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A Nonagenarian's View of Dietary Impacts on Cellular Immunology

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Abstract

Descriptions of immune functions and diets often use oversimplified terms that lead to misunderstandings plus expectations that conflict with reality. "*Unexpected events are a clear marker for the frontier of knowledge and a new opportunity to learn*" [1]. Terms like lipid, fluidity, unsaturated, essential, lipoprotein, receptor, immune and inflammatory have many unmentioned components and attributes that may be either causal mediators or associated epiphenomena in heath disorders. Including neglected details can help investigators design dietary interventions with observed consequences that fit their expectations. Over the years, new evidence and explicit terminology allow expected outcomes for interventions to fit reality. A recent review, "*Lipid nutrition: 'In silico' studies and undeveloped experiments*" [1], describes some aspects of fatty acid chemistry and nutrition with important consequences on chronic immune-inflammatory processes. The review points to long-known details of lipid-protein interactions which younger colleagues can consider as they develop new experiments to gather evidence on how food choices might prevent healthy physiology from drifting into pathophysiology.

Fatty acids and their esters bind to proteins and lipids rather than being solvated molecules like most metabolites. Some selective lipid-protein interactions can override expected lipid-lipid interactions of cell membrane "fluidity" in determining cell physiology. Recognition of the information carried in acyl chain structures was aided by Frank Gunstone (1923–2021) and his team of organic chemists who synthesized four extended sets of octadecenoic acid analogs with positional isomers of *cis* and *trans* ethylene, acetylene and *cis*-cyclopropane structures. An unknown number of acyltransferase enzymes selectively transfer saturated and unsaturated acyl chains to the 1-position and 2-position of phospholipids, respectively. However, they seem to respond to aspects of fatty acid structure other than a presence or absence of double bonds. Evidence of lipid-lipid interactions (i.e., "fluidity") not consistently limiting cell physiology disturbs some biomedical experts, and studies of selective acyl chain actions remain undeveloped.

By 1975, there was ample evidence for highly selective transfers in forming membrane phospholipids. However, isolating, cloning and determining selectivity of the many individual acyltransferases that make cellular phospholipids remained undeveloped for several decades. Important first steps were the 2006 cloning and sequencing of a lysophosphatidylcholine acyltransferase [2] and the subsequent sequencing of two more acyltransferases acting at the 2- position. How acyltransferases maintain saturated acids at the phospholipid 1- position remains unexplained. Forward progress needs isolated acyltransferases to fully understand how the enzymes recognize preferred substrates and control the typical balance of acyl chains in cell membrane phospholipids.

Most animal cells make unsaturated fatty acids with n-7 (omega-7) and n-9 (omega-9) motifs, but fatty acids with n-3 (omega-3) and n-6 (omega-6) motifs occur in animals only by eating plants (or animals that ate plants). Section 2 of the review describes a highly conserved set of elongation and desaturation enzymes that convert dietary 18-carbon n-3 and n-6 acids into 20- and 22-carbon highly unsaturated fatty acids (HUFA). The enzymes provide predictable proportions of accumulated n-3 and n-6 HUFA in cell membranes in a manner determined by the balance of n-3 and n-6 acids in the diet. A competitive, hyperbolic diet-tissue relationship was evident in data from 1963. It was formalized as an empirical equation in 1992 and successfully used with dietary fatty acid

intake data to predict tissue HUFA balance for mice, rats, and humans. In 2018, it fit data from nearly 4,000 people in 92 groups in 34 reports from 11 different countries [3]. It was also used to design diets that create intended HUFA balances in experimental animal models of a lupus-like chronic immune-inflammatory disorder [4].

The n-3 and n-6 motifs differently affect rates, extents, and consequences of forming n-3 and n-6 eicosanoids. These evanescent hormones act on selective G-protein coupled receptors with second messengers that alter cell physiology (Section 3 in [1]). The diet-determined balance of tissue n-3 and n-6 HUFA affects three destabilizing positive feedback loops that amplify signaling events and shift normal physiology to pathophysiology: peroxide tone affects prostaglandin and leukotriene formation, n-6 thromboxane forms faster than n-3 thromboxane, and the BLT-1 leukotriene receptor responds 10- to 100-fold more vigorously with n-6 LTB_4 than with n-3 LTB_5 [5]. The n-6 LTB_4 acting on BLT-1 increases 500-fold the expression of monocyte chemoattractant protein, MCP-1, which amplifies recruitment of monocytes to the region [6]. This creates positive feedback signals that destabilize cellular composition in vessel walls and progressively accumulate more inflammatory macrophages [7]. It seems likely that the diet-determined tissue balance of n-3 and n-6 HUFA affects many chronic immune-inflammatory conditions.

Excess food energy ingested as carbohydrate or protein is not appreciably stored in the body. Rather, it is converted *via* acetyl-CoA to fatty acids, triacylglycerols and cholesterol, products which can be biomarkers of food energy toxicity. Limits in the transport and removal of these products from the body link to many harmful events and chronic inflammatory health conditions such as the "metabolic syndrome". Interestingly, a 1995 report showed 25-year CHD mortality differed more intensely with serum cholesterol levels for ethnic groups with higher %n-6 in HUFA [8]. The data prompted a hypothesis that food energy toxicity, which elevates plasma cholesterol, may be fatal only to the degree that n-6 exceeds n-3 in tissue HUFA. There is a continual question of which biomarkers among the very large set of valid predictive biomarkers for CHD are in the small subset of valid causal mediators of CHD. Actions caused by excess food energy are not evaluated in enough detail, and the possibility of plasma cholesterol levels being an epiphenomenon in the etiology of CHD disturbs some biomedical experts. As a result, experiments testing the controversial hypothesis remain undeveloped.

The products of excess food energy are secreted from liver into plasma as very low-density lipoprotein (VLDL) complexes of protein, phospholipid, cholesterol and triacylglycerol and taken up as low-density lipoproteins (LDL) by cellular lipoprotein receptors. Imprecise names describing LDL as "native" or "modified" and LDL receptors as "native" or "scavenger" leave many detailed attributes unspoken and unattended. As a result, expected consequences from their interactions can easily fail to match observed behaviors. The sense of "scavenging" and "native" resembles other imprecise dichotomies like "saturated" and "unsaturated" for fatty acids or "self" and "non-self" for immune components. These terms need much more accompanying information to understand how etiological mediators cause the observed pathophysiology. A question underlying many chronic immune-inflammatory conditions is: *"How does circulating LDL change and interact less with LDLR and more with CD36 and LOX-1 receptors?"* [1].

The mission of preventive medicine is to decrease early causal mediators and prevent a drift to pathology. Progressive inflammatory disorders begin with subtle changes in cell signaling between endothelial cells and recruited monocytes. As monocytes change to macrophages, they develop signaling patterns that activate NLRP3 inflammasomes and release potent inflammatory cytokines that obscure the subtle actions of early causal lipid mediators. Accumulation of shape-shifting macrophages progressively changes the cell composition in arterial walls during atherogenesis and adipose tissue during obesity. It increases positive feedback signaling that amplifies the inflammatory disorder. As a result, macrophages can become 40% of adipose tissue in severe obesity, making the term "adipose tissue" too simple to convey expectations of the pathology.

The review posits a hypothesis that the balance of n-3 and n-6 HUFA in tissues plus the balance of food energy intake and expenditure have important predictable effects on health outcomes and are useful health risk assessment biomarkers. It notes that many reports on the etiology of chronic immune-inflammatory conditions have imprecise data on nutrients ingested during studies with "Western", "Mediterranean", "healthy" or "omega-3 supplemented" diets. The lack of detail makes it hard to predict and reproduce specific outcomes or identify a causal role for specific nutrients. To decrease this weakness in future studies, a computer tool (Omega Meals) was developed with an embedded database of nutrient contents of food items. This allows "*in silico*" predictions of a likely balance of n-3 and n-6 HUFA in blood lipids resulting from explicit designed daily meal plans. The predictions can be confirmed (or not) by measuring the blood fatty acids. Software can also combine aspects of daily energy intake and expenditure to help avoid excess food energy intake and its pro-inflammatory consequences with the energy balance confirmed by household scales.

The HUFA balance for different ethnic groups ranges from 32% to 87% n-6 in HUFA, and it associates with progressive inflammatory cardiovascular disease as well as asthma, allergies, cancer proliferation, and auto-immune "rheumatic" conditions. It would be interesting to see what blood HUFA balance is predicted by the Omega Meals software (and confirmed by blood fatty acid analysis) for diets named

"Western", "Mexican", "Mediterranean", "Greek", "Italian", "Chinese", "Japanese", "Thai", "Indian", "Vietnamese", "Ornish", "DASH", "Paleo" and "African Heritage". However, when building the daily diet plans there is no clear agreement on explicit food combinations that properly represent each type. Describing a "healthy" diet needs knowledge of nutrients in foods that affect the etiology of diet-related disorders.

Non-captive primates tend to eat foliage, fruit, and vegetation as a "normal healthy diet". Evolving hominid primates likely continued such a diet for a million years before developing agriculture 10,000 years ago. The diet of non-captive gorillas supports that idea [9]. High foliage diets appear to have negligible amounts of HUFA, similar amounts of 18:3(n-3) and 18:2(n-6), and about 10 percent of food energy as fat. An unexpected *in silico* prediction was that such a diet likely creates a tissue HUFA balance near 30% n-6 in HUFA, close to that observed for traditional Inuits and Japanese. It is important to confirm (or deny) this "*in silico*" prediction by a simple blood fatty acid analysis. However, the review notes that "*it may be as hard to acquire a blood sample from a wild gorilla as it would be to convince a dietitian to design a foliage-rich diet with <10 en% fat.*"

Efforts to guide Americans in eating healthy foods can confuse consumers when new evidence refutes a once-accepted hypotheses. Saturated fat and cholesterol in the diet have no clear etiological impact [10], and they are gradually diminishing in concern. In contrast, official advice on intakes of n-6 linoleic acid and n-3 linolenic acid continually fails to recognize the competitive non-linear dynamics involved in accumulating tissue HUFA from dietary polyunsaturated fatty acids. There is reason to give *"advice about a very small to non-existent therapeutic window for dietary linoleic acid in the absence of counterbalancing n-3 nutrients"* [11]. Guidelines that advise a nutritional goal of eating 10 times more n-6 than n-3 have no clear etiological rationale [1]. Knowing that more than half of American adults have one or more diet-related diseases gives an expectation that future nutrient goals for n-3 and n-6 intakes will differ from current average intakes.

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