, A.J. 1975. "Incorporation of radioactive polyunsaturated fatty acids into liver and brain of developing rat." *Lipids.* 1975 Mar;10(3):175-84.
- Simmer, K. 2000. "Long chain polyunsaturated fatty acid supplementation in infants born at term." *Cochrane Database Syst Rev* 2000;(2):CD000376.
- Soubias, O., W.E. Teague, and K. Gawrisch. 2006. "Evidence for specificity in lipid-rhodopsin interactions." *J Biol Chem*; 281(44):33233-41.
- Sprecher, H. 1993. "Interconversions between 20- and 22- carbon n-3 and n-6 fatty acids via 4-desaturase independent pathways." *IIIrd International Congress on essential fatty acids and eicosanoids*, Am. Oil Chem. Soc. ed A.J. Sinclair, R. Gibson, Adelaide, 18-22.
- Sprecher, H., Q. Chen, and F.Q. Yin. 1999. "Regulation of the biosynthesis of 22:5n-6 and 22:6n-3: A complex intracellular process." *Lipids* 34(suppl):S153-S156.
- Suzuki, H., S. Manabe, O. Wada and M.A. Crawford. 1997. "Rapid incorporation of docosahexaenoic acid from dietary sources into brain microsomal, synaptosomal and mitochondrial membranes in adult mice." *Internat. J. Vit. Res.*, 67: 272-278.
- Thomas, D. 2007. "The mineral depletion of foods available to us as a nation (1940-2002) — A review of the 6th Edition of McCance and Widdowson." *Nutr Health.* 2007;19(1-2):21-55.
- Trapani, J. 2008. "Quaternary fossil fish from the Kibish Formation, Omo Valley, Ethiopia." *J Hum Evol.* 55(3):521-30.
- Uauy, R., and A.D. Dangour. 2009. "Fat and fatty acid requirements and recommendations for infants of 0-2 years and children of 2-18 years." *Ann Nutr Metab.* 2009; 55(1-3):76-96.
- Weisinger, H.S., A.J. Vingrys, B.V. Bui, and A.J. Sinclair. 1999. "Effects of dietary n-3 fatty acid deficiency and repletion in the guinea pig retina." *Invest. Ophthalmol. Vis. Sci.* 40, 327-338.
- Yavin, E., E. Himovichi, and R. Eilam. 2009. "Delayed cell migration in the developing rat brain following maternal omega 3 alpha linolenic acid dietary deficiency." *Neuroscience*; 162(4):1011-22.
- Young, G., and J. Conquer. 2005. "Omega 3 fatty acids and neuropsychiatric disorders." *Reprod. Nutr Dev.* 45, 1-28.
- Yue, H., D. Khoshtariya, D.H. Waldeck, J. Grochol, P. Hildebrandt, and D.H. Murgida. 2006. "On the electron transfer mechanism between cytochrome C and metal electrodes" Evidence for dynamic control at short distances." *J Phys Chem B Condens Matter Mater Surf Interfaces Biophys*;110(40):19906-13.