EZTREK™

Novel Neuropathy Treatment

- The Problem
- EZTREK™ Explained
- How EZTREK™ Works

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The Problem: Diabetic Neuropathy

Patient Statistics

10% of Americans have diabetes and the number is increasing by 5% each year[1]

- 34 million Americans
- 88 million American adults — approximately 1 in 3 have prediabetes

50% - 66% of diabetic adults, during their lifetime, suffer Peripheral Neuropathy — associated with: substantial morbidity including pain, foot ulcers, and lower limb amputation[2]

95% of all diabetics have evidence of nerve damage[3,4]

20% -30% of diabetic adults suffer Autonomic Neuropathy (DAN) — including: instability of cardiac rhythm and blood pressure, loss of normal control of the gastro-intestine tract, impacted control of the bladder, and impotence[5]

Both *somatic* (sensory) nerves and *autonomic* nerves can be affected:

- <u>Somatic polyneuropathies</u> include: loss of sensation, weakness, paraesthesia ("pins and needles") and pain.

- <u>Autonomic neuropathies</u> include: instability of cardiac rhythm and blood pressure, loss of normal control of the gastro-intestine tract, impacted control of the bladder, and impotence.

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[2] Hicks, CW, Selvin, E, "Epidemiology of Peripheral Neuropathy and Lower Extremity Disease in Diabetes," *Curr Diab Rep*.; 19(10): 86. doi:10.1007/s11892-019-1212-8; Pirart J., "Diabetes mellitus and its degenerative complications: a prospective study of 4400 patients observed between 1947 and 1973," *Diabetes Care* 1978; 1(3): 168-183; Wu, J, et al., "PGE_1 improves diabetic peripheral neuropathy in patients with type 2 Diabetes," *Prostaglandins & Other Lipid Mediators* 126 (2016) 24-28.
[3] Dyck PJ, Thomas PK, Asbury AK et al (eds). Diabetic Neuropathy. Saunders, Philadelphia, 1987.
[4] Andreani D, et al., (eds). Diabetic Complications: Early Diagnosis and Treatment. John Wiley, Chichester, 1987.
[5] Vinik, AI, et al., "Diabetic Autonomic Neuropathy," *Diabetes Care* 26:1553–1579, 2003.

EZTREK™— The New Patented Medical Food
Treating Diabetic Neuropathy & Its Complications

It is well documented that diabetic patients have *impaired delta-6 desaturase (D6D) metabolic pathways* from impaired insulin production.[1,2,3] In particular, this metabolic defect causes a poor anti-inflammatory response in Type I patients. Even with insulin therapy, the pathway is still deficient.[4] Type II patients also have *significant impairment of D6D activity*.[5] This deficiency directly decreases PGE_1 output. PGE_1 is both a powerful anti-inflammatory and vasodilator.

PGE_1 is critical to expedited DFU healing. Diabetic patients may possess only 42% of PGE_1's binding functionality — a 58% decrease compared with normal, non-diabetic patients.[6] Steroids (glucocorticoids) further impair the Δ-6 desaturase pathway.[1,7] NASIDs also impede the Δ-6 desaturase pathway.[8] During hypoglycemic episodes, the hormone glucagon is produced, further impeding the Δ-6 desaturase pathway (by means of cAMP).[1,9]

Even with good blood glucose control, endocrinologists may still see patients with severe neuropathy — controlling blood sugars alone is often insufficient.[10]

Improvement in cardiovascular and microvascular blood flow, and oxygenation to the nerve is required for optimum results in treating diabetic neuropathy.[10]

PGE_1 compensates for impaired Δ-6 desaturase deficiency and uniquely addresses underlying etiology — simultaneously optimizing multiple metabolic pathways, including:

1. The Δ-6 desaturase metabolic pathway favors the omega-3 series. Alpha-linolenic acid is important for tissue structure and support. However, PGE_1 is produced exclusively from

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[1] Brenner, RR, "Hormonal modulation of Δ-6 and Δ-5 desaturases: case of diabetes," *Prostaglandins, Leukotrienes, and Essential Fatty Acids*, 68 (2003), 151-162.
[2] Das, UN, "Essential fatty acids: biochemistry, physiology and pathology," *Biotechn*., 2006, 1, 420-439.
[3] Mikhailidis DP, et al., "The effect of dihomogammalinolenic acid on platelet aggregation and prostaglandin release, erythrocyte membrane fatty acids and serum lipids: Evidence and defects in PGE_1 synthesis, and Δ5-desaturase activity in insulin-dependent diabetics," *Diabetes Research* (1986), 3, 7-12.
[4] Brown JE, Lindsay RM, Riemersma RA, "Linoleic acid metabolism in the spontaneously diabetic rat: Δ-6 desaturase activity vs. product/precursor ratios," *Lipids*. 2000 Dec;35(12):1319-23.
[5] Huang M, et al., "FADS Gene Polymorphisms, Fatty Acid Desaturase Activities, and HDL-C in Type 2 Diabetes," *Int. J. Environ. Res. Public Health*, 2017, 14, 572; Horrobin, DF, "Essential fatty acids in the management of impaired nerve function in diabetes," *Diabetes*, Vol 45, Suppl 2, Sept. 1997, pages S90-S93.
[6] Dutta-Roy, Asim, "Effect of Evening Primrose Oil Feeding on Erythrocyte Membrane Properties in Diabetes Mellitus," Omega-6 Essential Fatty Acids: Pathophysiology and Roles in Clinical Medicine, Wiley-Liss, NY, 1990, pages 505-511.
[7] Brenner, RR, "Nutritional and hormonal factors influencing desaturase of essential fatty acids," *Prog Lipid Res.*, 1981;20:41-7.
[8] Horrobin, DF, "Essential fatty acids in the management of impaired nerve function in diabetes," *Diabetes*, Vol 45, Suppl 2, Sept. 1997, pages S90-S93.
[9] De Gomez Drumm, IT, de Alaniz, MT, Brenner, RR, "Effects of glucagon and dibutyryl adenosine 3'5'-cyclic monophosphate on oxidative desaturase of fatty acids in the rat," *J. Lipids Res*., 16 (1975), 264-268.
[10] Jamal GA. Pathogenesis of diabetic neuropathy: the role of the n-6 essential fatty acids and their eicosanoid derivatives. *Diabetic Med* 1990; 7: 574-579; Hong, L, et al., "Clinical efficacy of different doses of lipo-prostaglandin E1 in the treatment of painful diabetic peripheral neuropathy," *Journal of diabetes and its complications* 29 (2015) 1283–1286.

the omega-6 series. **EZTREK™** solves this issue by specific calibration of both omega-6 / -3 series and with specific modulation of their long-chain metabolites.[1,2,1,2]

2. **EZTREK™** further enhances patients' production of PGE_1 — by calibration of gamma-linolenic acid with docosahexaenoic acid — significantly decreasing inflammatory symptoms of neuropathy.[3] "PGE_1 can reactivate Na(+)-K(+)-ATPase at the surfaces of nerve cells, improve neuronal metabolism and inhibit oxidation of the plasma membrane of a cell, all of which contribute to the improvements of DPN."[4]

3. Myelin is comprised of lipids.[5] Polyunsaturated fatty acids of the n-6 series also form key structural components of the neuronal cell membrane, membrane-bound enzymes and myelin.[1] The **EZTREK™** formulation maximizes nerve healing.

4. Diabetic patients frequently consume (processed) foods that decrease the most fundamental substrate precursor of PGE_1 — functional linoleic acid.[6,7,8] Furthermore, the important cellular unfolded protein response (UPR) in secretory cells, such as the pancreas, is activated not only by unfolded proteins, but also by aberrant lipid composition (induced by the diet) of the ER membrane referred to as lipid bilayer stress. This response can trigger long-term stress (chronic inflammation). **EZTREK™ calibrated EFA / eicosanoid modulating ratios are formulated to compensate for this and other obstacles that may impede the Δ-6 desaturase pathway**.[9]

5. "This effect [from PGE_1] might *prevent nerve tissue ischemia*… and *ameliorate nerve function* — by *increasing oxygen delivery*…."[10] **EZTREK™ is designed for maximum cellular oxygenation.**[11]

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[1] Brenner, RR, "Inhibitory effect of docosa-4,7,10,13,16,19-hexaenoic acid upon the oxidative desaturation of linoleic into gamma-linolenic acid and of alpha-linolenic into octadeca-6,9,12,15-tetraenoic acid," *Biochim. Biophys. Acta*., 137 (1967), 184-186.

[2] Cho, HP, Nakamura, MT, Clarke, SD, "Cloning expression and regulation of human Δ-5 desaturase," *J. Biol. Chem*, 274 (1999), 37335-37339.

[3] Jamal, GA & Carmichael, H, "The effect of γ-linolenic acid on human diabetic peripheral neuropathy: A double-blind placebo controlled trial," *Diabetic medicine: journal of the British Diabetic Association*. Vol.7 (4), 1990: 319-323; Brenner, RR, "Nutritional and hormonal factors influencing desaturase of essential fatty acids," *Prog Lipid Res*., 1981;20:41-7.

[4] Jang, D, et al., "Prostaglandin E1 plus methylcobalamin combination therapy versus prostaglandin E1 monotherapy for patients with diabetic peripheral neuropathy: A meta-analysis of randomized controlled trials," *Medicine* (2018) 97:44, pages 1-8.

[5] Trapp, BD & Bernsohn, J, "Essential fatty acid deficiency and CNS myelin. Biochemical and morphological observations," *J Neurol Sci*. 1978 Jul;37(3):249-66.

[6] Brenner, RR, "Hormonal modulation of Δ-6 and Δ-5 desaturases: case of diabetes," *Prostaglandins, Leukotrienes, and Essential Fatty Acids*, 68 (2003), 151-162.

[7] Das, UN, "Essential fatty acids: biochemistry, physiology and pathology," *Biotechn.,* 2006, 1, 420-439.

[8] Anton, SD, et al., "Differential effects of adulterated versus unadulterated forms of linoleic acid on cardiovascular health," *J Integr Med*, 2013; 11(1):2–10.

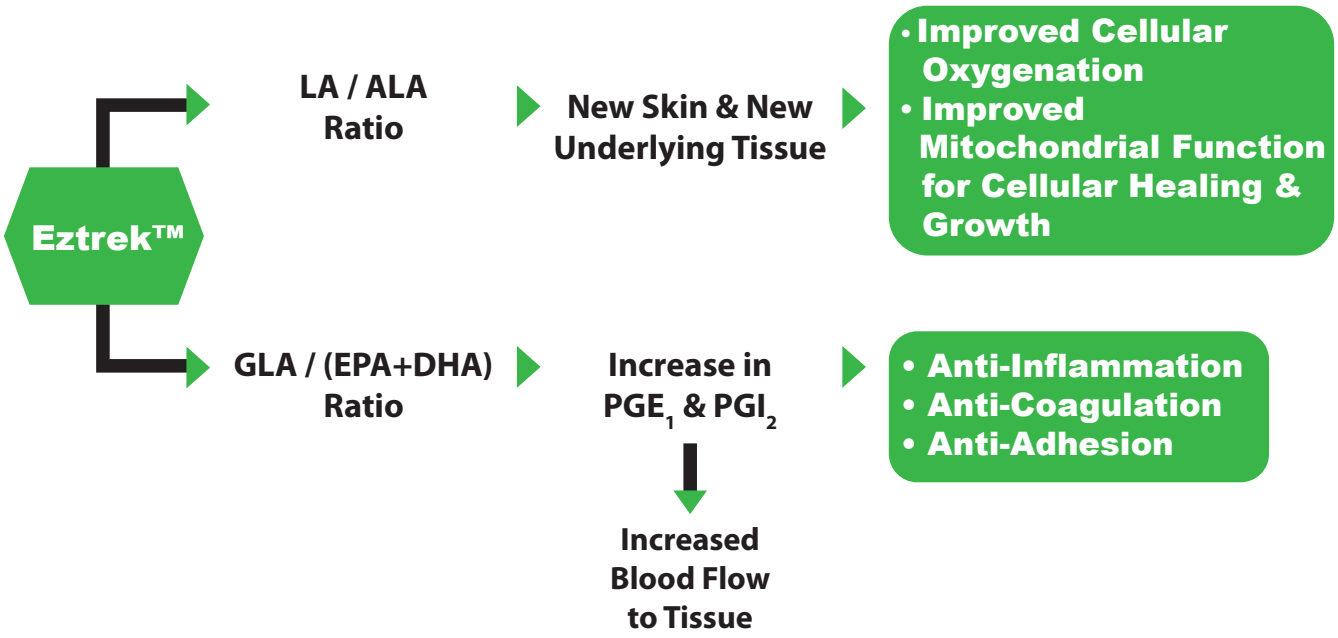
[9] Kristina Halbleib, et al., "Activation of the Unfolded Protein Response by Lipid Bilayer Stress," *Molecular Cell* (2017); "Molecular biologists discover an active role of membrane lipids in health and disease," August 4, 2017 https://phys.org /news/2017-08-molecular-biologists-role-membrane-lipids.html

[10] Okuda, Y, et al., "Hemodynamic Effects of Lipo-PGE_1 on Peripheral Artery in Patients with Diabetic Neuropathy: Evaluated by Two-Dimensional Color Doppler Echography," *Diabetes Research* (1993);22(2): 87- 95. ["The present study shows *PGE_1 increase both the vascular size and blood flow (*significantly *increasing from cross- sectional area of 2.6 ± 0.2 to 3.5 ± 0.2 mm^2; the adoralis artery blood flow index significantly increased from 4 0 ± 7 to 60 ± 11) in the a. doralis pedis.*"].

[11] Campbell, IM, et al., "Abnormal fatty acid composition and impaired oxygen supply in cystic fibrosis patients," *Pediatrics* 1976; 57: 480–486.

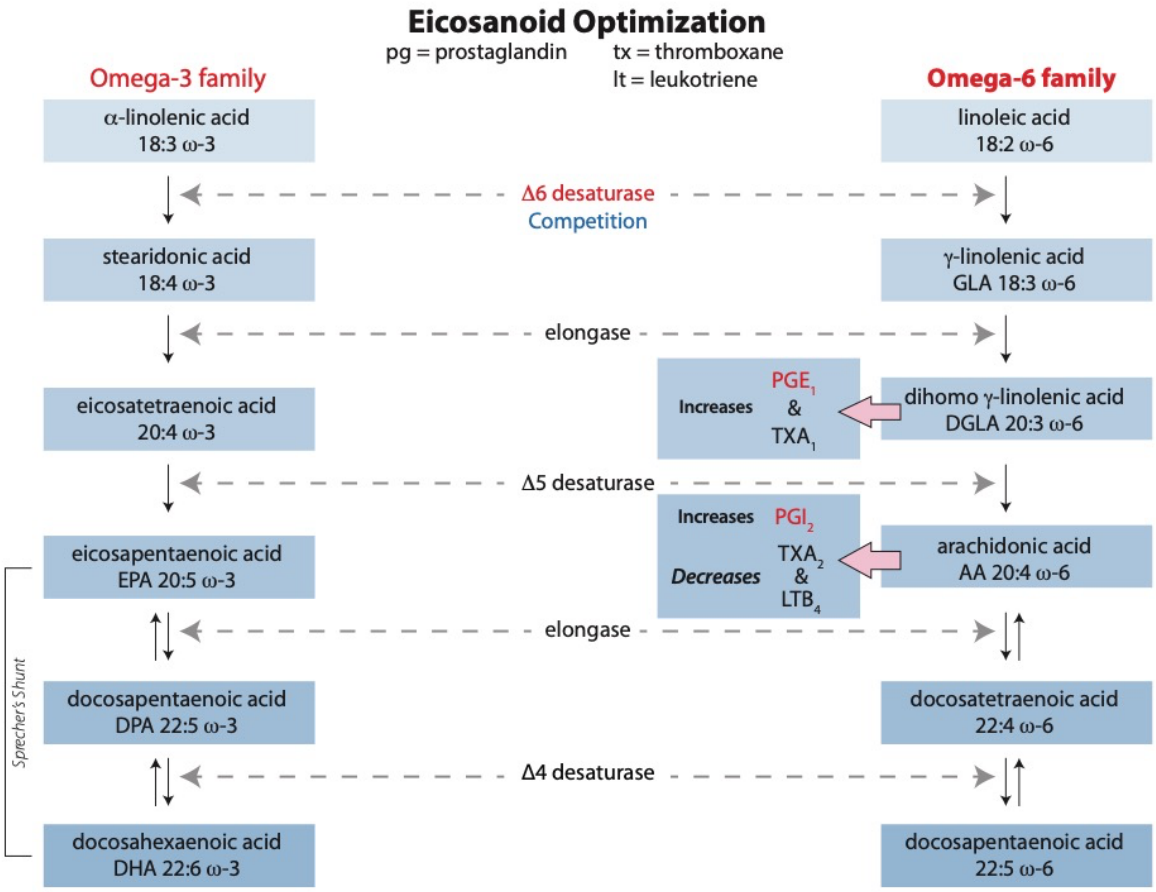
How EZTREK™ Works
Uniquely Treating Diabetic Neuropathy

Utilizing Novel Mechanisms of Action



Lipids are the #1 (Modifiable) Variable in Tissue Composition with Potential to Impact Healing.[1,2]

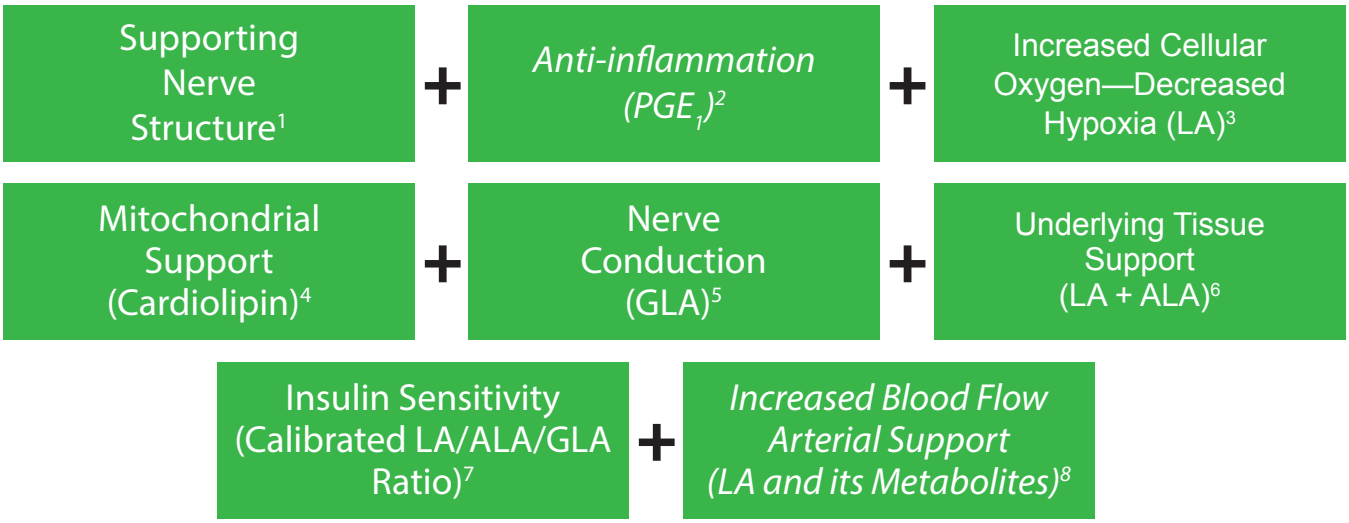
[1] E. Wainwright, Y. S. Huang, et al., "The effects of dietary n-3/n-6 ratio on brain development in the mouse: a dose response study with long-chain n-3 fatty acids," Lipids, vol. 27, no. 2, pp. 98–103, 1992; W. E. M. Lands, et al., "Quantitative effects of dietary polyunsaturated fats on the composition of fatty acids in rat tissues," *Lipids*, vol. 25, no. 9, pp. 505–516, 1990.
[2] C.V. Felton, et al., "Relation of Plaque Lipid Composition and Morphology to the Stability of Human Aortic Plaques," *Arteriosclerosis, Thrombosis, and Vascular Biology*," Vol. 17, No. 7, 1997, pp. 1337-1345.



"…Motor nerve conduction velocities of peroneal, median, and ulnar nerves all significantly improved in PGE_1 group …. Similarly, sensory nerve conduction velocity of sural and ulnar nerves showed a significant improvement after PGE_1 treatment. Microvascular dysfunction causes regional ischemia and oxygen deficiency in nerves, and impair blood-nerve barrier, which eventually results in neural edema and dystrophy and nerve degeneration. Studies have demonstrated that PGE_1 can limit injury by regulating blood flow, normalizing nitric oxide and superoxide release, limiting inflammation by reducing leukocyte infiltration, reducing circulating plasma endothelin-1 (ET-1) level, and inhibiting proinflammatory cytokine production." (Wu, J, et al., "PGE_1 improves diabetic peripheral neuropathy in patients with type 2 Diabetes," Prostaglandins & other Lipid Mediators 126 (2016) 24–28).

EZTREK™, the new patented Medical Food — specifically and uniquely formulated for the diabetic population. Positively impacts multiple metabolic pathways simultaneously. EZTREK™ distinctively compensates for impaired Δ-6 desaturase functionality — increasing PGE_1 output to expedite neuropathic healing.

Metabolic Pathways Required For Optimal Neuropathic Improvement



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[1] Jamal, GA & Carmichael, H, "The effect of γ-linolenic acid on human diabetic peripheral neuropathy: A double-blind placebo-controlled trial," Diabetic medicine: journal of the *British Diabetic Association*. Vol.7 (4), 1990: 319-323; Brenner, RR, "Nutritional and hormonal factors influencing desaturase of essential fatty acids," *Prog Lipid Res*., 1981;20:41-7. Jamal, GA. "Pathogenesis of diabetic neuropathy: the role of the n-6 essential fatty acids and their eicosanoid derivatives." *Diabetic Med* 1990; 7: 574-579.

[2] Libby P. "Inflammation in atherosclerosis." *Nature*. 2002 Dec 19–26;420(6917):868–874.

[3] Guo S, DiPietro LA. "Factors affecting wound healing." *J Dent Res*. 2010;89(3):219–229.

[4] Peskin BS. "Cancer and mitochondrial defects: New 21st century research," *Townsend Letter*, August/September 2009:87–90; Murray RK et al. Harper's Illustrated Biochemistry. 26th ed. New York: McGraw-Hill; 2003:97; Guyton AC, Hall JE. Textbook of Medical Physiology. 9th ed. W.B. Saunders Co.; 1996:16,861–862; Krebs, JJ, Hauser H, Carafoli E, "Asymmetric distribution of phospholipids in the inner membrane of beef heart mitochondria." *J Biol Chem.* 1979;254:5308–5316; Zhang M et al. "Gluing the respiratory chain together: cardiolipin is required for supercomplex formation in the inner mitochondrial membrane." *J Biol Chem*. 2002;277:43553–43556.

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[6] Alberts B et al. Molecular Biology of the Cell. 3rd ed. Garland Science; 1994:428.

[7] Asp ML et al. "Time-dependent effects of safflower oil [LA] to improve glycemia, inflammation and blood lipids in obese, post-menopausal women with type 2 diabetes: A randomized, double-masked, crossover study." *Clin Nutr.* 2011 Aug;30(4):443–449.; Kahleova H et al. "Vegetarian diet-induced increase in linoleic acid [LA] in serum phospholipids is associated with improved insulin sensitivity in subjects with type 2 diabetes." *Nutr Diabetes* 2013;3(6)e 75; Dutta-Roy A. "Effect of evening primrose oil feeding on erythrocyte membrane properties in diabetes mellitus." In: Horrobin D, ed. Omega-6 Essential Fatty Acids: Pathophysiology and Roles in Clinical Medicine. New York: Wiley-Liss; 1990:505–511; Ray TK, Dutta-Roy AK, Sinha AK, "Regulation of insulin receptor activity of human erythrocyte membrane by prostaglandin E1," *Biochim Biophys* Acta. 1986; 856(3):421-427.

[8] Das UN. "A defect in the activity of Δ-6 and D5 desaturases may be a factor in the initiation and progression of atherosclerosis." *Prostaglandins Leukot Essent Fatty Acids.* 2007;76(5):251–268; "'[O]mega-6 PUFAs also have powerful anti-inflammatory properties that counteract any proinflammatory activity,' say the advisory authors. 'It's incorrect to view the omega-6 fatty acids as 'proinflammatory.'" Ref.: Farvid MS et al. "Dietary linoleic acid [LA — Parent omega-6] and risk of coronary heart disease: a systematic review and meta-analysis of prospective cohort studies." *Circulation*. 2014;130:1568–1578; Terano T et al. "Effect of oral administration of highly purified eicosapentaenoic acid on platelet function, blood viscosity and red cell deformability in healthy human subjects." *Atherosclerosis*. 1983;46:321–331: Weiss, C., et al., "Hemostasis and fibrinolysis in patients with intermittent claudication: effects of prostaglandin E1," *Prostaglandins, Leukotrienes and Essential Fatty Acids*, Nov. 2000; 63(5):271–277; Lazaro, I, et al., "Linoleic Acid Status in Cell Membranes Inversely Relates to the Prevalence of Symptomatic Carotid Artery Disease," Stroke. 2021;52:703–706.