Chapter 14
Human Life: Caught in the Food Web

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14.1 Life in the web

14.1.1 Connections Make Complexity

Ecology develops awareness of dynamic interacting parts (whether enzymes and substrates, consumers and autotrophs, or predators and prey) which transfer energy, biomass, and information along chains of cause-and-effect connected events. This review will focus on polyunsaturated lipids that act in sequential steps that link cause to consequence, including some of the crosslinks that weave the chains into a complex web of interactions within habitats. In coastal areas, humans eat abundant supplies of finfish and shellfish that contain polyunsaturated fatty acids (PUFA) that originated from other life-forms. The PUFA are predominantly synthesized by phytoplankton. Phytoplankton production is mostly consumed by zooplankton or benthic invertebrates such as shellfish which are, in turn, consumed by fish and ultimately by humans when they eat fish.

In marine and freshwater systems, thousands of gene-defined organisms interact with a highly dynamic aquatic environment. Each species, cell, or enzyme transfers energy, biomass, and information into new forms consumed by other species, cells, or enzymes. Most animals survive by eating other life-forms that have already succeeded in gathering needed energy and biomass (minerals, vitamins, carbon, nitrogen, etc.). The chain of events connecting food supply to each species' survival involves enzyme-catalyzed molecular transformations within the cells of each participating organism. This in turn, depends, on DNA-defined proteins catalyzing and signaling different processes at different times in environment-triggered responses. The space and time occupied by each transient event differs greatly in terms of energy, biomass, or information. This review summarizes some information on the health consequences of these molecular events to build understanding that may change future human eating behaviors.

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Complex organisms develop their differentiated functions over time, accumulating long-term consequences from earlier short-term adaptations. Timing is vital because of limited storage ability at every stage of life. Each link in the chain of events depends on the arrival of supplies that influence the processes and consequences that lead to the next-step supplies. Whenever a species lacks metabolic machinery to make an essential component, this affects its nutritional physiology. Cumulative effects of successful or failed food transfers over time, both in quantity and/or in quality, can cause very different cognitive and physical health states in individuals with common genetic blueprints. For example, we see evidence linking essential PUFA and its critical subset of 20- and 22-carbon chain (C_{20} and C_{22}) highly unsaturated fatty acids (HUFA) with healthy cognitive functioning in the humans caught in a complex food web. There are harmful consequences in turning away from the aquatic foodstuffs that facilitated the transformation of hominids to *Homo sapiens* (Walter et al. 2000; Marean et al. 2007). We need researchers to carefully evaluate the past 100,000 years of adaptations in light of the food web that now supports human needs.

Choice of food consumed often seems based on proximity, convenience, taste/odor, and ingestability rather than on specific nutritional requirements. Similarly, enzyme catalysts seem unlikely to sense a need for the substrates they consume or the products they produce. Rather, most life events seem sustained by whatever food is available. Life thrives, survives, or dies within a changing web of energy, biomass, and information transfers where changed supplies can cause new patterns. Survivors fit in complex webs of interdependencies from which few on earth can be "independent." To avoid unintended outcomes that follow unrecognized causes, this review informs readers about the PUFA and HUFA they eat (examples in Table 14.1) and the resulting outcomes on human health. This transferred information may alter readers' perception and understanding of the importance of PUFA and HUFA in the aquatic and human food web and the future choices people may make as a species with respect to how to manage aquatic resources and how to select food.

14.1.2 Transfer of Essential Fatty Acids

The phytoplankton drifting in marine and freshwaters have genes that define molecular machinery to make and use chlorophyll, which uses solar energy to break water's H-O bonds and form molecular oxygen. The relocated energy-rich electrons move through various molecular intermediates in multistep pathways catalyzed by enzymes that couple this energy to permit the fixation of CO_2 into carbohydrate biomass. From this beginning, other steps couple the transfer of energy into new amino acids, proteins, nucleic acids, lipids, and specific cellular structures. Bacteria and both plant and animal eukaryotes convert metabolic fragments into energy-rich saturated and monoenoic fatty acids (see Table 14.1). In addition, some cyanobacteria (and eukaryotes containing chloroplasts with related DNA; Clegg et al. 1994) have gene-defined enzymes that create n-3 and n-6 PUFA structures from monoenoic acids. However, animals lack the DNA-encoded enzymes that permit the manufacture

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Table 14.1 PUFA and HUFA in different life-forms

Author	Life-form	Genus	Sat	Mono	18:2n-6	18:3n-3	18:4n-3	20:4n-6	20:5n-3	22:5n-3	22:6n-3	HUFA	%n-6HUFA
Ferr	Algae	*Scenedesmus*	44.4	15.3	2.1	1.3	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Keny	Algae	*Synechococcus*	49.0	44.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Keny	Algae	*Synechococcus*	33.1	56.1	1.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Keny	Algae	*Synechococcus*	32.0	29.0	18.0	10.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Keny	Algae	*Chlorogloea*	42.0	34.0	2.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Otle	Microalgae	*Spirulina*	55.7	11.2	17.4	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Otle	Microalgae	*Chlorella*	25.3	28.0	12.0	15.8	0.0	0.0	0.0	0.0	0.3	0.3	0.0
Colo	Macroalgae	*Nereocystis*	27.0	15.8	6.0	7.6	12.2	16.8	12.6	0.0	0.2	29.5	56.8
Colo	Macroalgae	*Ulva*	30.9	14.5	3.7	24.1	17.1	1.1	3.4	0.0	0.5	5.0	22.2
Colo	Macroalgae	*Gloiopeltis*	70.8	22.0	1.0	1.7		1.0	1.9	0.0	1.1	3.9	25.5
Colo	Macroalgae	*Soliera*	64.6	17.0	7.8	7.6		0.8	1.0	0.0	0.7	2.4	32.9
Wen	Diatoms	*Nitzschia*	33.4	40.1	2.6	1.7	0.0	4.1	17.3	0.0	0.0	21.4	19.1
Wen	Diatoms	*Nitzschia*	31.7	45.6	3.4	0.7	0.0	3.5	14.5	0.0	0.0	18.1	19.5
Aren	Diatom	*Thalassiosira*	35.7	25.0	1.9	1.5	1.5	0.8	8.4	0.0	1.9	11.1	7.2
Aren	Chlorophyte	*Dunaliella*	39.5	21.7	2.5	0.8	4.2	0.8	1.6	1.0	4.7	8.2	10.0
Aren	Haptophyte	*Phaeocystis*	31.4	15.8	3.8	3.2	14.2	0.2	1.0	0.2	7.7	9.0	1.9
Aren	Haptophyte	*Isochrysis*	20.4	10.6	5.8	22.6	2.3	0.0	0.0	0.1	0.0	0.1	0.0
Fern	Microalgae	*Isochrysis*	43.5	23.2	2.8	3.2	11.7	0.8	0.5	0.3	8.0	13.4	34.3
Velo	Algae	*Dunaliella*	23.2	16.1	9.1	51.4	0.2	0.0	0.0	0.0	0.0	0.0	0.0
Velo	Algae	*Rhodomonas*	32.8	5.9	8.1	21.0	19.6	0.0	6.0	0.0	6.4	12.5	0.4
Velo	Protist	*Oxyrrhis*	34.9	11.0	4.5	12.0	0.0	0.0	0.2	0.0	37.4	37.6	0.0
Velo	Dinoflaggelate	*Oxyrrhis*	34.5	7.2	5.1	6.5	0.2	0.2	4.4	0.2	41.8	46.5	0.4
Velo	Copepod	*Acartia*	56.3	14.5	0.0	7.5	6.6	0.0	8.1	0.0	7.0	15.2	0.3
Velo	Copepod	*Acartia*	57.5	8.5	0.1	23.6	0.1	0.1	4.5	0.1	5.7	10.3	0.7
Velo	Copepod	*Acartia*	42.2	7.9	0.0	13.8	13.9	0.0	9.8	0.0	12.3	22.2	0.2
Velo	Copepod	*Acartia*	57.8	7.0	0.1	3.8	0.1	0.1	5.4	0.1	25.8	31.3	0.2
Shie	Fungus	*Schizochytrium*	57.1	11.0	0.4	1.2	0.2	0.5	0.6	0.1	18.1	27.9	32.6
Shie	Brachiopod	*Artemia*	19.4	35.2	4.0	19.1	2.1	1.5	5.3	0.1	5.1	14.5	27.6
Shie	Copepod	*Eurytemora*	28.9	29.1	2.0	1.3	0.6	1.8	10.8	0.2	21.8	35.5	7.6
Pers	Copepod	*Heterocope*	34.3	10.3	3.6	4.1	6.7	3.7	10.9		20.7	35.3	10.5

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Table 14.1 (continued)

Author	Life-form	Genus	Sat	Mono	18:2n-6	18:3n-3	18:4n-3	20:4n-6	20:5n-3	22:5n-3	22:6n-3	HUFA	%n-6HUFA
Pers	Copepod	*Arctodiaptomus*	32.8	12.6	4.8	7.4	14.4	1.7	6.9		13.6	22.2	7.7
Pers	Cladoceran	*Bythothrephes*	30.8	19.2	3.6	5.3	4.1	9.3	23.0		2.1	34.4	27.0
Pers	Cladoceran	*Holopedium*	33.6	16.0	4.1	6.7	11.0	6.8	17.5		2.1	26.4	25.8
Pers	Cladoceran	*Bosmina*	32.6	20.8	5.3	7.6	10.4	4.7	14.4		2.6	21.7	21.7
Pers	Cladoceran	*Daphnia*	51.8	20.2	4.5	5.7	6.0	1.6	3.0		2.1	6.7	23.9
Bara	Cladoceran	*Daphnia*	21.7	26.4	7.1	8.3	0.5	1.3	0.5		0.0	1.8	71.3
Bara	Cladoceran	*Daphnia*	24.4	25.7	11.6	22.2	0.1	0.6	0.2		0.1	0.9	65.0
Hess	Cladoceran	*Daphnia*	33.9	25.4	6.7	5.9	11.9	0.8	8.6		1.5	11.0	7.6
Hess	Cladoceran	*Daphnia*	30.6	32.3	5.8	8.0	7.4	0.9	10.1		0.3	11.3	8.2
Hess	Cladoceran	*Daphnia*	29.7	23.4	4.3	6.7	11.1	1.2	12.5		1.0	14.7	7.9
Hess	Cladoceran	*Daphnia*	28.9	32.9	5.2	19.6	3.8	1.2	5.7		0.0	6.9	17.1
Hess	Cladoceran	*Daphnia*	31.6	29.8	5.3	5.3	7.3	5.3	12.9		0.5	18.7	28.4
Phle	Crustacea-krill	*Euphasia*	27.8	20.4	3.2	1.3	5.2	0.0	20.5		22.6	43.1	0.0
Dela	Oysters	*Crassostrea*	18.2	19.9	1.5	0.9	1.3	3.7	13.5	1.4	21.2	40.8	11.5
Soud	Mix of algae + diatoms for oyster diet		33.4	23.1	3.4	4.1	5.4	0.7	10.4	0.1	3.2	14.9	8.1
Soud	Oysters	*Crassostrea*	28.4	11.1	0.9	0.6	1.2	2.3	12.3	1.6	17.3	34.3	9.0
Soud	Oysters	*Crassostrea*	34.6	20.4	2.8	2.4	0.5	1.4	12.3	0.6	11.9	26.6	6.8
Fern	Clams	*Ruditapes*	28.1	31.6	1.9	2.6	7.0	1.5	1.1	0.4	16.0	20.5	14.6
Toch	Arctic charr	*Salvalinus*	22.1	36.7	4.4	3.3	2.7	0.7	6.7	1.5	18.5	27.4	2.6
Mour	Sea bass	*Dicentrarchus*	24.5	26.0	3.8	1.1	1.2	0.9	9.3	1.5	17.3	29.0	3.1
Cast	Smelt	*Osmerus*	22.3	49.7	0.2	0.0	0.0	4.8	3.5	0.3	15.0	23.6	20.3
Cast	Alewife	*Alosa*	24.1	34.9	3.7	3.6	2.9	2.4	8.2	1.5	6.0	19.4	19.1
Cast	Cod	*Gadus*	18.6	39.2	1.9	0.6	0.5	1.4	12.9	1.1	12.7	28.4	6.0
Cast	Trout	*Oncorhynchus/Salmo*	18.1	32.3	4.6	5.2	1.5	2.2	5.0	2.6	19.0	28.8	7.6
Cast	Herring	*Clupea*	17.2	60.5	0.7	0.3	1.5	0.4	7.4	1.1	3.9	12.8	3.1
Cast	Herring	*Clupea*	28.1	46.2	1.6	0.6	2.8	0.4	6.6	1.3	7.6	15.9	2.5
Cast	Menhaden	*Brevoortia*	40.9	27.2	1.1	0.9	1.9	1.2	10.2	1.6	12.8	25.8	4.7
Cast	Salmon	*Salmo*	22.4	40.3	2.0	1.0	2.0	0.9	6.7	2.3	16.1	26.0	3.5
Huyn	Herring	*Clupea*	28.7	46.5	1.0	0.3	0.6	0.9	7.5	0.6	10.0	19.1	4.9
Mora	Sole	*Solea*	29.1	36.8	10.1	10.3	1.2	0.8	2.0	1.3	3.0	7.1	11.6
Roll	Salmon	*Salmo*	22.8	41.5	7.1	8.9	3.8	0.8	2.2	1.0	7.7	11.6	7.0

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Sta2	Greenland	*Homo*	43.6	19.2	14.0	0.1	5.2	4.9	1.6	7.9	21.3	32.5
Koba	Japan, 57-year	*Homo*	47.6	13.6	17.3	0.2	6.4	3.7	1.2	7.3	18.6	34.4
DE1b	Quebec Inuits	*Homo*			22.2	0.0	6.2	3.0		5.0	14.2	43.9
Toku	Nagoya, Japan	*Homo*	30.4	21.3	31.7	0.2	6.6	2.6	0.7	5.4	16.3	46.8
Kuri	Japan dietitians	*Homo*	32.1	21.0	27.8	0.9	4.9	1.7	0.4	3.2	10.9	51.4
Sand	England	*Homo*	30.7	20.1	33.3	0.8	7.2	1.5	1.2	3.0	15.1	62.5
Raat	Minnesota	*Homo*	40.9	12.3	21.6	0.2	12.2	0.7	1.0	4.5	18.4	66.2
Chaj	Spain	*Homo*	47.1	19.7	15.9	0.1	6.8	0.6	0.4	5.5	22.7	71.7
DE2	James Bay Cree	*Homo*			21.1	0.0	9.3	0.7		3.0	13.0	71.5
DE1a	Quebec	*Homo*			22.1	0.0	6.4	0.5		1.3	8.2	78.0
BEYD	ARIC study	*Homo*	49.3	9.2	22.0	0.1	11.5	0.6		2.9	14.9	76.9
STA5	Detroit, 25 year-old	*Homo*	31.1	24.1	26.5	0.4	7.6	0.2	0.3	1.8	12.0	81.8
Kiec	Ohio elderly	*Homo*	45.0	15.0	25.7	0.6	10.2	0.7	0.2	0.8	13.2	86.8

Information on the fatty acids in diverse samples is arrayed with literature citations noted by the first four letters of the first author's last name,[a] a general description of the life-form, and the taxonomic genus name. *Sat* saturated fatty acids; *Mono* monoenoic fatty acids. Values are the percent in total fatty acids, except for the %n-6 in HUFA listed in the last column on the right. Not all reports listed every fatty acid, and some less common n-6 fatty acids are in the calculated HUFA and %n-6 in HUFA, but omitted to keep the table simple

[a]Except for citations: (*DE1a* Dewailly et al. 2001a; *DE1b* Dewailly et al. 2001b; *DE2* Dewailly et al. 2002; *STA2* Stark et al. 2002; *STA5* Stark et al. 2005)

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of these structures, and they therefore must obtain PUFA by eating plants (or herbivorous animals). Because the n-3 and n-6 PUFA and the HUFA have important consequences for the healthy development of animals, they are termed dietary essential fatty acids (EFA; see also Parrish – Chap. 13). The supply of EFA, especially the C_{20} and C_{22} HUFA, in the food web and its link to human health is the primary focus of this review.

Examples of suppliers and consumers of PUFA and HUFA are listed in Table 14.1. For example, different species of *Synechococcus* form and accumulate linoleate (18:2n-6) ranging from 0 to 18% of cellular fatty acids with no 20 or 22 carbon acids. On the other hand, diatoms (e.g., in the genus *Nitzschia*) form and accumulate appreciable amounts of HUFA, mostly with the n-3 structure. Veloza et al. (2006) showed transfer and accumulation of PUFA and HUFA when they fed the crustacean copepod, *Acartia tonsa*, with protist dinoflagellates (*Oxyrrhis marina*) that had eaten algae (*Dunaliella* or *Rhodomonas*). *Oxyrrhis* elongated and desaturated the PUFA 18:3n-3, abundant in *Dunaliella*, accumulating the HUFA 22:6n-3. It also accumulated PUFA and HUFA obtained from *Rhodomonas*. In turn, the *A. tonsa* accumulated PUFA and HUFA obtained from eating *Oxyrrhis*. In these cases, n-3 forms predominated in HUFA, and n-6 HUFA were less than 1% of the accumulated HUFA (although n-6 HUFA are abundant in some algae (Bigogno et al. 2002)). Shields et al. (1999) fed brine shrimp (*Artemia salina*) grown with the marine algae (*Schizochytrium sp.*) or calanoid copepods (*Eurytemora velox*) to halibut larvae (*Hippoglossus hippoglossus*), which then accumulated the PUFA and HUFA that they could not make from simple metabolic fragments.

When Persson and Vrede (2006) compared PUFA and HUFA in herbivorous and carnivorous zooplankton genera of *Daphnia*, *Bosmina*, *Holopedium, Bythotrephes*, *Arctodiaptomus*, and *Heterocope*, the accumulated HUFA ranged from 7 to 35% of total fatty acids with 8–27% n-6 in HUFA. Other collections of the small crustacean genus, *Daphnia,* contained 8–71% n-6 in HUFA depending on their local food supplies (Hessen and Leu 2006; Barata et al. 2005). In studying eutrophication with a cyanobacterial bloom, Müller-Navarra et al. (2000) suggested that an undesirable reduction in growth of *Daphnia* could be due to a relative deficit of diatoms and their 20:5n-3. In a similar way, reproductive success of the calanoid copepod, *Temora longicornis*, was related to availability of n-3 HUFA in the food web (Arendt et al. 2005). Different critical life events may require different specific EFA, and negative effects may come from either too little supply or too much supply. Researchers can productively examine mechanisms by which the just-noted impact of HUFA supply on crustacean success has parallels for vertebrate, mammal, and human success.

Table 14.1 shows about half of the fatty acids in diverse living systems are saturated and monoenoic acids, whereas HUFA can be from 0 to 40% of tissue fatty acids. Transfers of PUFA and HUFA along food chains and around the food web likely affect how different animal species thrive or survive. Human life in coastal regions has been well supported by easy access to crustacean and molluskan shellfish and abundant, oil-rich fish such as herrings, salmonids, and tunas. We need to know how important zooplankton HUFA are in sustaining harvests of these species. The HUFA in marine species are predominately n-3 HUFA (see Table 14.1), with

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somewhat higher proportions of n-6 HUFA in some freshwater species (e.g., smelt and alewife). For optimally sustaining pike (*Esox lucius*), access to adequate levels of both n-3 and n-6 HUFA is required (Engstrom-Ost et al. 2005). Optimal conditions for sustaining humans (Lands 2003c; Hibbeln et al. 2006b) and crustaceans seem to require about 20–40% n-6 HUFA in the total HUFA. However, biomass transfers to *Homo sapiens* from the worldwide food web currently lead to different ethnic populations having anywhere from 20% to more than 80% n-6 in HUFA (see Table 14.1). These differences in HUFA proportions are not as much determined by different genes as by culture-oriented food choices with little attention to n-3 or n-6 contents. The differences are also clear from the composition of fatty acids in human mother's milk, which varies worldwide and is influenced by diet composition (Kuipers et al. 2005, 2007) Thus humans are caught in a food web that has serious outcomes. Evidence from observational and interventional studies indicates that low dietary intakes of marine foods and their 20- and 22-carbon n-3 HUFA are associated with serious human disabilities worldwide.

14.1.3 Prevalent Problems for Humans

The consequences of moving vitamin-like essential fatty acids along the food web that supports human health will be discussed in later sections. They can viewed in the context of the two most prevalent human disabilities worldwide, cardiovascular disease and major depression (Murray and Lopez 1997a, b). These may account for 23% of disability-adjusted life years (DALY) among developed nations (Table 14.2). Additionally, cancers, traffic accidents, alcohol abuse, osteoarthritis,

Table 14.2 The most abundant forms of human disability

	Worldwide			Developed nations		
Rank	Disease or Injury	DALYs	Cum. (%)	Disease or Injury	DALYs	Cum. (%)
	All causes	1,389	6	All causes	161	
1	lschemic Heart disease	82	12	lschemic Heart disease	18	11
2	Unipolar major depression	79	17	Cerebrovascular disease	10	17
3	Road traffic accidents	71	21	Unipolar major depression	10	23
4	Cerebrovascular disease	61	25	Lung and throat cancers	7	28
5	Chronic pulmonary disease	58	28	Road traffic accidents	7	32
6	Lower respiratory infections	43	31	Alcohol abuse	6	36
7	Tuberculosis	43	34	Osteoarthritis	5	40
8	War injuries	41	37	Dementia & CNS disorders	5	43
9	Diarrheal diseases	37	40	Chronic pulmonary disease	5	46
10	HIV-AIDS	36		Self-inflicted injuries	4	48

The disability-adjusted life years (DALY) were calculated by Murray and Lopez (1997a, b)

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dementia and central nervous system (CNS) disorders, chronic pulmonary disease, and self-inflicted injuries account for another 25% of DALY, and these events may also have important associations to food selections. We need more research to identify the chains of molecular events causing these consequences so that we can design effective preventive interventions.

14.2 Evidence of Impaired Neural Development

Low intakes of n-3 HUFA in foods are associated with low levels in tissues and with impaired development of healthy neurobehavioral acts in humans. For example, results from thousands of subjects in the Avon Longitudinal Study of Parents and Children (ALSPAC) show maternal seafood intakes of more than 340 g per week have beneficial effects on child development, suggesting that advice to limit seafood consumption may be detrimental (Hibbeln et al. 2007). Seafood intake less than 340 g per week during pregnancy was associated with higher risk of children being in the lowest quartile for verbal intelligence quotient (IQ) (overall trend, $p = 0.004$), and with higher risk of suboptimum score for prosocial behavior, fine motor, communication, and social development. Unfortunately, the US Environmental Protection Agency currently advises pregnant women to limit their seafood intake to 12 ounces (i.e., ~340 g per week; US 2004). Careful revision of that advice intended to decrease exposure to mercury is now needed.

14.2.1 Stress, Corticotrophins, and Aggression

Fear and anxiety, components of defensive and violent behaviors, accompany elevated levels of corticotrophin-releasing hormone in the cortical–hippocampal–amygdala pathway. A small observational study correlated higher levels of cerebrospinal fluid corticotrophin-releasing hormone with lower percentage of docosahexaenoic acid (DHA; 22:6n-3) in total plasma fatty acids (Hibbeln et al. 2004a). Placebo-controlled trials may determine if dietary omega-3 fatty acid interventions can reduce excessive corticotrophin-releasing hormone levels and psychiatric illnesses. One pilot study of psychiatric patients with alcoholism, depression, or both, showed lower n-3 HUFA status was associated with higher concentrations of neuroactive steroids (Nieminen et al. 2006).

Deficiencies in DHA and eicosapentaenoic acid (EPA, 20:5n-3) at critical periods of neurodevelopment may lower serotonin levels and result in a cascade of suboptimal development of neurotransmitter systems, limiting regulation of the limbic system by the frontal cortex (Hibbeln et al. 2006a). Maladaptations to transient environmental stress and elevated corticoids in young animals can lead to "glucocorticoid programming" and altered neurophysiological and neuropathological status of

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adult laboratory animals and humans (Seckl and Meaney 2006). Accumulated effects of earlier transient trauma may give permanent disorders of depression, aggression, and hostility in adults. More data are needed to distinguish influences of diet on long-term accumulated neurodevelopmental defects from short-term reversible influences on adult pathology (e.g., Gesch et al. 2002).

In a sample of 3,581 urban white and black young adults (Iribarren et al. 2004), the multivariate odds ratios of scoring in the upper quartile of hostility were significantly associated (0.90; $p = 0.02$) with one standard deviation decrease in DHA intake. Prior consumption of any fish rich in n-3 fatty acids was independently associated with lower odds of high hostility (0.82; $p = 0.02$). Also, aggressive cocaine addicts (Buydens-Branchey et al. 2003) had significantly lower levels of DHA and the n-6 HUFA docosapentaenoic acid (DPA; 22:5n-6). Finally, the shifts that occurred in HUFA contents of those people during therapy support considering possible links between aggression in humans and a deficit in n-3 relative to n-6 nutrients.

14.2.2 How Food Helps

Food provides the n-3 PUFA precursors as well as the fully formed HUFA, DHA, which uniquely promotes neurite growth in hippocampal neurons, and its deficiency may contribute to cognitive dysfunction (Calderon and Kim 2004). Deficiency of DHA during development accompanies impaired learning and memory. Supplementing with DHA increased the population of neurons with longer neurite length per neuron and with higher number of branches, whereas added oleic (18:1n-9), arachidonic (20:4n-6), or n-6 DPA did not. DHA may promote neuronal integrity by facilitating membrane translocation/activation of Akt[1] while increasing phosphatidylserine (PS) in cell membranes (Akbar et al. 2005). The n-6 DPA which replaces DHA during n-3 fatty acid deficiency is less effective in accumulating PS, in translocating Akt and in preventing loss of neurons.

Depletion of DHA from neuronal tissues may also have a compounding effect on Raf-1[2] translocation in growth factor signaling (Kim et al. 2003). G protein-coupled signaling is impaired when a deficiency of n-3 EFA causes replacement of tissue n-3 DHA with n-6 DPA and gives suboptimal function in learning, memory, olfactory-based discrimination, spatial learning, and visual acuity (Niu et al. 2004). Replacement of n-3 by n-6 HUFA is correlated with desensitization of visual signaling in rod outer segments as evidenced by reduced rhodopsin activation, rhodopsin-transducin (G(t)) coupling, cGMP phosphodiesterase activity, and slower formation of metarhodopsin II (MII) and the MII-G(t) complex relative to rod outer

[1] Akt or protein kinase B (PKB) is an important molecule in mammalian cellular signaling. The name Akt does not refer to its function. Presumably, the "Ak" in Akt was a temporary classification name for a mouse strain developing spontaneous thymic lymphomas. The "t" stands for "transforming" the letter was added when a transforming retrovirus was isolated from the Ak strain.

[2] Raf-1 is a serine/threonine-specific kinase.

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segments of n-3 FA-adequate animals. Reduced amplitude and delayed response of the electro-retinogram a-wave observed during n-3 EFA deficiency is attributed to impaired signal transduction by G protein-coupled receptors. Thus, adequate transfer of visual information from the environment to an individual depends on prior transfer of n-3 biomass to support optimal retinal function.

Neural cells exposed to ethanol accumulated considerably less phosphatidyl serine (PS) in response to the DHA enrichment and were less effective at phosphorylating Akt and suppressing caspase-3 activity (Akbar et al. 2006). Reduction of PS and a resulting neuronal cell death are undesirably enhanced by ethanol exposure during fetal development. These impairments may contribute to the long-recognized cumulative impairments that characterize fetal alcohol syndrome. The impairments illustrate the importance of maintaining adequate supplies of the essential n-3 HUFA in neural and retinal tissues. Levels of PS were consistently reduced in brain cortices of pups from ethanol-exposed dams, mainly due to the depletion of the n-3 PS18:0/22:6 species (Wen and Kim 2007).

14.2.3 Fish Also have Neural Development

Castel et al. (1972) reported that feeding rainbow trout (*Oncorhynchus mykiss*) the n-3 alpha-linolenic acid (ALA; 18:3n-3) at 0.5% or more of dietary calories prevented poor growth, fin erosion, heart myopathy, and a shock syndrome seen with PUFA-deficient diets. That report contrasted with many others that assigned an essential role only to n-6 linoleic acid (LIN; 18:2n-6) for man and other animals (e.g., Holman 1958) while denying assignment of n-3 nutrients as "essential." Rejecting an essential role for n-3 acids was then based on the limited view that n-3 acids provide no more benefit than n-6 acids (Tinoco et al. 1971). However, in trout, neuropathological shock symptoms (Sinnhuber 1969) began to appear 4 weeks to 3 months after feeding a PUFA-deficient diet, depending upon the age of the fish when the diet was started. Eating 1% LIN made this symptom appear sooner and more severely than any other diet tested. The shock syndrome resembles transportation shock reported as a "common experience of the fish culturist" (Black and Barrett 1957). In those times, commercial trout feed was usually high in LIN and low in n-3 fatty acids (Sinnhuber 1969). Such proportions in the food supply are often controlled by financial priorities of suppliers rather than physiologic outcomes of consumers.

Trout had highly variable individual somatic growth responses when fed LIN (compare photos in Fig. 3, Castel et al. 1972) suggesting diverse individual responses to transient environmental stimuli had accumulated during development (which did not occur when diets contained n-3 EFA). Maladaptations to transient environmental stress and elevated corticoids in young individuals can lead to altered neurophysiological and neuropathological status of adult laboratory animals and humans (Seckl and Meaney 2006). Such nongenetic develop-

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mental differences are well known for individual response levels of corticotrophin-releasing hormone and plasma corticosteroids, biomarkers related to aggression, homicide, suicide, and other serious human disorders. Readers might wonder if cumulative maladaptations of corticoid responses will occur in mammals with less frequency or intensity when daily food during development has higher proportions of n-3 EFA.

Because so many life-forms share related DNA-determined events, the ability of a dietary balance in n-3 and n-6 EFA to diminish or prevent maladaptations during development could be important for many species in our food web. We may wonder how n-3 and n-6 EFA affect developmental stages of zooplankton or other crustacea, which also carry echoes of our shared DNA-defined responses. Constructive research can determine how HUFA imbalances in the food web exacerbate developmental maladaptations (see Arts and Kohler – Chap. 10) and whether accumulated outcomes in adults can be reversed.

14.2.4 Self-Harm is a Depressing Adaptation

Depression, impulsivity, and suicidal intent were measured in patients with self-harm and matched controls, together with plasma lipids and EFA. Patients presenting with self-harm had more pathology on psychometric measures of depression, impulsivity, and suicidal intent than did controls (Garland et al. 2007). They also had lower mean total EFA levels (88 vs. 106 μg ml^{-1}, $p = < 0.001$), total n-3 and n-6 EFA levels, and a higher %n-6 in HUFA (73% vs. 66%). Impulsivity and depression scores were inversely correlated with both n-6 and n-3 EFA. Supplementation with n-3 HUFA for 12 weeks led to substantial reductions in surrogate markers of suicidal behavior and to improvements in well-being for patients recruited after acts of repeated self-harm (Hallahan et al. 2007). Low levels of DHA (22:6n-3) and elevated ratios of n-6/n-3 acids are associated with major depression and, possibly, suicidal behavior (Sublette et al. 2006). A lower DHA percentage in plasma PUFA and a higher n-6/n-3 ratio predicted suicide attempt over a 2-year period.

Higher concentrations of DHA in mothers' milk ($r = -0.84$, $p < 0.0001$, $n = 16$ countries) and greater seafood consumption ($r = -0.81$, $p < 0.0001$, $n = 22$ countries) both predicted lower prevalence rates of postpartum depression (Hibbeln 2002). However, ARA and EPA contents of mothers' milk were unrelated to postpartum depression prevalence. To test the efficacy of supplemental n-3 fat, subjects received 0.5 g day^{-1} ($n = 6$), 1.4 g day^{-1} ($n = 3$), or 2.8 g day^{-1} ($n = 7$) in an 8-week trial. Across groups, pretreatment Edinburgh Postnatal Depression Scale (EPDS) and Hamilton Rating Scale for Depression (HRSD) mean scores were 18.1 and 19.1, respectively; post-treatment mean scores were 9.3 and 10.0 (Freeman et al. 2006a). Percent decreases on the EPDS and HRSD were 51.5% and 48.8%, respectively; changes from baseline were significant within each group and when combining groups.

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However, groups did not significantly differ in pre- or post-test scores, or change in scores. Nevertheless, greater seafood consumption predicted lower lifetime prevalence rates of bipolar I disorder, bipolar II disorder, and bipolar spectrum disorder (Noaghiul et al. 2003). Bipolar II disorder and bipolar spectrum disorder had an apparent vulnerability threshold below 50 lb year^{-1} (i.e., ~430 g week^{-1}) of seafood/person.

14.2.5 Recognizing Cognitive Benefits from Seafood

Recently, the American Psychiatric Association appointed a subcommittee to prepare a report that was reviewed and approved by its Committee on Research on Psychiatric Treatments, Council on Research, and Joint Reference Committee (Freeman et al. 2006b). The report concluded that the preponderance of epidemiologic and tissue compositional studies supports a protective effect on mood disorders of n-3 EFA intake, particularly EPA and DHA. Randomized controlled trials showed EPA and DHA appear to have negligible risks and statistically significant benefit in unipolar and bipolar depression ($p = 0.02$). A recent literature survey regarded fish as a food with unique psychotropic properties (Reis and Hibbeln. 2006). It described how fish have been culturally labeled as symbols of emotional well-being and social healing in religious and medical practices among independent cultures for at least six millennia. Recent reports about dietary HUFA preventing cognitive decline in older adults (Connor and Connor 2007; Baydoun et al. 2007; vanGelder et al. 2007) continue the transfer of hopeful healing information.

14.3 Evidence of Impaired Cardiovascular Development

Evidence of vascular injury developing progressively in young Americans has been documented repeatedly over the past 50 years (Enos et al. 1953; Newman et al. 1986; Rainwater et al. 1999; Zieske et al. 2002), but prevention of its primary dietary causes remains neglected. Risk scores predict advanced coronary artery atherosclerosis in middle-aged persons as well as youth (McMahan et al. 2007). Thus, each generation follows earlier ones in a tragic chain of preventable, cumulative errors that cause disability and death of adults. As with psychiatric disorders that have cumulative effects on individuals during development, clinical cardiovascular disease has cumulative maladaptations that eventually become recognized long after the time when they were reversible. A recent epidemiological study (Robinson and Stone 2006) noted that lifetimes of eating n-3 HUFA showed more consistent cardiovascular benefit than did clinical intervention trials with limited times of eating n-3 HUFA. Primary prevention of coronary heart disease (CHD) needs to begin in childhood.

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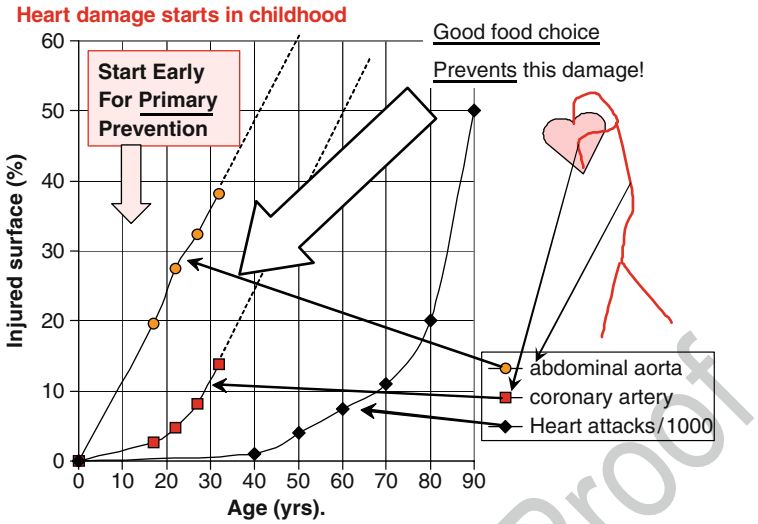

Fig. 14.1 Evidence of CHD pathology begins in childhood. Results of progressive vascular injury from the Pathobiological Determinants of Atherosclerosis in the Youth (PDAY) program are in many reports, including (McGill et al. 2000; McMahan et al. 2007; Rainwater et al. 1999.)

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From a US perspective, greater awareness of worldwide human living conditions developed after 1946 when the USA transferred energy and attention from war to new biomedical research programs at the National Institutes of Health. The Seven Countries Study introduced researchers to different mortality rates for CHD among different populations with different food habits. Epidemiologists at the time associated death with ingesting saturated fats and total fat energy, but said little about seafood or n-3 HUFA. Subsequently, much attention went to the hypothesis that cholesterol in the diet and the bloodstream of individuals may cause CHD death, but a molecular mechanism was never proved.

Wilbur and Levine (1950) noted a near absence of cardiovascular disease among Alaskan Inuits who had consistently high serum cholesterol. Other reports showed clearly that dietary cholesterol was NOT causing death, although elevated cholesterol in the blood was associated with death in the USA. In 1984, an appointed committee substituted political consensus for rigorous logic and asserted that elevated plasma cholesterol was a *cause* of death (Consensus 1985). This assertion was also accompanied by stern advice to lower caloric imbalances in daily life. Unfortunately, the advice about food energy was not effectively transferred or implemented in primary prevention programs, and an epidemic of obesity developed over the next twenty years.

The HUFA proportions for diverse human populations in Table 14.1 illustrate diverse impacts of the food web on various human groups. A lower incidence of CHD deaths among people eating more marine food (with higher n-3 HUFA contents) is illustrated in Fig. 14.2.

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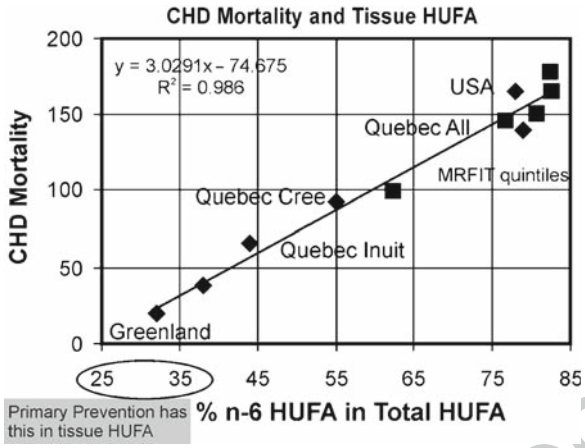

Fig. 14.2 Higher proportions of n-6 in HUFA predict higher CHD mortality rates. The figure is derived from an earlier version (Lands 2003a). *Squares* indicate quintiles in the MRFIT Study in the USA, where 80% individuals clustered closely

14.4 Which DNA-Coded Proteins Discriminate N-3 and N-6 Structures?

14.4.1 Putting EFA into Triacylglycerols and Phospholipids

Many enzymes are like animal species that consume readily available food without regard to downstream consequences. They are promiscuous and relatively indiscriminate in handling fatty acids with different structural features. Enzymes converting nonesterified fatty acids (NEFA) of 14–24 carbons to acyl-CoA esters consume whatever fatty acids are supplied without appreciably selecting for chain length or for numbers and locations of double bonds. Nevertheless, a selective transfer of palmitic acid (16:0) from its CoA ester to the 1-position of glycerol-3-phosphate begins the "*de novo*" lipid pathway that includes transfer to the 2-position of readily available unsaturated 16- or 18-carbon acids (e.g., palmitoleate (16:1n-7), oleate (18:1n-9), or linoleate (18:2n-6)). This leads to diacylglycerols with a saturated acid at the 1-position and an unsaturated acid at the 2-position (Hill et al. 1968).

Enzymes converting diacylglycerols (DAG) to triacylglycerols (TAG) consume acyl-CoA mostly in accord with supply abundance and not with chain length or number and location of double bonds. The nonessential saturated and monoenoic acids are steadily maintained in their CoA esters by synthesis and transport. However, a greater daily dietary supply of an EFA gives linearly greater amounts of EFA accumulated in tissue acyl-CoA and TAG. Rearrangements occur as lipases cleave TAG to DAG and provide mixtures of diverse DAG that can be acylated to TAG with little specificity for acyl-CoA structure or for the acyl content of the DAG

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(Slakey and Lands 1968). Thus, tissue TAG provides a flexible, nonselective expandable storage pool of unlimited size. Its energy-rich biomass contains mainly whatever is accessible in the local microenvironment. Little selectivity for n-3 or n-6 acyl structures occurs when forming or cleaving triacylglycerols. The 18-carbon PUFA, 18:2n-6 and 18:3n-3, accumulate in tissue TAG in linear response to their percent abundance in daily dietary calories (Lands et al. 1990; Lands et al. 1992).

Cellular 1,2-diacylglycerols are reversibly transformed into phospholipids by enzymes that attach phosphate derivatives to the 3-position. These enzymes also seem fairly promiscuous and able to form diverse molecular species that reflect the DAG units available (although transfer of ethanolamine phosphate slightly favors DAG units with 22-carbon HUFA at the 2-position). Subsequent transacylase and acyltransferase actions "retailor" phospholipids with acyl chains available from acyl-CoA esters. Highly specific selections occur when placing acyl chains into phospholipids (Lands 2000, 2005b). The DNA-coded selectivities favor accumulation of HUFA at the 2-position of phospholipids. However, the number of enzymes involved and the precise acyl group interactions of each remain unknown. The resulting accumulated phospholipids retain a dominant pattern of saturated acids at the 1-position and unsaturated acids at the 2-position. These diacylglycerol units of phospholipids can form DAG (by reversible actions of enzymes like CDPcholine:DAG cholinephosphotransferase) that are acylated and accumulate nonselectively in tissue TAG. The proportions of n-3 and n-6 in HUFA of all accumulated tissue glycerolipids show little evidence of an ability of acyl-CoA transferases to discriminate between n-3 and n-6 structures.

The mixture of acyl groups in cellular acyl-CoA esters includes newly synthesized and newly imported acids plus those released from TAG and phospholipids by hydrolases. Dietary PUFA that enter the acyl-CoA mixture compete with each other when interacting with enzymes catalyzing the elongation:desaturation reactions that form longer and more highly unsaturated acyl-CoA esters. The paths involve 18:2n-6 > 18:3n-6 > 20:3n-6 > 20:4n-6 > 22:4n-6 > 24:4n-6 > 24:5n-6 > 22:5n-6 and 18:3n-3 > 18:4n-3 > 20:4n-3 > 20:5n-3 > 22:5n-3 > 24:5n-3 > 24:6n-3 > 22:6n-3. The n-3 and n-6 acids compete for the enzymes more effectively than n-7 and n-9 acids, and some transient intermediates (e.g., 20:4n-3 and 24:5n-6) do not accumulate appreciably in glycerolipids. The limited conversion rates through this multistep system make dynamic handling of 18-carbon PUFA differ appreciably from that for the derived 20- and 22-carbon HUFA.

Limited space and time become evident whenever discriminating "consumer" enzymes rapidly transform *only* preferred supply items into next-step supplies, while nondiscriminating "consumers" transform all supply items *in proportion to their abundance* to next-step supplies. Also, limited space for next-step supplies allows only rapidly formed product items to accumulate, whereas unlimited space for next-step supplies allows all product items to accumulate indiscriminately. Quantitative studies related accumulated tissue HUFA to amounts of competing PUFA supplied in daily food (Mohrhauer and Holman 1963a, b; Lands et al. 1990), giving an empirical competitive, hyperbolic "saturable" equation (Lands et al. 1992). Revised constants (see http://efaeducation.nih.gov/sig/hufacalc.html) fit later data sets (Lands 2003b)

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and better predict diet:tissue outcomes. The equation predicts the nonlinear hyperbolic impact of dietary EFA abundance on the proportions of n-6 in HUFA accumulated competitively in mammalian tissues (*Mus, Rattus, Canis, Homo*) and allows rational interpretations of the impact of food choices on health.

14.4.2 Hormone-Like Signaling By N-3 and N-6 Eicosanoids

HUFA-mediated adaptive responses to environmental stimuli have many steps. Activation of cellular phospholipase A_2 (PLA_2) increases release of HUFA from the 2-position of phospholipids where they accumulate in relatively high amounts. Although PLA_2 appears to interact with 20-carbon HUFA better than with 18-carbon PUFA, it discriminates little between n-3 and n-6 structures when producing nonesterified HUFA. Fatty acid oxygenases (cyclooxygenase and lipoxygenase) act on nonesterified n-3 and n-6 HUFA to form hydroperoxide derivatives that stimulate faster oxygenation. Producing the hydroperoxide activator gives explosive formation of eicosanoids in response to stimuli. Predatory cellular peroxidases remove the hydroperoxide and slow this amplifying step during synthesis of prostaglandin H and leukotriene A.

Although peroxidases and lipoxygenase discriminate little between n-3 and n-6 structures, the cyclooxygenase activity of PGH synthase forms hydroperoxide product several times faster with n-6 than n-3 HUFA (Kulmacz et al. 1994; Chen et al. 1999; Laneuville et al. 1995). This is one of the few DNA-coded protein-catalyzed events known to discriminate between n-3 and n-6 acids. One consequence of the faster explosive positive feedback in formation of n-6 eicosanoids, PGG_2 and PGH_2, is that levels of peroxidase activity that remove enough n-3 product/activator (PGG_3) to prevent its explosive positive feedback do not appreciably hinder the faster n-6 amplified actions. This dynamic difference gives more vigorous overall formation and action of n-6 than n-3 prostaglandins (Lands 2005a; Smith 2005; Liu et al. 2006). As a result, the proportion of n-6 in HUFA of tissues, a biomarker that predicts likelihood of CHD mortality (see Fig. 14.2), also predicts the likely intensity of n-6 eicosanoid-mediated events. A strong preference of trout PGH synthase for n-6 over n-3 structures allows even small proportions of n-6 arachidonate in fish HUFA to form sufficient active n-6 hormone (Liu et al. 2006). However, that preference may also cause a too-intense eicosanoid action during the earlier-noted "transportation shock" in rainbow trout (when imbalanced diets had much more n-6 than n-3 fats).

Isomerases form active hormone-like prostaglandins (PGD, PGE, PGF, PGI, TXA) from the intermediate PGH_2 and PGH_3 formed by PGH synthase. We still know little of the selectivity of these isomerizing enzymes for n-3 and n-6 structures. Slow formation of transient active hormone can allow continual degradation by predatory dehydrogenases to inactivate slowly formed eicosanoids. In this situation, significant amounts of active hormone may be formed during a 24-h period but never accumulate sufficiently at tissue receptors at any point in time to give significant signals. For thromboxane, TXA (which mediates thrombosis), the active hormone spontaneously decomposes to inert TXB within seconds. Thus, TP receptors will

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give appreciable signals only when a very rapid pulse of TXA is being formed to create the needed local abundance.

At this time, we know little of the n-3:n-6 selectivity of the diverse cellular receptors that bind active eicosanoid and stimulate inside the cell signaling actions by kinases and phosphatases that regulate cell physiology. A slower receptor response to a bound hormone could allow the continual removal of transient signal mediators to dissipate the signal and prevent sufficient response. Although little selectivity is known for many leukotriene-mediated events, an important selective response by the leukotriene B (LTB) receptor provides much greater chemotactic signaling with the n-6 LTB_4 than for the n-3 analog, LTB_5. This produces more vigorous inflammatory events with n-6 than n-3 mediators. Wherever cellular systems respond differently to n-3 and n-6 eicosanoid signals, we can begin understanding the chain of events by which the food web impacts human health. Important insights were recently provided by Wada et al. (2007), confirming that many DNA-coded proteins act more vigorously in n-6 eicosanoid signaling than in n-3 eicosanoid-mediated events. Over-reactions mediated by n-6 eicosanoids are targets for inhibition by highly profitable therapeutic patented drugs. Perhaps primary prevention with greater proportions of n-3 in HUFA might decrease the need for such medication.

14.4.3 How Food Hurts

When humans eat food, the carbohydrates, proteins, and nucleic acids are hydrolyzed (digested) in the gut to simple sugars, amino acids, and nucleosides that diffuse during the next hour into intestinal cells. They then enter portal blood flowing to the liver and onward to the general bloodstream flowing throughout the body. Hydrolyzed fats are reassembled in intestinal cells and secreted into lymph as lipoprotein complexes which enter the general bloodstream during the next few hours. In this way, each meal (like a frequent periodic flood) provides the bloodstream and associated tissues with more energy and biomass than can be fully metabolized to CO_2 as it arrives. The transient postprandial surplus of energy-rich biomass is handled by different tissues in different ways: forming CO_2, forming fat, forming isoprenoids, and forming eicosanoids. In the process, transient oxidant stress creates temporary tissue insults that mostly reverse over time, but occasionally become the long-lasting vascular injuries noted in Fig. 14.3.

Within cells, the carbon and electrons of fats, carbohydrates, and proteins readily transform in multistep paths to acetyl-CoA (Fig. 14.3), CO_2 plus cofactor-carried electrons. The limited capacity to store electrons is met in part by transferring them to oxygen, forming water. This transfer is strongly coupled with formation of energy-transmitting ATP from ADP. However, without coupled work returning ATP to ADP, the stalled system cannot form much CO_2 and "leaks" some of the flood of electrons to oxygen, forming reactive molecules that cause transient oxidative stress and amplifies it into harmful inflammatory tissue insults (Lands 2003c).

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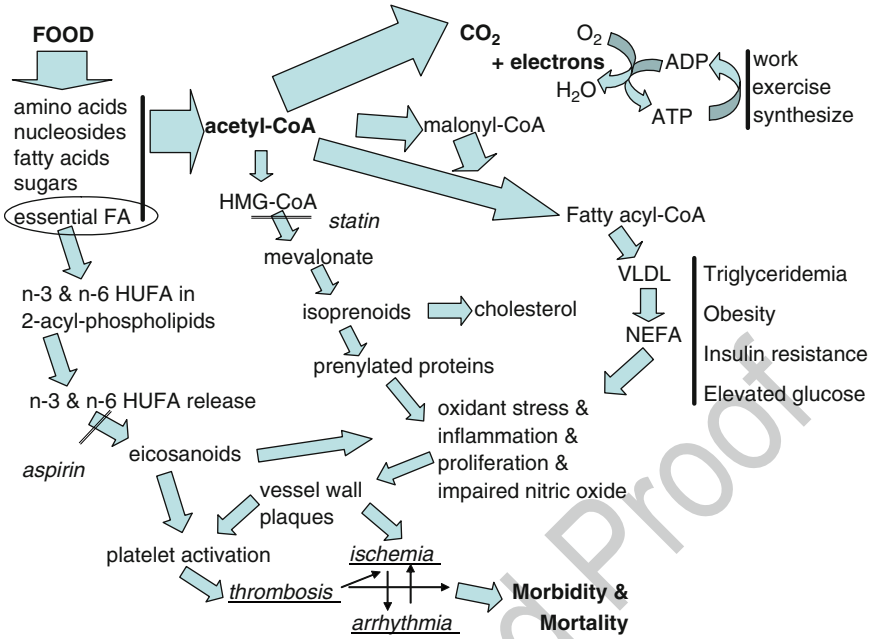

Fig. 14.3 Pathways to morbidity and death. Associated biomarkers are not always causal mediators. Transient inputs of food energy and biomass move to plasma lipids and are stored for later useful work. However, transient postprandial inflammatory states are amplified by n-6 eicosanoids.

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In cells unable to convert the transient flood of metabolites to CO_2, excess acetyl-CoA forms malonyl-CoA (which polymerizes in combination with excess electrons in multistep paths that form energy-rich fats) and some hydroxymethyl glutaryl-CoA (which forms mevalonate and polymerizes in multistep paths that that form diverse isoprenoid products). Many transient intermediates (e.g., eicosanoids, prenylated proteins, and NEFA) do not accumulate in large amounts, but have important roles in mediating overall pathophysiology (Lands 2003c). Figure 14.3 shows how the transient postprandial flood of biomass "pushes" acetyl-CoA through steps that increase plasma NEFA and cellular prenylated proteins, which lead to oxidant stress and inflammation. These transient conditions can be amplified by n-6 eicosanoid actions and accumulate long-term inflammatory vessel wall plaques. Thus, two food imbalances act together to create chronic conditions that ultimately cause CHD death: imbalances in food energy which are then amplified by elevated n-6 eicosanoid-mediated inflammation, thrombosis, and arrhythmia (Fig. 14.3). Elevated plasma TAG and cholesterol are indicators of transient food energy imbalance, and the % n-6 in HUFA of plasma indicates imbalances in intakes of n-3 and n-6 fats.

The much-discussed clinical indicator of CHD risk, plasma total cholesterol (TC), poorly predicted the absolute death rates observed in a 25-year follow-up of the Seven Countries Study (Verschuren et al. 1995). In fact, it had no clear ability

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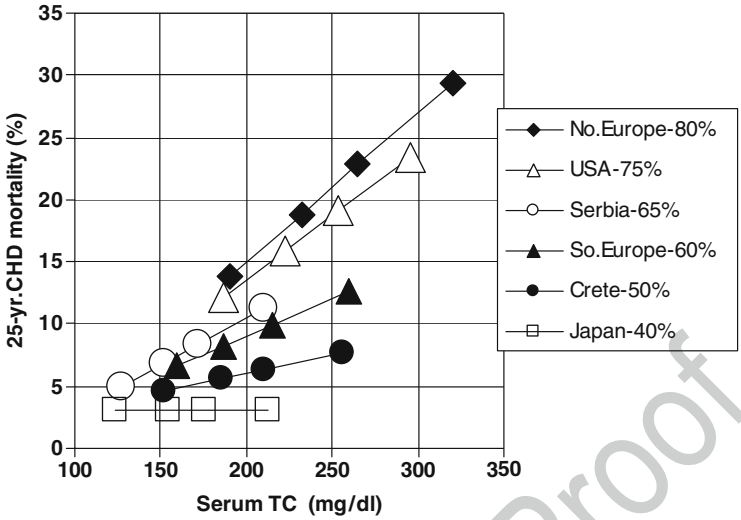

Fig. 14.4 Food energy impact on mevalonate products is fatal only to the degree that n-6 exceeds n-3 in HUFA. Deaths (as % of subjects studied) reported by Verschuren et al. (1995) are predicted quantitatively using mg total cholesterol (TC) per deciliter plasma and %n-6 in HUFA: death from CHD = 3 + 3 × (%n-6 in HUFA − 40) × (TC − 100)/1,000.

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to predict death in Japan. However, the observed CHD mortality was well predicted when the likely proportion of n-6 in HUFA for the different populations was combined in the following way: CHD death = 3 + 3 × (%n-6 in HUFA − 40) × (TC − 100)/1,000. Figure 14.4 shows that higher values for total cholesterol (TC) predicted higher death rates only to the degree that the %n-6 exceeded the %n-3 in HUFA. This result suggests that higher tissue proportions of n-3 HUFA may diminish vigorous inflammatory and thrombotic signals of n-6 eicosanoids and prevent the transient food energy-induced increases in NEFA and isoprenoids (for which TC is a biomarker) from being amplified into fatal outcomes. In this way, the toxicity of food energy imbalances depends on the context of ambient tissue n-3 HUFA.

14.4.4 Choosing Healthy Foods

Most transfers of fatty acids among individual organisms, cells, or enzymes are somewhat indifferent to n-3 or n-6 structures, allowing both to compete with each other for many processes. However, when physiologically important events discriminate n-3 from n-6 structures, the relative abundance of these two forms in food supplies may cause unintended consequences. The wide range of disorders

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linked to imbalances in n-3 and n-6 are discussed in detail in Lands (2005a). Humans may eat indiscriminately whatever is available, much like most species do in the food web within which they survive. However, the high proportion of n-3 in the food web of estuaries is not matched by food in the current commercial agriculture-based food web for Americans. Financial and marketing priorities that are controlling the supply of the food web may depend more on aspects of storage, transport, and profits rather than biological sustainability, nutrient content, or human physiology (Nestle 2002). Humans and their companion animals now are in a web of widely publicized and marketed foods that gives little information or interpretation of the PUFA and HUFA content.

One possible unintended consequence might be the higher rates of homicide (Hibbeln et al. 2004b) that are correlated with a greater apparent consumption of n-6 linoleic acid over a 20-fold range (0.51–10.2/100,000) for the years 1961–2000 in Argentina, Australia, Canada, the United Kingdom, and the United States ($r = 0.94$, $p < 0.00001$). The apparent linoleic acid intake from seed oil sources ranged from 0.29 en% (percentage of daily food energy) (Australia in 1962) to 8.3 en% (US in 1990s). This supply may be seen, in hindsight, to be an oversupply. Scientists have long known that an adequate intake of linoleate for humans may be less than 0.5% of daily food energy (Cuthbertson 1976; see http://efaeducation.nih.gov/sig/dri1.html). However, multibillion dollar profits from selling vegetable oils rich in n-6 fats help fund marketing messages that inform the public of benefits from replacing saturated with unsaturated fats, but fail to describe clinical conditions linked to excessive n-6 eicosanoid actions. The public could benefit from wider distribution of balanced information from which to make food choices, but it provides few financial incentives to fund such distribution.

To estimate a healthy dietary allowance for n-3 HUFA that would meet nutrient requirements for 97–98% of the world's population, a deficiency in n-3 HUFA was defined as attributable risk from 13 morbidity and mortality outcomes (Hibbeln et al. 2006b). The outcomes included death from all causes, coronary heart disease, stroke, cardiovascular disease, homicide, bipolar disorder, and major and postpartum depressions. The potential attributable burden of disease ranged from 20.8% (all-cause mortality in men) to 99.9% (bipolar disorder). The n-3 HUFA intake for Japan (0.37% of energy, or 750 mg/d) met criteria for uniformly protecting > 98% of the populations worldwide.

Table 14.3 provides information on average PUFA and HUFA intakes for some countries in the context of how much n-3HUFA would be needed daily to balance the other EFA and maintain a tissue biomarker level of 40% n-6 in HUFA. The low intake of linoleate in the Philippines would need only small intakes of n-3 HUFA to sustain that tissue biomarker level. With the current US food web, a healthy dietary allowance for n-3 HUFA was estimated to be 3.5 g/d for a 2,000-kcal diet. Because of the well-established competition between n-3 and n-6 structures in lipid metabolism (Mohrhauer and Holman 1963b, Lands et al. 1992), this allowance can likely be lowered to one-tenth of that amount by consuming fewer n-6 fats.

Interactive computer software (http://efaeducation.nih.gov/sig/kim.html) informs users of n-3, n-6 and caloric contents of nearly 12,000 different servings of food. It

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Table 14.3 PUFA and HUFA in the food web

	Current avg dietary intake (en%)			n-3 HUFA needed for 40% n-6 in HUFA	
Country	LIN	ALA	ARA	(en%)	(mg/d)
Philippines	0.80	0.08	0.06	0.125	278
Denmark	2.23	0.33	0.09	0.45	1,000
Iceland	2.48	0.33	0.10	0.54	1,200
Colombia	3.21	0.24	0.04	0.51	1,133
Ireland	3.57	0.42	0.06	0.62	1,378
UK	3.91	0.77	0.07	0.72	1,600
Netherlands	4.23	0.28	0.08	0.88	1,956
Australia	4.71	0.49	0.07	0.90	2,000
Italy	5.40	0.51	0.06	0.95	2,111
Germany	5.57	0.62	0.06	1.00	2,222
Bulgaria	7.02	0.06	0.05	1.25	2,778
Israel	7.79	0.67	0.07	1.45	3,222
USA	8.91	1.06	0.08	1.65	3,667

AU30 The results were provided by Hibbeln et al. 2006a,b. The major dietary PUFA are: LIN = 18:2n-6, ALA = 18:3n-3, and the major dietary n-6 HUFA is ARA = 20:4n-6. The daily intake of n-3 HUFA predicted to maintain tissue biomarker value of 40% n-6 in HUFA (an average value for Japan) is indicated in the two right-hand columns as percent of daily food energy (en%) and mg d^{-1}

predicts the calorie balance and likely tissue proportions of n-6 in HUFA that result from eating the servings. The freely available information allows people to plan individual daily menu plans to meet their personalized sense of taste and risk aversion. Examples of PUFA and HUFA contents of various types of food and of diverse daily menu plans can be found in Lands (2005a).

14.5 Making a Better Future

Human interactions with the food web have shifted from hunter-gatherer to domestic farmer to functional food fabricator. Hunters ate species that carried genes permitting survival in the competitive food web of nature, whereas farmers selectively bred species that carried genes permitting optimal financial profits. Now, functional foods may come from mixing gene products of diverse species or transferring genes to provide new species with previously unknown mixtures of nutrients. Human concerns for sustainability involve questions of quality of life for individuals and their environment. Biomedical research thrived with the transfer of information about the homology of DNA coding patterns among genera of bacteria (*Escherichia* and *Cyanobacteria*), simple eukaryotes (*Saccharomyces*), and more complex plants (*Arabidopsis*) and animals (*Caenorabditis, Drosophila, Danio, Mus and Homo*). The research provided

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deep insight into molecular events that cause health and disease. Converting that information into daily practice has been vigorously pursued by biomedical corporations to develop profitable treatments for wealthy people in distress with evident disease. Unfortunately, a sense of need or will to use that information to prevent disease and avoid too expensive treatments is not rewarded by current market forces and is in little demand.

Sustaining the diverse food web that once provided humans with foods needed for good health and quality of life will be a challenge. Hopefully, efforts to provide those supplies will carefully avoid the unintended consequences noted in this review.

The simplicity of management effort favors "monoculture" agricultural programs that return well-recognized profits and contrast sharply with the priority ecological programs that sustain diverse species and are supported by no traditionally defined profits. The interdependence of diverse life-forms that evolved over time led to some species thriving and some vanishing. The genus *Homo* continues to increase in abundance and adds greater pressure on existing supplies in the estuarine (and aquatic in general) food web. The current commercial food web in which *Homo sapiens* is currently "trapped" depends much upon easily stored grains, cereals, and nuts that contain much n-6 PUFA and little or no n-3 HUFA. Ironically, *Vigna mungo* (black gram), rich in n-3 PUFA, provides major food energy and biomass to poor people in India and southeast Asia. However, *Vigna radiata* (green gram) commercially developed in richer nations has much more n-6 than n-3 PUFA. Awareness of the contents of PUFA and HUFA may some day be a priority in efforts to sustain a healthy food web for humans. Rational selections of food can be aided with the interactive planning software noted earlier (http://efaeducation.nih.gov/sig/kim.html). However, the future food web will need more items containing more n-3 PUFA and HUFA if humans are to sustain healthy proportions of tissue HUFA.

Current experiments in gene transfer are considering ways to "short-circuit" the historic stepwise transfer of PUFA and HUFA through diverse species of phytoplankton, crustaceans, mollusks, and fish to humans. Inserting DNA-coded machinery into domesticated plant and animal species (Lai et al. 2006) may increase their tissue contents of n-3 PUFA and HUFA and help humans thrive with less food from estuarine food webs. This domestic agricultural alternative of mixing genes among previously wild species may compensate for the greatly increased human consumption of the species that have survived till now in an estuarine food web that supplied so much n-3 HUFA for human health. The diverse chapters in this book may further help readers better understand what can be done to improve human life caught in the food web.

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