

Phospholipids: Versatile Nutraceuticals for Functional Foods

Parris M. Kidd, PhD

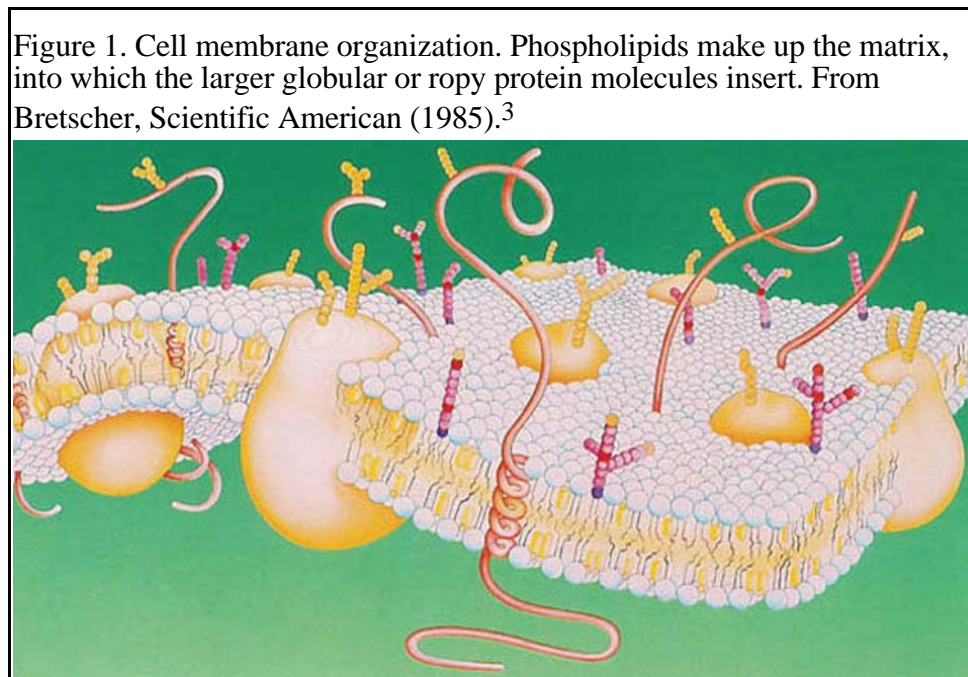
For more, in-depth information on phospholipids, go to
www.phospholipidsonline.com

The phospholipids (pronounced *fos-fo-lipi-ids*) are prime building blocks of life.¹ They are found in humans, all animals, plants, and the simplest life forms. Some phospholipids are most likely conditionally essential nutrients: for their *in vivo* synthesis multiple enzymes and cofactors are required. Dietary phospholipid intake has declined, mainly due to increased food refining and processing. Phospholipid mixtures (“lecithin”) were among the first health foods, and more sophisticated preparations have emerged as versatile nutraceuticals and functional food constituents.

Phospholipids are orthomolecules—“molecules orthodox to the body”, as defined by the late Nobel biochemist Linus Pauling.² Phospholipids have a unique molecular organization that probably rendered them integral to life since its very beginning.

The phospholipid molecule is charged at one end and uncharged at the other (amphipathic). This endows phospholipids with emulsifying, wetting, and self-assembly properties, all of which are successfully employed in the human body design. Self-assembly generates the membranes which all cells require for their essential functions. These three-dimensional, sheet-like molecular assemblies consist mostly of catalytic proteins built into a continuous matrix assembled from phospholipids (Fig. 1).³

The human body uses phospholipids as emulsifiers (in the bile digestive fluid) and as surface-active wetting agents (in the lungs, intestines, and kidneys for example). Phospholipids are also used to assemble the circulating lipoproteins (LDL and HDL) that transport fat-soluble nutrients around the body.

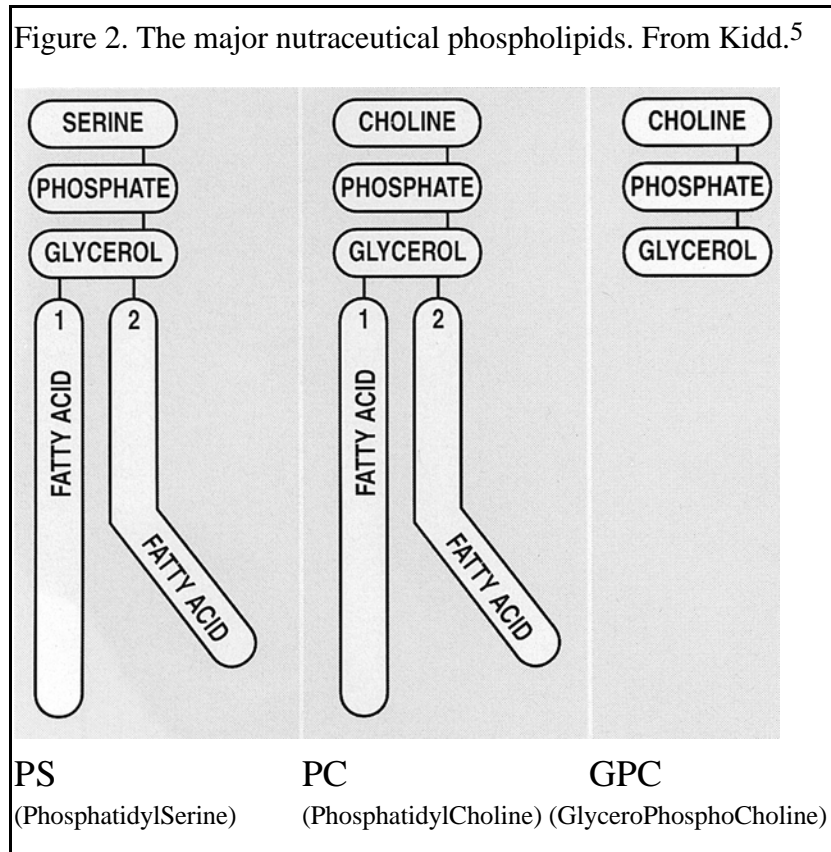


The phospholipid story began with lecithin, named from “lekithos”, the Greek name for egg-yolk, by M. Gobley when he isolated it from eggs around 1847.⁴ But egg lecithin was much too expensive for industrial use, and serious commercial application had to await production from the lowly soybean.

Commercial soybean lecithin was first prepared in Germany in the 1920s, and quickly became one of the earliest “health foods”. Nowadays lecithin is utilized widely in the food industry as an emulsifier, wetting agent for food instantizing, flow agent for chocolate manufacture, baking stabilizer and pan release slip agent, flour improver, and animal feed additive.

Industrially, lecithins are initially prepared as an oily crude derived from the oil degumming process following the soybean crush. Using selective solvent extraction, the less water-miscible, oily components (mostly triglycerides) are first removed. The resulting oil-free, “deoiled” lecithin, enriched in phospholipids, can then be further processed to enrich selected phospholipids in the mixture. These are the raw material bases for the commercially available, nutraceutical phospholipid formulations.

Chemically, the term “phospholipid” relates to the fact that these molecules contain phosphorus. They are polar (charged) lipids, insoluble in acetone but soluble in polar solvents such as ethyl alcohol. Hundreds of different phospholipids exist, but currently the nutraceutical phospholipids all come from one class: the glycerophospholipids. These major nutraceutical phospholipids are shown in Fig. 2.



PS (PhosphatidylSerine)

PS (PhosphatidylSerine, pronounced *fos-fa-tie-dil-see-reen*), has been extensively researched. Its efficacy is established through 20 double-blind trials. During the 1990s two definitive USA trials were conducted by memory pioneer Thomas Crook and colleagues.^{6,7} The past two years have seen two new United Kingdom trials.^{8,9} Altogether, the controlled trials with PS unequivocally establish its benefits for higher brain functions such as memory, learning and word recall; mood elevation; and coping with stress.¹

Initial research with PS utilized preparations laboriously extracted from bovine brains. With the advent of Mad Cow disease this source became commercially nonviable and a soy source was developed. Subsequently, several double-blind trials

have validated this plant-source PS.^{1,10} The soy material differs from the bovine source in fatty acid tail profile, but this is not biologically important since the tails are shuffled *in vivo* by acyltransferase enzymes, according to local requirements. Thus brain PS tail profile differs from testis PS, for example. Notwithstanding, in the brain PS carrying DHA (docosahexaenoic acid) is likely crucial for brain function.¹¹

The bulk of the controlled clinical research with PS involved subjects aged fifty or older. From his landmark double-blind trial on over-50 subjects with age-related cognitive decline, Crook concluded that for a subgroup with more severe memory loss, PS could “turn back the clock on aging”.⁶ These and other findings strongly suggest PS has a salutary revitalizing effect on the aging brain.¹

The cumulative findings on PS include benefits for young adults and perhaps even children. One recent double-blind trial indicates soy PS helps young, healthy people cope with the stresses of daily life.⁸ David Benton and his collaborators at the University of Wales recruited 48 young male university students, evaluated them by questionnaire for “neurotic personality”, then randomly divided them between a PS test group (300 mg/day) and a placebo group (given triglycerides). After 30 days of supplementation, the subjects were given a standard acute stress test: a series of hard mental arithmetic calculations, with 4 seconds for each and without a calculator. Those with a higher “neurotic” score experienced significantly less stress from the test if they were taking PS. “Neurotics” who received only the placebo reported a statistically significant level of stress from the test, along with a highly significant worsening of mood, both significantly worse than their counterparts who were on PS.

In a second, related Benton double-blind trial, young male university students made to exercise vigorously on a bicycle were significantly protected against heartbeat elevation by PS (300 mg daily, 30 days).⁹ This finding is consistent with two previous double-blind trials by Monteleone *et al* in Italy, in which PS significantly lowered stress hormone levels in young men subjected to stressful exercise exertion.^{12,13}

PS may also be helpful to children with cognitive and mood problems.¹⁴ C.A. Ryser, MD, consecutively recruited 27 ADHD children (aged 3-19 yrs), with their parents' informed consent. She individualized their ADHD regimens with nutrients and pharmaceuticals, as per her usual practice, then added PS into their treatment

plans. Each received 200 or 300 mg PS daily, depending on body size, for 4 months. Twenty-seven (27) children aged 3-19 years completed the study.

Dr. Ryser found that PS afforded clinically meaningful benefit to 25 of the 27 children. PS improved attention, concentration, learning, and behavior, and benefited academic performance. PS also consistently benefited the depression and anxiety commonly seen in these children, and seemed to extend the benefits experienced from nutritional supplementation with fish oil or primrose oil. Those prescribed Ritalin (methylphenidate) or other pharmaceuticals also seemed to derive additional benefit from PS. No adverse effects or drug interactions were noted, consistent with PS's 20-year record of safe clinical use.

The evident clinical benefit to children from PS in this uncontrolled preliminary study is consistent with its benefits to memory conservation, brain revitalization, and stress management in adult subjects. The physico-chemical characteristics of PS are suited for the conventional dietary supplement dosage forms, and for inclusion in functionalized spreads, powder mixes, cereals, and bars. It is unstable in water solution, and thus poorly suited for beverage applications.

PC (PhosphatidylCholine)

PC (PhosphatidylCholine, pronounced *fos-fa-tie-dil-ko-lean*) used to be called lecithin, being the most abundant single lecithin constituent. Multiple double-blind trials indicate PC is a highly effective nutraceutical for recovery of the liver following toxic or chronic viral damage.¹

The liver is the workhorse organ of the body, and its parenchymal cells depend heavily on membranes to (a) process newly absorbed nutrients, (b) assemble circulating lipoproteins (LDL, HDL, others), (c) detoxify thousands of potentially toxic incoming chemicals. The average human liver has about eight football fields of membrane surface, all of which is vulnerable to toxic or infectious-inflammatory activity. PhosphatidylCholine is the most abundant phospholipid of cell membranes, therefore the most important building block for making replacement membrane mass.

Through its choline headgroup, PC supplies another ingredient for liver regeneration: methyl groups, which support many key metabolic pathways and are necessary for the gene duplication that precedes cell division. These complementary

qualities endow PC with unparalleled importance in liver cell activation, proliferation, maturation and regeneration following damage. Under double-blind trial conditions, PC exhibited potentially lifesaving benefit against pharmaceutical and deathcap mushroom poisoning, alcoholic liver damage, and the hepatitis B virus.¹⁵ In a multicenter, DB trial,¹⁶ 176 patients with chronic viral hepatitis (B or C) were begun on interferon alpha for 24 weeks then randomized to PC (1.8 gms/day) or placebo for 24 weeks. Significantly more patients responded to PC, particularly in the hepatitis C subgroup.

PhosphatidylCholine has exceptional emulsifying properties, on which the liver draws to produce the digestive bile fluid. The lung and intestinal lining cells use PC to make the surfactant coatings essential to their gas and fluid exchange functions. And PC is the predominant building block for the circulating lipoproteins. PC is safe and well tolerated well beyond several grams' daily intake, and is highly cost-affordable for manufacture into functionalized foods of all kinds. However (like PS), PC is not well suited for beverages.

GPC (GlyceroPhosphoCholine), Pro-Phospholipid

GPC (GlyceroPhosphoCholine, pronounced *gli-sero-fos-fo-ko-lean*) is a pro-phospholipid nutrient, lacking the “tails” of membrane phospholipids. Precisely because it lacks these hydrophobic tails, GPC is readily soluble in water and will not produce off-flavors from fatty acid rancidification.

GlyceroPhosphoCholine is readily absorbed by mouth, and appears to be the major metabolic precursor for membrane phospholipids.¹⁷ Enzymes can readily tack fatty acid tails onto GPC, or modify the headgroup to generate other phospholipids. Like the membrane phospholipids PS and PC, GPC has orthomolecular status and is proven safe and well tolerated.

GlyceroPhosphoCholine is metabolically versatile.^{5,18} Once absorbed it readily enters the brain, where it is used to make acetylcholine (ACh). GPC attains high concentrations in mother's milk, being a major source of choline for the developing organs of the newborn child. And GPC helps protect against metabolic fluctuations in ions and charged molecular species.

Being positively charged on one side and negatively charged on the other (zwitterionic), the GPC molecule is an effective osmotic buffer. Its tissue levels

become increased in response heightened osmotic stress.¹⁹ In muscle, GPC levels are linked to contractile activity, and Duchenne muscular dystrophy features markedly lowered GPC.²⁰

GlyceroPhosphoCholine has been evaluated in at least 20 controlled clinical trials. It markedly benefits mental sharpness, in young healthy subjects as well as in the middle aged and elderly.⁵ In two controlled trials conducted by Canal and others in Italy,^{21,22} GPC benefited immediate recall and attention in a group of young adult males (ages 19-38), as compared against a control group given placebo. In middle-aged and elderly subjects it benefited reaction time, improving energy generation and electrical coordination across the brain.^{23,24} In several controlled trials on older subjects with vascular dementia, GPC improved aspects of cognition along with emotional state, confusion, and apathy.²⁵ In other clinical studies involving some 2,500 subjects, GPC accelerated the recovery of subjects afflicted by stroke or other ischemic damage.^{25,26}

Several controlled trials with GPC involved comparisons against other brain nutrients or pharmaceuticals.²⁵ GPC (at 1200 mg by mouth or 1000 mg intramuscularly) tested superior to citicoline (CDP-choline), acetylcarnitine, idebenone, aniracetam, and oxiracetam, on measures of attention, concentration, immediate recall, verbal fluency, and overall mental performance.

As humans reach middle age they produce less than optimal quantities of key hormones from the pituitary, the body's "master gland." In pilot studies GPC seemingly enhanced the pituitary's capacity to respond to hormone releasing stimuli from the brain.²⁷

Another dimension of GPC's importance to brain vitality is its contribution to acetylcholine's transmitter action. This is reflected in GPC's improvement of the EEG (ElectroEncephaloGraphic) profile, seen even in healthy young subjects.²⁸ GPC's pro-ACh action should also benefit brain-muscle and mind-body integration.

GlyceroPhosphoCholine is a clinically remarkable and versatile phospholipid precursor. Important for its protective properties in the water phase, it is also on the main metabolic pathway to PC, which is a key building block for nerve cell membranes. Unlike phospholipid preparations, GPC is stable in water but is limited in the solid phase by being hygroscopic. A chewing gum for mental sharpening

would be possible. GPC's fast access to the human brain and its capacity to sharpen mental performance also suit it well for drink formulations.

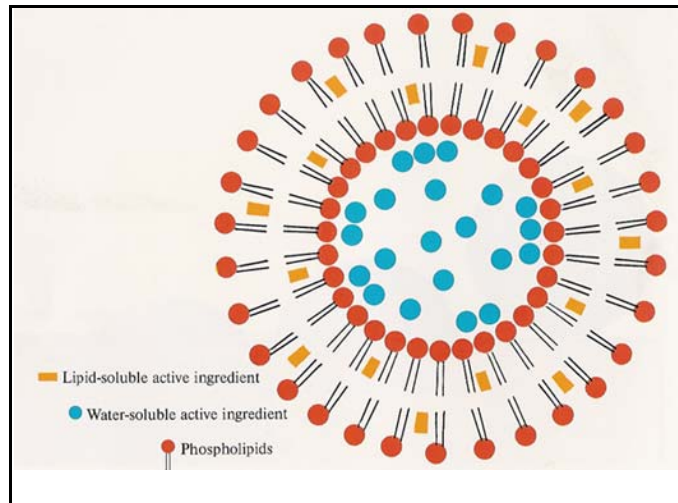
Phospholipid Mixtures Benefit the Circulation

Impaired blood cholesterol regulation continues to be an enormous health issue in Western populations. Mixtures of phospholipids prepared from soy, and containing PC together with smaller amounts of other phospholipids, were proven through twelve (12) double-blind trials to consistently reduce blood cholesterol levels.¹ Soy phospholipid mixtures also can improve blood flow and reduce the risk of clot formation in the circulation.^{29,30} These preparations offer the promise of cost-effective circulatory improvement, and offer the very emulsification, dispersibility, and surfactant characteristics that would enable the preparation of free-flowing and instantized shake mixes, or chewy and sticky health bars.

Phospholipids for Liposomes

Liposome technology came to the fore several decades ago, and in the ensuing years has evolved to become ever more sophisticated. While the lofty promises of liposome targeting of cancer drugs or gene insertion are still under investigation, liposomes may yet prove useful for a modest yet important application. This is to protect biochemically vulnerable nutrients against premature breakdown in the stomach, until they can reach the intestine for absorption. The closed-sphere environment of the liposome is a stabilizing influence against degradation by digestive enzymes or other potentially harmful influences. New technology offers phospholipid concentrates that conveniently generate liposome-encapsulated nutrients simply upon stirring into water.

Figure 3. Molecular organization of a liposome.



The Future of Phospholipid Nutraceuticals

Consistent positive outcomes from double-blind trials, backed by hundreds of clinical studies and thousands of experimental studies, establish PS, PC, GPC and mixed phospholipids' nutraceutical benefits for the brain, liver, and circulation. The nutraceutical phospholipids are extremely well tolerated and pose no toxic threat, consistent with their orthomolecular status. PC's emulsifier and surfactant properties are valuable to homeostasis, and early clinical research indicates PC can be co-administered with aspirin to protect the intestinal lining from the latter's notorious toxicity.³¹

The natural tendency of phospholipids to form ultrafine molecular dispersions in water should be further explored to improve the bioavailability of non-phospholipid nutrients, especially those that are costly and relatively poorly absorbed. Monomolecular nutrient dispersion using phospholipids also will improve the physical characteristics of the phospholipid-nutrient combinations, such that the resulting functionalized product becomes considerably more convenient and effective for the consumer.

This combined phospholipid-nutrient approach is suited to producing chewable tablets, confections, cookies, granulates, spreads, bars, emulsified or purely aqueous-phase beverages, even liquid sprays. Further product value comes from the health benefits of the phospholipids being combined with the benefits of the selected nutrient(s); one prime combination would be phospholipids with omega-3 fatty acids.

Their perfect safety record and well-documented array of health benefits qualify PS, PC, and GPC as first-rate nutraceuticals. Their unique physico-chemical

characteristics make them premier functional food constituents. A wide range of consumers, whether aged, youthful or in ill-health, all stand to benefit from the phospholipids' life-affirming properties.

References

- Kidd PM. Dietary Phospholipids as Anti-Aging Nutraceuticals. In:Klatz RA, Goldman R, eds. *Anti-Aging Medical Therapeutics*, Vol. IV. Chicago, IL:Health Quest Publications;2000:282-300.
- Pauling, L. Orthomolecular psychiatry. *Science* 1968;160:265-271.
- Bretscher MS. The molecules of the cell membrane. *Sci Am* 1985;253:100-108.
- Gobley M. Examen comparatif du jaune d'oeufe et de al matiere cerebrale. *J Pharm Chim* 1847; 11:409.
- Kidd PM. GPC, Nutraceutical breakthrough for mental performance. *Total Health* 2001;23:55-56.
- Crook TH, et al. Effects of phosphatidylserine in age-associated memory impairment. *Neurology* 1991;41:644-649.
- Crook TH, et al. Effects of phosphatidylserine in Alzheimer's disease. *Psychopharmacol Bull* 1992; 28:61-66.
- Benton D, et al. The effects of phosphatidylserine supplementation on mood and heart rate when faced with an acute stressor. *Nutr Neurosci* 2001;4:169-178.
- Kidd PM. Phosphatidylserine (PS) research update:clinical and scientific advances. *Total Health* 2002;24:68-69.
- Crook TH. Adderly BD. *The Memory Cure*. New York, NY: Pocket Books;1998.
- Salem N, Niebylski CD. The nervous system has an absolute molecular species requirement for proper function. *Mol Mem Biol* 1995;12:131-134.
- Monteleone P, et al. Effects of phosphatidylserine on the neuroendocrine response to physical stress in humans. *Neuroendocrinol* 1990;52:243-248.
- Monteleone P, et al. Blunting by chronic phosphatidylserine administration of the stress-induced activation of the hypothalamo-pituitary-adrenal axis in healthy men. *Eur J Clin Pharmacol* 1992;41:385-388.
- Ryser CA, Kidd PM. Manuscript in preparation;2002.
- Kidd PM. Phosphatidylcholine (Monograph). *Alt Med Rev* 2002;7:150-154.
- Niederau C, et al. Polyunsaturated phosphatidylcholine and interferon alpha for treatment of chronic hepatitis B and C:a multicenter, double-blind, placebo-controlled trial. *Hepatogastroenterol* 1998;45:797-804.
- de Moliner P, Abbiati G, Colombo M, et al. Pharmacokinetics of choline alfoscerate in the healthy volunteer. *Le Basi Razionali della Terapia* 1993;23:75-80.
- Schettini G, et al. Molecular mechanisms mediating the effects of L-alpha-glycerylphosphorylcholine. *Pharmacol Biochem Behav* 1992;43:139-151.
- Burg MB. Molecular basis of osmotic regulation. *Am J Physiol* 1995;268:F983-F996.
- Infante JP. Defective synthesis of polyunsaturated phosphatidylcholines as the primary lesion in Duchenne and murine dy muscular dystrophies. *Med Hypoth* 1986;19:113-116.
- Canal N, et al. Effect of L-a-glyceryl-phosphorylcholine on amnesia caused by scopolamine. *Intl J Clin Pharmacol Ther Toxicol* 1991; 29:103-107.
- Canal N, et al. Comparison of the effects of pretreatment with choline alfoscerate, idebenone, aniracetam and placebo on scopolamine-induced amnesia. *Le Basi Razionali della Terapia* 1993; 23:102-107.
- Moglia A, Bergonzoli S, de Moliner P. Effect of aGFC in brain mapping changes in patients with age associated memory impairment (AAMI). *Le Basi Razionali della Terapia*, 1990;20:83-89.
- Sicurella L, et al. Changes in VEP in subjects treated with alphaGFC. Preliminary study. *Le Basi Razionali della Terapia* 1990;20 (3 Suppl. 1):91-93.

25. Parnetti L, Amenta F, Gallai V. Choline alfoscerate in cognitive decline and in acute cerebrovascular disease: an analysis of published clinical data. *Mechs Ageing Development* 2001; 22:2041-2055.
26. Barbagallo Sangiorgi G, et al. Alpha-Glycerophosphocholine in the mental recovery of cerebral ischemic attacks. *Ann NY Acad Sci* 1994;717:253-269.
27. Ceda GP, et al. Alpha-glycerolphosphorylcholine administration increases the GH responses to GHRH of young and elderly subjects. *Horm Metabolic Res* 1991;24:119-21.
28. Locatelli M, et al. Neurophysiological evaluation of aGFC (choline alfoscerate) by means of computerized electroencephalogram (CEEG). *Le Basi Razionali della Terapia* 1990;20:79-82.
29. Schneider J. Experimental and clinical effects of polyenoyl phosphatidylcholine on erythrocytes and platelets. In:Ricci G, et al, ed. *Therapeutic Selectivity and Risk/Benefit Assessment of Hypolipidemic Drugs*. New York, NY:Raven Press;1982:263-268.
30. Schneider J, et al. Influence of essential phospholipids on human platelet aggregability. In: Peeters H, ed. *Phosphatidylcholine*. New York, NY:Springer-Verlag;1976:244-248.
31. Swarm RA, et al. Protective effect of exogenous phospholipid on aspirin-induced gastric mucosal injury. *Am J Surg* 1987;153:48-53.

Dr. Parris Kidd is an internationally recognized nutritional educator who has been researching phospholipids since 1987. For more of his work on phospholipids, go to www.phospholipidsonline.com