
Interview with Edward Siguel, MD, PhD

Dr. Siguel (MD specializing in clinical pathology (lab medicine, blood tests); PhD in experimental design, statistics, and computers; MS in Physics; MS in Math) is a *Fellow* of the Am. Assoc. for the Adv of Science (publishers of *Science*); a member of the AMA, the Mass. Medical Society, ASPEN, and the Am. Oil Chem Society (AOCS) (among others); and recipient of some of the highest US Public Health Service Awards. As principal investigator for a study of fatty acids in the Framingham Heart Study, Dr. Siguel analyzed the fatty acids of > 600 Framingham subjects. He also analyzed the fatty acid profiles of hundreds of other research subjects and patients, and characterized EFA status in humans.

Dr. Siguel's expertise in fatty acids is internationally recognized. He has given lectures to major medical centers (Harvard's Nutrition Dept, Tufts' Nutrition Center, Mass. General Hospital, Brigham & Women's Hospital, Boston Med. Center, etc.), HMOs, corporations, government agencies (NIH, Canadian Govt), industry trade shows (Natural Products Expo East & West, NNFA), and national and international conferences. He is planning a post-graduate seminar on fat, immunology, GI disorders, and CAD at ASPEN '99.

Background. Dr. Siguel described the pillars that lay the foundation for the diagnosis and treatment of fatty acid abnormalities: (a) human desaturase enzymes (which form double bonds) have preferences $\omega 3 > \omega 6 > \omega 9 > \omega 7$; (b) increased blood (or tissue) levels of 16:1 $\omega 7$ or 20:3 $\omega 9$ indicate PUFA deficiency in some cells (he established reference ranges and showed that it is possible to have normal PUFA levels in some tissues and deficiencies in others); (c) there are two fundamental types of deficiencies: those caused by absolute low levels of PUFAs in the body, and those caused by imbalances of fatty acids. (In the latter, an excess of one type of fatty acid limits PUFA access to cells. Dr. Siguel calls this the "junk mail" effect: it is frequently caused by excessive calories that lead to excessive SFA and MUFA in blood, which limits the transport of PUFAs.); (d) PUFA metabolism is a key determinant of lipoprotein metabolism. This finding lead to a radically new classification of lipoprotein abnormalities (instead of classifying lipoprotein abnormalities by density, we should classify them by metabolic defects, such as PUFA abnormalities); (e) PUFA levels are probably the single most significant nutritional determinant of TC/HDL.

Dr. Siguel characterized the fatty acid abnormalities in CAD (disorders of excessive fat) and malabsorption (disorders of too little fat) as prototypes for other conditions. He described a new type of fatty acid imbalance associated with conditions such as diabetes and neurological disease. His findings allow us to design healthier foods more effectively, by allowing us to determine whether the foods produce desirable biochemical changes. We can use diet to modify fatty acid body composition and thus alter membranes and cell metabolism, or improve our immune systems to better attack cancer and infectious organisms. Other applications include improving IQ, increasing longevity, identifying the nutritional needs of endangered animals, etc.

What implication do these values have for dietary recommendations?

Because human enzymes have the preference $\omega 3 > \omega 6$, most $\omega 3$ in blood is in the form of $\omega 3$ children or derivatives (i.e., DHA), while most $\omega 6$ in blood is in the form of the $\omega 6$ parent or precursor (linoleic acid). There is 10x more $\omega 6$ than $\omega 3$ (in %) in the blood of most Americans. [As a % of total fatty acids in blood, $\omega 6 = \sim 40\text{-}50\%$, $\omega 3 = 3\text{-}6\%$]. These are rough values; for different percentiles in humans, see Dr. Siguel's book "EFAs in Health and Disease."

With rare exceptions, most people can make all the essential fats they need from linoleic acid (**LA**) and linolenic acid (**ALA**) (i.e., from eating essential fats available in vegetables). This means that most people have the enzymes to convert LA and ALA to the EF derivatives such as GLA, EPA, DHA, and others and can live on vegetarian diets. Many people spend considerable money on GLA (from evening primrose or borage oil) and EPA + DHA (from fish oils). However, except for specific conditions, similar results can be achieved with cheaper and more stable oils, such as soybean or flax seed oil. However, there are many exceptions which I will discuss in 1999.

Dr Siguel, how did you become interested in EFAs?

I worked on health care delivery systems (HMOs, drug abuse, health planning), and realized that most health problems are worsened by lifestyle. I helped develop a mathematical model of phase transitions (changes in fluidity) of polymers similar to the changes in fluidity that occur in membranes. Looking for a common factor in acquired disorders, I realized that optimal *body* function requires optimal *cell* function. Optimal *cell* function relies on optimal *membrane* function. Membrane fluidity determines what gets in and out of cells. Fat composition is a critical determinant of membrane fluidity. In western societies, dietary intake and body stores of fat are often suboptimal. Thus, I proposed that suboptimal fatty acid composition was a major contributing factor to acquired diseases.

Did anyone have similar ideas?

A few. Dr. Sinclair, a prominent British scientist, proposed that EFA deficiency (**EFAD**) was a major factor in acquired western diseases [Sinclair, HM. Essential Fatty Acids in Perspective. *Hum Nutr: Clin Nutr* 1984; 38(4): 245-260]. Unfortunately, his theory was discarded because it conflicted with existing data. Cardiovascular diseases (**CVDs**, hypertension, stroke, CAD, abnormal lipids) are the most prevalent disorders in the US. Thus, if these disorders were due to EFAD, most Americans would be EFAD. However, blood tests found EFAD only in very rare cases, such as in very sick patients with severe fat malabsorption fed intravenously without fat. It was estimated that < 1/10,000 people had EFAD. Therefore, EFAD was ignored as a cause of CVD and was not mentioned in medical textbooks (my med. school training did not address EFA abnormalities).

What did you do?

In the 1970s, I decided that EFA abnormalities *must* be the major factor in acquired CVD, and that the measures of EFAD therefore had to be wrong. I sought to invent a better test for EFAD.

At that time, a common test for EFAD was the T/T ratio (=trienoic to tetraenoic or 20:3 ω 9/20:4 ω 6 or Mead/ Arachidonic acid ratio). [Dr. R. Holman, who also coined the " ω " description and did fundamental research on EFAs, invented the T/T ratio]. With EFAD, biochemical pathways shift to produce ω 9 derivatives, so 20:3 ω 9 increases while 20:4 ω 6 declines. It was believed that a T/T >0.4 (and, by the 1980's, a T/T >0.2) indicated EFAD. [These are still the values presented in medical and nutrition textbooks and used in many research studies (see Siguel E. Diagnosing Essential Fatty Acid Deficiency. *Circulation*, Jun 30 1998; 97(25): 2580-2583.)]

I decided that the reason EFAD was rarely found was that *the tests were not sensitive and specific enough*. If you could only detect Total Cholesterol (TC) > 1,000, you would find that everybody had "normal" TC and that there was no relationship between TC and CAD. So I created a new test for EFAD.

What did you find?

Using new methods I invented, I found that healthy people have T/T < 0.025. My method better separates fats in blood. While previous researchers found ~ 50 fats, I found ~ 200. Thus, my methods are more specific and more sensitive. I also found that most patients with CAD or GI malabsorption have EFAD or EFA abnormalities; more than 25% of adult Americans are deficient in w6s; and more than 50% of adult Americans are deficient in w3s. My methods showed that many people > 40 y.o. have accumulated complex EFA imbalances that require very sophisticated blood testing and special diets to correct. I showed that levels of PUFAs are probably the *most significant nutritional factor* in elevated TC/HDLC, CAD, Crohn's disease, neurological disorders, and other conditions.

What else did you find?

Consistent with cell studies by Dr. Brenner (see *Inform*, AOCS, July '98, p.74), I found that the FA elongation enzymes have these preferences in the body: w3> w6> w9> w7. My findings are used to diagnose EFA abnormalities and to prescribe optimal fat mixtures: a new strategy to prevent or treat premature heart disease or abnormal brain function (and thus prolong life).

Did you achieve recognition for these findings?

Ironically, news media and scientists still poorly understand my major scientific discoveries. Instead, *Time* magazine and newspapers across the US made me (in)famous for proposing that low fat diets can be harmful for many people. When I wrote in the *Am. J Clinical Nutr* that eating low fat diets in accordance with the USDA Food Pyramid was counterproductive and could cause heart disease, practically everybody considered my ideas ridiculous (in '94, *Time* called them "controversial" and cited well-known scientists who disagreed with me). (Read my articles to understand the basis for statements reporting the dangers of low fat diets, how low-fat diets plunge HDL and increase TGs, or the lack of w3s in the diet.) Now it seems that everybody repeats my ideas.

Do you have new developments?

I finished developing a new classification of fatty acid abnormalities for patients with CAD and GI malabsorption (known as the relative/absolute deficiency/insufficiency states). Each state requires a different treatment approach. I explained how people could have too much fat and be EFAD, a paradox that evaded other researchers and explains why some people improve with existing treatment while others don't.

I am developing a new classification of related disorders for patients with diabetes. My findings explain the atherosclerotic complications of diabetes and open the door to radically different nutrition treatments for diabetes, hypertension, and obesity. I am working on a new laboratory test and improved treatment for premature CAD and severely abnormal lipids. I hope to design "functional foods" to treat these conditions.

I disagree with the NIH/AHA Step I and II diets and with most current nutritional treatments for CAD and abnormal lipids. I disagree with current nutrition treatments for diabetes as proposed by the ADA. I disagree with "best sellers" such as "The Zone" and the Ornish program (my exchange of letters with Dr. Ornish was published in *JAMA*). I created the concept of an *inverse U-shape* for benefits from antioxidants: too little and we oxidize needed parts, too much and we can't protect against cancer and foreign invaders.

I disagree with Dr. Willett and some of his colleagues at the Harvard Nutrition Dept (I lectured to them about *trans* fatty acids and EFAs)-- I consider diets high in MUFAs to be counterproductive. I consider many current nutritional programs for mothers and children more harmful than good (no wonder obesity and cardiovascular disease are increasing among children!).

I am working on optimal doses for fish oils (at some levels they improve the immune system while at different doses they reduce immune function). Although I discovered an undesirable link between *TFAs*, lipids, and cardiovascular disease, for reasons I will soon publish, *TFAs* are a minor part of the picture. The keys to treating CAD are identifying complex variations in fatty acid metabolism caused by genes and diet, and changing fatty acid status to optimize longevity.

What are the most common misinterpretations of fatty acid metabolism?

Some people read my research superficially and misunderstand my findings. Some authors believe that eating too much $\omega 6$ interferes dramatically with the formation of $\omega 3$ derivatives from ALA. We studied adults with a wide range of $\omega 6$ values and health conditions (healthy and very ill). Except for a few rare exceptions, everyone converted practically all their ALA to long chain $\omega 3$ s. We found that excessive amounts of $\omega 6$ s may slightly reduce formation of $\omega 3$ derivatives, and can substantially reduce the levels of $\omega 3$ s in cells.

Some scientists claim that Americans eat too many $\omega 6$ s. This may be true for some people, but most Americans eat so many calories that if they ate fewer $\omega 6$ s they would become relatively deficient. The solution, of course, is to eat far fewer calories and eat more $\omega 3$ s. But cutting $\omega 6$ s without cutting calories is counterproductive and can contribute to hypertension and diabetes.

My data indicates that >25% of Americans are $\omega 6$ deficient. Some are eating so many processed carbohydrates that they do not get enough $\omega 6$ s. However, most people who are $\omega 6$ deficient are also $\omega 3$ deficient (many with adequate levels of $\omega 6$ s are $\omega 3$ deficient). This need for more $\omega 3$ s have let many authors to recommend that people eat more $\omega 3$ s. However, there are dangers of eating too many $\omega 3$ s.

Unfortunately, many patients are treated with the wrong mixtures of fatty acids. A few companies have created mixtures they call "optimal" containing ALA, LA and perhaps GLA, EPA, and DHA. I do not find any credible scientific basis for those mixtures (one even contains MCT, medium chain triglycerides, as if Americans needed more empty calories from saturated fats!). Optimal mixtures depend on *individual* health condition and PUFA status. For most people, eating a mixture of natural foods and losing weight is the best (and cheapest) treatment.