“Eat your fish, it’s brain food!” was one of those childhood dinnertime entreaties—along with promises of increased height and strength, and reminders of starving children overseas—to eat something on my plate that was often singularly unappealing. It antedates by many decades the recent evidence that ingesting omega-3 fatty acids present in fish oils benefits not only your brain but also your heart and various other organs. The premise that eating fish will make you smart has its roots in the distant past and has survived more than a century of scientific and popular conjecture, as if it had a life of its own.

A documented basis for the notion had its beginnings in 1669, with the discovery of the element phosphorus by Hennig Brandt, a German alchemist.1 This was followed by the discovery in 1719 by J.T. Hensing that the brain had a high phosphorus content.2 With the later knowledge that phosphorus occurs in nature in combination with oxygen in the form of organic phosphates, it remained for J.L.W. Thudichum, an otolaryngologist and chemist in London, in 1861, to show that much of the phosphate in the brain was to be found in molecules we now know as phospholipids,3 which are structural components of cell membranes, including the brain’s many interconnecting nerve fibers. The dramatic property of elemental phosphorus to glow in the dark, first demonstrated by Brandt, along with the knowledge that phosphorus is enriched in the brain, and the emerging evidence of the electrical properties of the nervous system undoubtedly contributed to heady thoughts about the mysteries of brain and mind well into the nineteenth century. Materialism as a natural force, in contrast to spirituality, was gaining traction. The German chemist Jacob Moleschott had proclaimed in 1852, “Ohne Phosphor, kein Gedanke” (Without phosphorus there can be no thought).4 This provocative and widely quoted statement was likely an intentional attack on spiritualism. According to a periodical account from 1887, the Harvard biology professor Louis Agassiz, a famous paleontologist and world authority on fish species, took Moleschott’s dictum a bit further in an address on behalf of a fisheries commission in Massachusetts. To the fact that the brain was rich in phosphorus Agassiz added the finding by French chemist Jean-Baptiste André Dumas that fish were rich in phosphorus. Agassiz is quoted as having later said, “I simply put the two (observations) together.” Apparently playing to his audience, Agassiz is said to have added that the consumption of fish was reflected in the marked intellectual activity of the people of Massachusetts.5

Famous as Agassiz was, his quote would doubtless have received less public attention had Mark Twain in 1871 not published his response to an inquiry from an aspiring young writer about the wisdom of eating fish:

Yes, Agassiz does recommend authors to eat fish, because the phosphorus in it makes brain. So far you are correct. But I cannot help you to a decision about the amount you need to eat—at least, not with certainty. If the specimen composition you send is about your fair usual average, I should judge that a couple of whales would be all you would want for the present. Not the largest kind, but simply good middling-sized whales.6

Agassiz might have been miffed at Twain’s inclusion of cetaceans as fishes, but the humorous remark served to spread Agassiz’s concept of fish as brain food around the world. Demand for fish was reported to have increased in New York shortly thereafter. It soon became rumored in Calcutta that Bengalis were intellectually superior because of their consumption of fish. William James took issue with the concept, based on experiments showing that mental exercise did not increase urinary excretion of phosphates.7 We now know that high-energy phosphorus-containing metabolites such as ATP (adenosine triphosphate) do play a dominant role in the brain’s energy metabolism, but they are largely recycled and retained within body tissues. In addition, our terrestrial foods contain plenty of phosphates, further invalidating the possibility that additional dietary phosphorus could satisfy a brain requirement.
Meanwhile, the popular belief that eating fish could benefit mind and body sailed on. Cod-liver oil, traditionally used as a shipboard cure-all, became a popular panacea on land as well. It was found to be effective in a number of conditions, especially in the prevention of rickets, a bone-deforming disease prevalent early in the twentieth century in the growing populations of sun-deprived urban children. We now know the disease was prevented by the vitamin D in the cod-liver oil.¹

Cod-liver oil is further enriched in essential fatty acids (EFAs), so named because our bodies require them but are not able to make them. They therefore must come from what we eat. The EFAs represent a quantitatively small but important fraction of the fatty acids in our diets, not as fuels to be consumed for energy but for the unique roles they play in our cellular structures and functions. While we commonly speak of dietary fatty acids, we don’t actually eat them in the free form because they would taste terrible; the alkali salts of fatty acids constitute plain, old-fashioned soap. The fatty acids in our food are in a bound form, as components of triglycerides, nature’s compact energy-storage molecules. Chemically, fatty acids are even-numbered chains of hydrogen-bearing carbon atoms, generally sixteen to twenty-two carbon atoms long, with the carbon atom

Above: A painting of the discovery of phosphorus by Hennig Brandt in 1669. By heating a dried residue of urine with carbon in the absence of air, a mysterious glow appeared, which was eventually identified as white phosphorus. The discovery of the thirteenth known element marked the transformation of alchemy to chemistry. COURTESY OF DERBY MUSEUM & ART GALLERY © 2007
at the head end linked to oxygen, by which each of three fatty acids is tethered to the tri-alcohol glycerol. Glycerol serves as a three-carbon mooring site for the much larger fatty acids, which then account for the bulk of a triglyceride molecule. The position of the carbon atom at the tail end of a fatty acid is referred to as number one, or omega, often denoted by the Greek letter ω. Most of the fat in our diets consists of triglycerides that are present in plant-seed oils, meats, and dairy products. Triglycerides are the principal component of salad and cooking oils, of the delicious white fat in and around well-marbled steaks, and of solid cooking fats such as butter, lard, and hydrogenated fats. We metabolize the fats and oils we eat for energy or store them as triglycerides in our adipose tissues. Although our bodies contain the enzymatic machinery to biosynthesize a variety of fatty acids, there are others we need but cannot make, because of our inability to insert double bonds at locations along the fatty acid carbon chain closer to its carbon one tail (the omega carbon) than carbon atom 9. The six EFAs occur as two families of three members each, based on the location of the double bond closest to the omega carbon: the omega-3s and omega-6s. They are polyunsaturated, each bearing between two and six double bonds.

As shown on page 83, the three omega-6 family members, LA (linoleic acid), AA (arachidonic acid), and DPA (docosapentaenoic acid), are eighteen, twenty, and twenty-two carbon atoms long, respectively. Each has a numerical nickname indicating sequentially its carbon chain length, the number of double bonds, and the location of the double bond closest to the omega carbon. Thus, LA becomes 18:2ω6, while AA is 20:4ω6. All three members of the omega-6 family may be ingested in our diets and may end up in our body’s structure, as components of phospholipids. LA is the most prevalent of the omega-6 fatty acids in our diets, coming mostly from seed triglycerides, especially corn, sunflower, soy, and peanut oils, and in food products that contain them. We ingest much smaller amounts of AA and DPA, mostly in meat, eggs, and nuts, but since we are able to convert LA to the other omega-6 family members, dietary deficiency of any of the omega-6 EFAs is rare.

The other three EFAs constitute the well-publicized omega-3 family members, LNA, EPA, and DHA. Like their omega-6 counterparts, they are eighteen, twenty, or twenty-two carbon atoms long, respectively, and have the same double bonds and locations along the fatty acid chains as their omega-6 cousins but bear an additional double bond, at omega-3. LNA is present in most seed oils, generally in a lower amount than LA, exceptions being flaxseed and canola oils. EPA and DHA are virtually absent from seed and grain oils. All three of the omega-3 EFAs are produced by aquatic microorganisms such as algae, fungi, marine plants, and invertebrate animals, with LNA advancing to EPA and DHA via progressively larger prey along the food chain, finding their way to us mainly via fish and fish oil, in pill or capsule form. The old standby, cod-liver oil, like other fish oil preparations, must first be purified to remove toxic metals and organic chemicals that have been passed up the food chain along with the EFAs. Unlike LA, its eighteen-carbon omega-6 cousin, LNA is not a significant component of our body structure, nor (also unlike LA) is it readily converted in our bodies to its next-in-line family member, EPA. This is especially the case when there is more LA than LNA in an oil due to competition for molecular recognition, as well as various aspects of cell metabolism, such as transport into cells and binding to enzyme catalytic sites. We are left with fish and fish oil as the preferred dietary sources of EPA and DHA.

Interest in EPA and DHA was intensified in the 1940s, when it was observed that Inuits and other Arctic dwellers subsisted over winters with a high-fat diet of dried fish, whale meat, and seal meat, all high in EPA and DHA. Remarkably, on this seemingly unhealthy high-fat diet, there was a low incidence of cardiovascular disease. It was subsequently reported that heart disease, stroke, and a number of other life-threatening conditions were relatively infrequent in fish-eating populations, including some Japanese and Scandinavian communities. The lower the omega-6 to omega-3 ratio in the diet, the less likely a studied community was to suffer from strokes and heart attacks. Many subsequent studies involving thousands of subjects supported the concept of a competition between the omega-3 and omega-6 fatty acids in our diet. Generally speaking, it was found that omega-3 fatty acids are good for us, while the excessive amounts of omega-6 fatty acids in the food most of us eat are bad. Only long after the early epidemiological data were confirmed did scientists begin to understand the reasons why.

We now know that a molecular basis for this competition lies in chemical messengers in our bodies that are derived from the two twenty-carbon-atoms-long EFAs: the omega-6 EPA, AA, and the omega-3 EPA, DHA. As indicated in the figure on page 83, both are converted to eicosanoids, a word derived from eicosa, the Greek word for twenty, by cyclo-oxygenase enzymes (cox-1 and -2). The eicosanoids regulate many of our physiological responses to trauma. Unlike hormones, which circulate throughout the body via the bloodstream, eicosanoids are released locally by tissue or blood cells to mediate cellular defenses under conditions
of physical challenge. For example, they stanch the loss of blood at the site of a wound by promoting clotting or marshaling white blood cells and antibodies in response to bruises or a bacterial invasion. The eicosanoids have also been referred to collectively as autacoids, meaning “self-healing.” The same cyclo-oxygenases that generate eicosanoids from AA also act on EPA to generate a family of doppelgänger analogs of their AA-derived cousins that are much milder in their cellular actions. By competing with the AA-generated eicosanoids at enzyme and receptor sites, the net effect of the EPA-derived eicosanoids is a diminishing of what would result had the AA-derived eicosanoids exerted their actions unopposed. The production of antibodies stimulated by a balanced combination of omega-6 and omega-3 eicosanoids fends off bacterial invasion by destroying the coatings of foreign bacteria and digesting them. Unchecked and unopposed, the powerful omega-6 eicosanoids would attack even the body’s own protein and induce crippling autoimmune diseases. Similarly, by stimulating the clotting mechanism beyond what is needed to stop bleeding at a wound site, pulmonary, cerebral, or cardiac thrombosis could ensue. Commonly used anti-inflammatory drugs often taken for joint pain, such as ibuprofen and aspirin, exert their pain-relieving effects by reducing the production of eicosanoids that are overexpressing their actions.

One might then ask, if this balance between the omega-3s and omega-6s in our bodies arose during phylogenesis and was optimized by evolutionary survival pressures, why has it now gone awry? Explanations have been proposed that the food we eat, particularly those of us in the Western industrialized world, is not what our prehistoric hunter-gatherer ancestors, or even what our antecedents of a hundred years ago, ate: we consume too much of the omega-6s than omega-3s. Estimates of the omega-6:omega-3 ratio in the human diet of our preagrarian past range from less than 1:1 (more omega-3 than omega-6), to four times more omega-6s than omega-3s. Today, we might be eating a diet having an omega-6:omega-3 ratio as high as 20:1 or more. Major culprits for us are corn, soybean, cottonseed, sunflower, and safflower oils, all of which contain more LA than LNA. A further problem is the feeding of corn and soybeans to domestic animals that we then eat. Furthermore, as noted, the efficiency of conversion of LNA to EPA in our bodies is not robust, so even flaxseed oil, which is much richer in LNA than LA, is not as reliable a source of EPA and DHA as are products of the sea.

There are additional functions of the omega-3 EFAs beyond the way they compete at the eicosanoid level. EPA and DHA are enriched in the brain, as components of membrane phospholipids. Phospholipids, you will recall, are what make the brain so rich in phosphorus. In contrast to triglycerides, which are consumed as metabolic fuel, phospholipids are structural elements of our bodies’ cells. Phospholipid molecules, like triglycerides, have in common glycerol and two fatty acid components. In place of a triglyceride’s third fatty acid, a phospholipid has a phosphate-bearing component, which dramatically alters the molecule’s properties. Fatty acid chains in triglycerides have a much greater affinity for each other than they do for water molecules (which is why oil and water do not mix). The fatty acid chains in phospholipids cling to one another but are also attracted to water because of their ionically charged phosphate component. The result is that in the aqueous environment of living tissues, phospholipids self-assemble into two-dimensional molecular bilayers to constitute membranes, the ultrastructural wrapping material of cells that separates intracellular compartments from the extracellular environment. This envelopment also includes cellular extensions, such as nerve processes, which are bundled and further wrapped many times over. This abundance of membrane phospholipids in the brain then accounts for its long-known enrichment in phosphorus. The multiple double bonds in the EPA components of phospholipid molecules produce kinks along fatty acid chains, reducing the tight side-by-side packing that fatty acids in membrane phospholipids would otherwise have. This increases membrane flexibility and is thought to play a role in the intensive messaging functions across neural membranes.

DHA is the major fatty acid in the retina, where it is concentrated in the light-sensitive outer segments of photoreceptor cells. Dietary EPA and DHA are thus especially important during brain and eye development in utero and during infancy. Bovine milk is much lower in EFAs than human breast milk, a result of bacterial hydrogenation of fatty acid double bonds in the bovine stomach. This problem can be remedied by the addition of EPA and/or DHA to nursing formulas.

Based on all of these considerations, nutritionists conclude that we should decrease omega-6 EFAs in our diets and increase omega-3s. We could avoid the seed oils that have more than 50 percent LA, including corn, sunflower, safflower, and cottonseed. So many common food and snack labels lists these oils that the task of avoiding them might be an unwelcome challenge. Eating more omega-3 EFAs is the other path to a more favorable dietary omega-6:omega-3 ratio. Supermarket shelves contain an ever-increasing number of products whose labels proclaim “Contains...”
omega-3s!" Too often this claim refers in part or in full to LNA, the not-so-certain precursor of EPA and DHA, and the product might contain a higher amount of LA to boot!

What, then, is an achievable and acceptable omega-6 to omega-3 ratio? Nutritionists recommend that we eat, as a reasonable limit, about six times more omega-6 than omega-3. None of the preceding oils makes the grade, with ratios as high as 80:1 to 300:1. Soy oil is relatively acceptable, with ratios of 50 percent LA and 7 percent LNA, yielding an omega-6 to omega-3 ratio of about 7:1.17 Canola oil would seem better than most seed oils, with a ratio of 2:1 (22 percent LA, and 11 percent LNA). Flaxseed oil is high in LNA (53 percent) and low in LA (13 percent), with an omega-6:omega-3 ratio of 1:4, but it is less stable than other seed oils and should be refrigerated. Complete exclusion of omega-6s from the diet, in addition to being extremely difficult, would be ill-advised, since we do need omega-6–generated eicosanoids, just not too much of them. Butter and some butter substitutes are low in EFA. Olive oil has very few EFA and contains over 90 percent oleic acid. Olive oil, like butter, has very few polyunsaturated fatty acids, making it relatively heat-stable and suitable for frying.

As for how much omega-3 we require, nutritionists’ recommendations for healthy adults vary in the range of 0.5 to 1.0 grams a day of EPA plus DHA, although higher doses have been administered in experimental therapies for many neurological and psychiatric illnesses. DHA has been investigated as a therapy for several eye ailments. Food and Drug Administration approval for a prescription omega-3 preparation was based on its ability to lower serum triglycerides (although the mechanism of this action is unclear).18 There are numerous other medical indications for taking omega-3s. EPA has been shown to reduce abnormal sensitivity of the heart muscle, and its dietary supplementation was reported to decrease the rate of ventricular fibrillation and death from a second heart attack. However, various heart conditions might be aggravated by taking the omega-3s,19 so that for cardiac patients, a medical opinion is indicated. The brochure for prescription-grade omega-3 notes that patients who are taking various blood thinners should consult their physicians. This caveat should also hold for those of us consuming more than a gram a day of EPA/DHA in over-the-counter pills. A less serious untoward effect of EPA and DHA is a “fishy” eructation (burp) stemming from taking fish-oil

Above: Dietary sources of the six essential fatty acids (EFA). The upper row lists the three omega-6 EFA with their trivial (biochemical shorthand) names. Linoleic acid (LA) is 18 carbons long and has 2 double bonds, starting at the omega-6 position, hence its biochemical name, 18:2ω6. Similarly, arachidonic acid, AA, is 20:4ω6, and docosapentaenoic acid, DPA, is 22:5ω6. The bottom row shows their omega-3 family analogs, each having an additional double bond at ω3. They are linolenic acid, LNA (18:3ω3), eicosapentaenoic acid, EPA (20:5ω3), and docosahexaenoic acid, DHA (22:6ω3). The figure emphasizes that the major source of our dietary LA and LNA are seed oils, while EPA and DHA come mainly from sea life. LNA is often referred to as ALA on food labels. Each arrow indicates an enzyme-catalyzed step: 2-carbon elongation or dehydrogenation (double bond formation). Also shown is the reverse reaction by which DHA may be converted to EPA. The indicated conversion of LNA to EPA can be questioned. AA and EPA are antagonistic in regard to eicosanoid formation and eicosanoid-mediated actions, such as inflammation and blood clotting.
preparations, the result of the breakdown of EFAs into various long aldehydes, ketones, and alcohols. Over-the-counter fish-oil preparations, in common with vitamin pills or herbal extracts, are classified as GRAS (generally regarded as safe) and are thus not subject to the more rigorous government oversight of the prescription capsules. We are then left to read the labels and to judge, if possible, their provenance. They should be reasonably fresh (not dark or smelly) and kept in a cool, dark place to avoid degradation over time.

Cold-water fish, especially salmon, remain a popular source of dietary omega-3s. A problem for the consumer is in establishing the EPA and/or DPA content of what one buys at the fish counter. Authoritative, documented sources show much variation in the published omega-3 content in farmed versus wild salmon, in Atlantic versus Pacific salmon, and so forth. This undoubtedly reflects genetic variation, seasonal fluctuation, and what the analyzed salmon, whether wild-caught or farmed, had been eating. As our oceans become depleted of wild fish, and as the genetic nature and diet of farmed salmon become regularized, perhaps salmon and other aquacultured products with stated EPA and DHA contents will be brought to market. Feeding farmed fish omega-6-rich grain, such as corn, is a step in the wrong direction, healthwise. It has been argued that feeding farmed salmon on ocean fare such as net-harvested smaller fish, fishmeal, or oil in pellets might deprive larger food fish species remaining in the wild of their food supply. Food pellets for farmed fish containing commercially cultivated algae, rotifers, or other omega-3-rich organisms are possibilities that are being actively explored. The diet of farmed fish affects their texture, color, and taste—all important considerations for commercial aquaculturists. Consumer interest is a potentially powerful force that could lead to more information about the EPA-DHA content of farmed fish, as well as for packaged or canned fish products. Finding jars of herring or cans of tuna packed in vegetable oil at the supermarket can be disheartening (literally).

In regard to other sources of omega-3-rich foods, it is understandable that animal brains are not always popular sources of omega-3 EFAs. In addition to the fact that many people do not find brain aesthetically appealing as food, reluctance also stems from fear of contracting a fatal viral or prion disease. Nevertheless, cooked brain remains a delicacy throughout the world, from pig brains ‘n’ eggs in the southern United States to French tête de veau. That sheep’s eye you turned down at a Moroccan feast was loaded with DHA! We can now readily find and buy EPA- and DHA-fortified butter substitutes and eggs. In addition, EFAs are present in varying amounts in free-range or grass-fed steer and bison that have escaped the feedlot, and in free-range chickens that have eaten grass, weeds, and insects. A possibility for the future is the use of selective breeding and genetic modifications to produce seed plants and animals that have a low omega-6 to omega-3 ratio. Canola oil is derived from modified rapeseed. Finding microorganisms or their enzymes that can introduce a double bond at the omega-3 position of an omega-3 fatty acid would give us two for one: it would hypothetically convert the “bad” AA to the “good” EPA. Although there are agronomic and gastronomic hurdles to overcome, there are also potential fortunes to be made that will keep these possibilities very much alive.

As we learn more about the omega-3 and -6 fatty acids, personal factors to be considered in the future will be our own genetic makeup and preexisting medical conditions. In the end, taste will undoubtedly also be a factor in the success or failure of new and healthier foods. So, it seems that you should still eat your fish. It is indeed brain food. But now, it’s not just your mother looking over your shoulder, but your doctor and your nutritionist, too.

NOTES

I am grateful to Professor William Smith, Dr. Simon Evans, and T.R. Durham for their helpful review of this article.


4. Jacob Molechott, Für meine Freunde: Lebens-Erinnerungen (1894, republished Giesen, Germany, E. Roth, 1894), 207.


9. Most of our body organs can oxidize either glucose or fatty acids to carbon dioxide and water. We can convert carbohydrates to fat, but not the reverse. Our brain uses only glucose, but under certain conditions, such as starvation, it will utilize four-carbon breakdown products of fatty acid metabolism, called ketone bodies, to meet about half of its energy needs. Ketone bodies also appear in the blood and urine (ketosis) in uncontrolled diabetes and in carbohydrate-restrictive diets (as in the Atkins diet). In the book Last Suppers Dr. Robert C. Atkins imagines for himself a last meal of lamb drenched in olive oil, lemon juice, garlic, and rosemary (see Last Suppers, J.L. Dickerson, ed [New York: Lebhar-Friedman Books, 1999], 92). Hospitalized following a fall in 2003, Atkins died in a coma. Ironically, his final sustenance was probably intravenous glucose, the bête noire of his eponymous diet.
In addition to varying in chain length, fatty acids vary in the number and location along the fatty acid chain of double bonds, also called unsaturations. They are numbered according to the locations of double bonds along the fatty acid chain relative to the omega carbon atom (no. 1). The presence of double bonds in triglyceride fatty acids lowers the melting point. Hydrogenation of vegetable oils, by eliminating the double bonds from fatty acids, turns oils to solid fats. This is commercially appealing because it produces melt-in-your-mouth baked goods and margarine that is spreadable at room temperature. It also increases the shelf life of food products and the stability of fats at frying temperatures. Double bonds can exist in one of two possible configurations, cis or trans. EFA double bonds are all cis. Trans double bonds are an undesirable byproduct of industrial hydrogenation. Adverse health effects of trans fatty acids as well as excessive saturated fatty acids have led to a decreased use of hydrogenated food products.

Sequential double bonds in the efas are three carbons apart. Thus LNA has double bonds at ω3 (between carbons 3 and 4), at ω6, and at ω9. DHA has double bonds at ω3, ω6, ω9, ω12, ω15, and ω18. Our body enzymes can introduce double bonds only at ω9 and beyond. We can biosynthesize oleic acid, which is 18:1ω9, and interconvert within the two efa families as shown on page 83.

However, they suffered from poor blood clotting, secondary to low levels of omega-6 fatty acids. An early pioneer in promoting diets high in fish oil was the brilliant, if quirky, British biochemist Hugh Sinclair, who attempted such a diet, eating from freezers full of seal meat and whale meat, until he predictably developed bleeding tendencies. Jeannette Ewin, Fine Wines and Fish Oil: The Life of Hugh Macdonald Sinclair (New York: Oxford University Press, 2001).


The presence of other nonessential fatty acids makes up the 100 percent total. The major other seed-oil triglyceride component is the nonessential (we can make it) fatty acid, oleic acid (18:1ω9).

Lovaza, originally known as Omnacor, is an FDA-approved prescription capsule containing ethyl esters of ω3 (465 mg) and ω6 (175 mg). It is made by Reliant Pharmaceuticals, Liberty Corner, N.J 07938.
