Phosphatidylserine:

A remarkable brain cell nutrient Phosphatidylserine, or PS, is a naturally occurring, phospholipid nutrient. PS is essential to the functioning of all the cells of the body, but is most concentrated in the brain. Its relative abundance in this organ reflects its proven involvement in an assortment of nerve cell functions, including nerve transmitter release and synaptic activity. Clinical studies have suggested that PS can support brain functions that tend to decline with age. Until recently, PS was only available from animal sources (brain), and occurred in commercial lecithins only in trace amounts; however, a plant source for PS has now been developed.

Phosphatidylserine (PS or PtdSer) is a phospholipid nutrient found in fish, green leafy vegetables, soyabeans, and rice, and is essential for the normal functioning of neuronal cell membranes, activating protein kinase C (PKC), which has been shown to be involved in memory function.

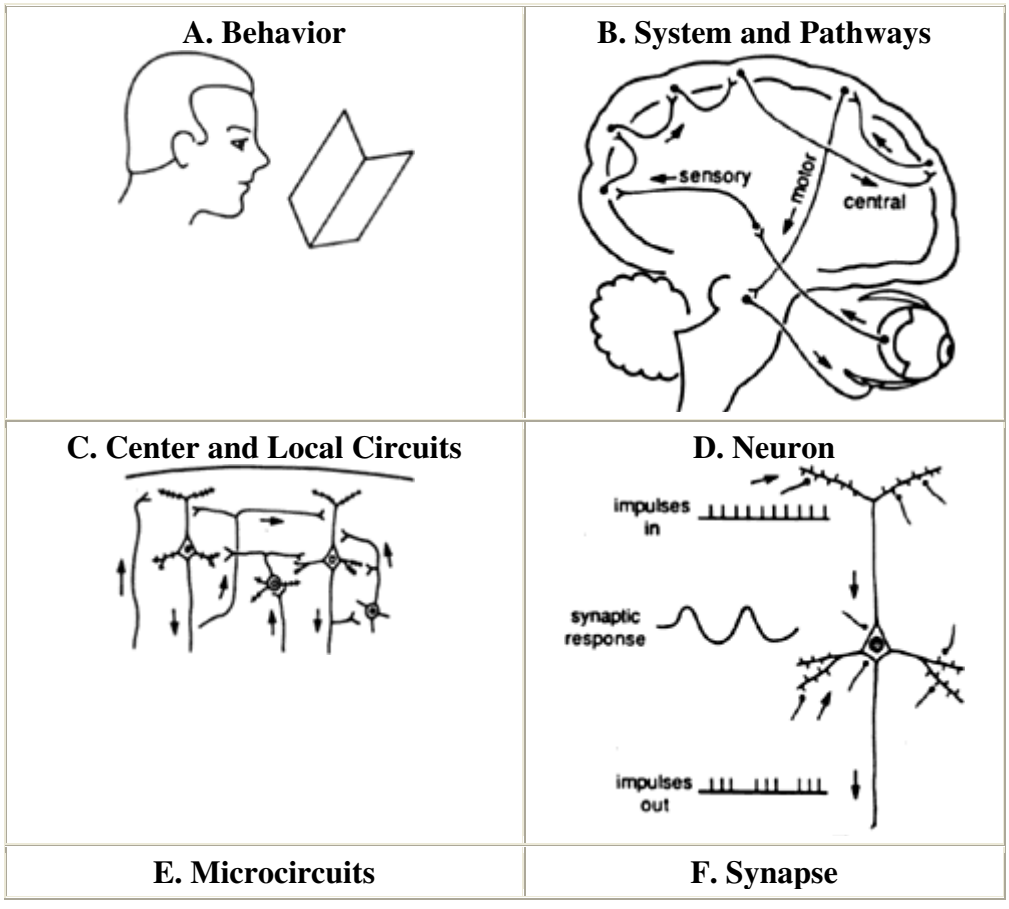
Phosphatidylserine is usually kept on the inner-leaflet of cell membranes by an enzyme called translocase. In apoptosis, caspase 3 activation culminates in deactivation of translocase and activation of scramblase, which allows free movement of PS down its concentration gradient, and activation of flippase, which transports PS to the outer-leaflet of the plasma membrane. This is part of the process by which the cell is targeted for phagocytosis.

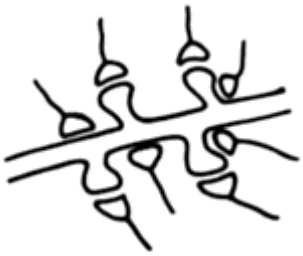
Your body makes all the PS it needs. However, the only way to get a therapeutic dosage of PS is to take a supplement.

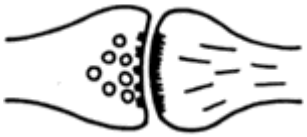
The dietary supplement was originally processed from bovine sources, however prion disease scares in the 1990s outlawed this process, and a soya-based alternative was adopted. The fatty acids attached to the serine in the soy product are not identical to those in the bovine product, which is also impure. Studies using the soya

version indicate a possible improvement in mood, but no clear evidence of an effect on mental function.

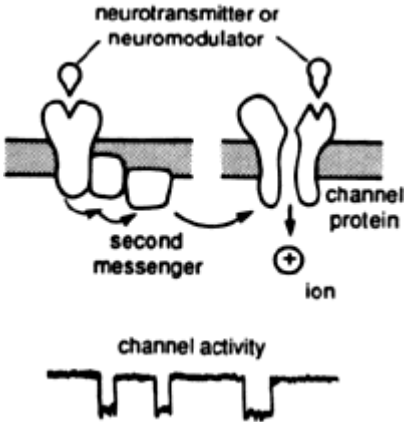
PS was originally manufactured from the brains of cows, however, because animal brain cells can harbor viruses, that form is no longer accepted for human use. Most PS today is made from soyabeans or other plant sources. There are reasons to expect that plant-source PS should function very similarly to PS made from the cow's brains, and some animal studies suggest that it is indeed effective. However, in preliminary trials, soya-based PS and cabbage-based PS failed to prove beneficial.





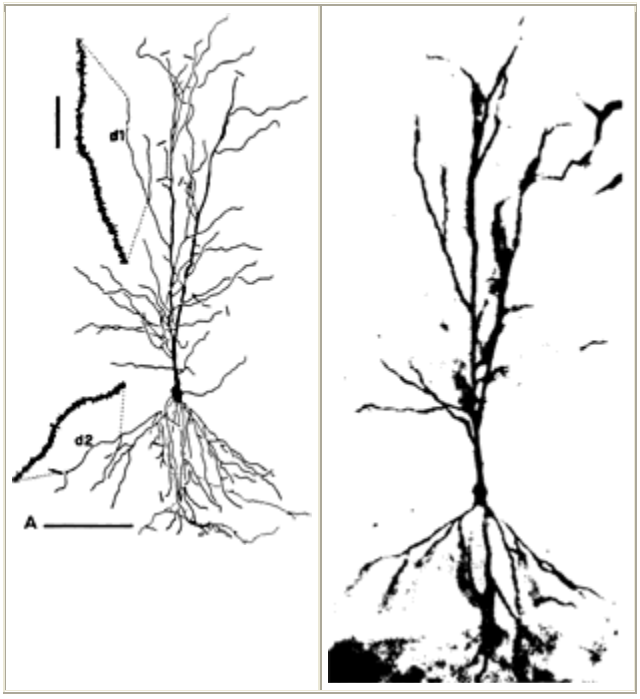


G. Membranes, Molecules, Ions



As Virgil put it long ago, "Time bears away all things, even our minds" (ca. 34 B.C.)

Cognitive decline in the healthy can begin as early as the fifth decade of life; of these more than half are likely experiencing impaired capacities to recall names and numbers, to manipulate words, or to concentrate at work and maintain focus while at play. Progressive loss of mental functions can have a telling effect on personal productivity, can damage self-esteem, and brings considerable distress to many aging adults.



Pyramidal cell from the hippocampus, the main memory center of the brain; the leaves on this tree-shaped cell shown ad d1 and d2 on the diagram at left may represent sites of memory fixation; their numbers decline with age.

The fundamental contributions of PS at the level of the individual brain cell are actually expressed in the performance of the brain as a whole. Human trials dating back to the 1970s indicate that when consumed as a supplement to the diet, PS can benefit diverse measures of cognitive functions.

Dietary supplementation with PS can alleviate, ameliorate, and sometimes reverse age-related decline of memory, learning, concentration, word skills, and mood. PS also may improve the body's capacities to cope with stress and maintain the internal circadian rhythms.

As people age, they inevitably lose some sharpness in the higher-level functions of memory, and cognition (defined most simply as the capacity to think and reason). These functions have been found to decline during middle age and later life, often in people who are clinically healthy. The decline can become evident as early as the fifth

decade of life. As memory and cognition slows, nerve cell density falls - a kind of 'dropout' occurs, partly in nerve cell number and also in the density of the synaptic connections within the network.

Over the adult life span, healthy individuals can lose as much as half (50%) of their ability to perform everyday tasks related to memory and cognition. Research is proceeding at a fast pace in this field, with the hope of slowing brain deterioration at an early stage, thereby to conserve the quality of mental function in later life.

Results from clinical trials conducted in the U.S. and Europe indicate that dietary supplementation with PS can play an important role in the support of mental functions in the aging brain. Among the clinical trials conducted with PS, most were done with subjects who had experienced measurable losses in memory, judgment, abstract thought, and other higher mental functions, and sometimes also changes in personality and behavior. In these trials data was generated by detecting categories of affected functions, applying tests that measure such functions, and tracking changes on the tests with time in the PS and the placebo groups.

Phosphatidylserine can also be of benefit for abnormal seizure activity. Based on findings that PS (used in combination with GABA, gamma-amino-butyric acid) could ameliorate experimental seizure activity in rats, Loeb and collaborators (1987) administered PS+ GABA to human subjects suffering from sporadic seizure abnormalities, for periods ranging from 30 to 90 days. The combination worked against absence seizures; one-third of the subjects experienced a greater than 50 percent reduction of this seizure type. In a subsequent trial (Cocito et al, 1994), a one-time acute administration of PS did not work as well. This is not surprising, since PS is a fat-soluble nutrient and would be expected to require at least several days dosing to build up in the nerve cell membranes.

Interestingly, the combination PS+GABA when given intravenously to rats had an immediate calming effect on seizure activity (Loeb, 1989). This effect could only achieved by combining GABA with PS, and not with PC or other phospholipid. PS may have increased the bioavailability of GABA to the brain.

PS can benefit brain dysfunctions other than the strictly cognitive. In an exploratory open trial by Funfgeld and Nedwidek (1987) on subjects with dopamine transmitter deficiency, 8 of the 12 subjects given PS showed improvement. Another patient improved when the PS intake was increased. This trial went for only 3 weeks; a longer dosing period and customized dosing might have produced more consistent results. In a previous study (Argentiero and Tavolato, 1980), subjects exhibiting severe cognitive deficit combined with motor impairment responded to intravenous PS (about 35 mg, administered as 200 mg total bovine brain cortex phospholipids). As their motor performance improved, they showed elevations in homovanillic acid (a marker for the transmitter dopamine) in their cerebrospinal fluid.

PS can have beneficial effects on mood. In a double blind trial conducted on elderly women, PS brought about consistent improvement of memory and behavior (Maggioni and others, 1990). In an open trial, Manfredi's group (1987) obtained statistically significant improvement of various 'psycho-organic' parameters in elderly women given 50 mg PS per day intramuscularly. The addition of the nutrient PS to a conventional drug regimen led to marked improvements in asthenia, insomnia, anxiety, and capacity for recollection, versus the drug regimen alone (all $p<O.O5$). A trend towards improvement was seen for vertigo and depression. Findings from the 1995 trial by Gindin and collaborators suggested PS can also improve mood in elderly men. Sengupta and fellow researchers (1981) documented significantly lowered PS levels in the membranes of platelets and red cells drawn from subjects with clinical depression.

Supplementation with PS may also help conserve hypothalamic function and benefit the aging hypothalamus-pituitary-adrenal axis (HPAA). One example is the Early Cortisol Escape Phenomenon. In young, healthy people the oral administration of 1 mg of dexamethasone (DEX, a synthetic glucocorticoid) normally suppresses the production of cortisol and other adrenal steroids for more than 24 hours. In contrast, many older people do not show this suppression by DEX. Called Early Cortisol Escape, this phenomenon of escape from DEX suppression is thought to indicate disintegration or dysfunction of the HPAA in the elderly. Nerozzi's group (1987) found that oral supplementation with PS restored DEX suppression in a group of 14 institutionalized elderly (ages 66-78; $p<0.02$). Rabboni et al (1990) administered PS at 400 mg/day to 30 elderly outpatients diagnosed either with (a) Alzheimer's, (b) dementia resulting from stroke, or (c) mild depression. PS benefited all 3 groups by 30 days, and normalized DEX suppression in those 9 patients who began the study with abnormal DEX resistance.

Further evidence that PS can benefit the aging HPAA comes from Masturzo and collaborators (1990), who did an open, placebo-controlled trial on institutionalized elderly men (ages 6585, average age 73.7) with disturbed 24-hour circadian rhythm of thyrotropin (TSH) hormone secretion. While those on placebo deteriorated further, PS restored the daily rhythm of TSH secretion to a level comparable with the young male adult controls (mean age 22.3 years; $p<0.001$). In another human study (Nizzo et al, 1978), the intravenous administration of PS in liposome form led to 'spikes' of growth hormone release. This effect was interpreted as likely the result of activation of dopamine metabolism in the pituitary gland by PS.

Stressful conditions typically elicit the release of cortisol, ACTH, and related stress hormones into the circulation. Phosphatidylserine appears able to down-regulate cortisol release, even in the healthy young adult. Intense muscle workouts often raise blood levels of the stress hormones, and when cortisol remains elevated muscle can be

broken down and amino acid uptake compromised. In 1992, Monteleone's group reported on an open, placebo-controlled trial of young, healthy men subjected to exercise-induced stress. Oral intake of PS, for 10 days prior to a session of bicycling to near-exhaustion, lowered the cortisol production normally associated with strenuous exercise. This confirmed findings from a 1990 study by the same group, in which PS was given intravenously just prior to exercise.

These findings of benefit from PS to stress coping and the HPAA axis must be considered somewhat preliminary due to the small sizes of the trials. Yet they are consistent with an influence of PS on brain function at all levels of complexity and integration. Further controlled trials may well confirm a clinically significant influence of PS on the body's age-related capacities to integrate its nervous, immune, and hormone systems.

PS is a Building Block for Cell Membranes

PS is <u>not</u> abundant in common foods, so it is limited in the human diet. Moreover, the body can make it only through a complex series of reactions and with substantial investment of energy. Given orally, PS is rapidly absorbed and readily crosses the blood-brain barrier to reach the brain. There, its sites of action appear to be exclusively in cell membrane.

Membranes are the major work surfaces of all known cells, and PS is a universal cell membrane building block. Nerve cells especially depend on membranes to carry out their specialized functions. The generation of the electrical current, the transmission of the current along the cell, and the relaying of the current across the cell-to-cell chemical synapse are all membrane-driven events. Membrane proteins play key roles in all these processes, and PS is important for regulating the activities of such proteins.

PS and other phospholipids (PL, for short) are large 'lipid' molecules that hold together the diversity of large molecules in the cell's membrane systems. The PL pack together side-to-side, and in a two-

layer molecular sandwich (a bi-layer), creating a membrane matrix into which the proteins and other membrane constituents are inserted and secured. The phospholipids of the membrane literally are a solvent for the proteins of the membrane.

PS phospholipids are one of five phospholipid classes that fulfill these physico-chemical functions. The others are:

- *Phosphatidylcholines (PC),*
- *Ethanolamines (PE),*
- *Inositols (PI),*
- *Sphingomyelins,* which have a molecular organization different from the phosphatidyls.

Each phosphatidyl molecule has a head group that contains phosphorus and one other chemical subgroup, which in the case of PS is serine. To the head group is attached a three-carbon backbone which is structurally identical to glycerol. Extending from this glycerol backbone are two so-called tails**,** each of which is a fatty acid**.** The sphingomyelins do not have the glycerol backbone, and carry only one fatty acid tail. The different phospholipids and their biological activities are identified and characterized via their differing head groups. The unique atomic and electronic topography of the head piece of the PS molecule destines it for a preferential association with membrane "integral proteins," that is enzymes, receptors, and ion channels that insert deep into the membrane. The head piece is identical between bovine source and soy source PS, just as it is identical with PS from bacteria, algae, or fungi.

The two tails of the PS molecule are fatty acids. As with the other phospholipids, the fatty acid tails of PS have a high rate of turnover. What is more, the tail patterns vary between the various organs. While position 1 almost always carries a saturated or monounsaturated fatty acid, position 2 can carry a variety of fatty acids. Thus PS from blood has mostly C18:1 (oleic acid, OA) or C20:4 (arachidonic acid, AA) in the 2 position. In the testes, C14:0

and C20:4/AA predominates. In PS from the brain, no C20:4/AA is found in Tail 2, and instead mostly C18:1/OA is present.

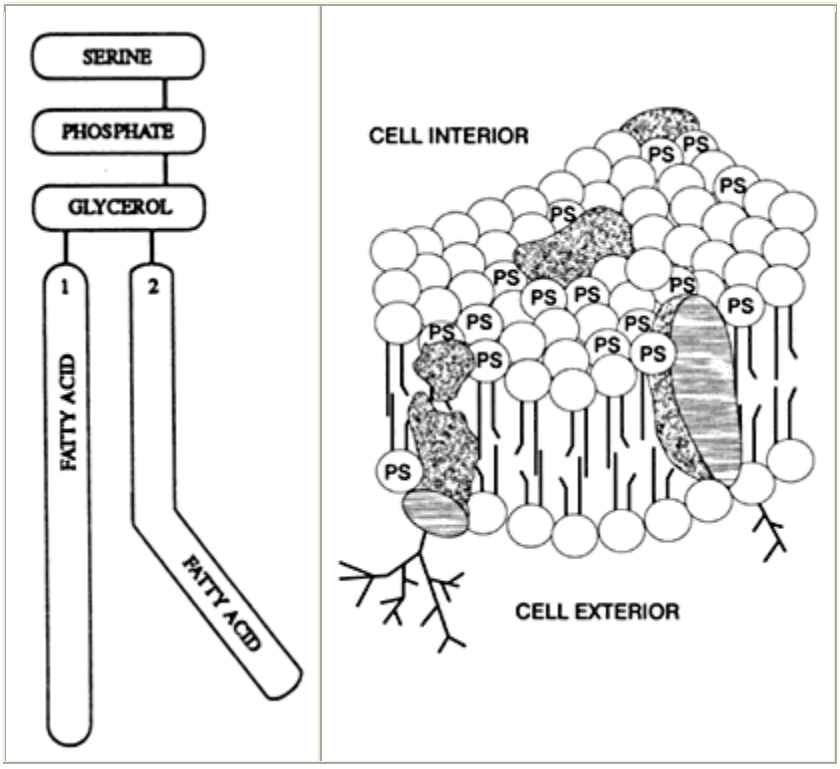
PS Supports Multiple Membrane Functions in Nerve Cells

Nerve cell functions that have been linked to PS include the conduction of the nerve impulse; the accumulation, storage, and release of the nerve transmitter substances; and nerve transmitter action by way of 'receptors' located on the target cell surface. PS also is important for 'housekeeping' in the nerve cell, by supporting the processes of homeostasis.

The membranes of nerve cells are particularly high in PS. The outermost membrane of the cell, called simply the cell membrane, is a kind of master switch for the cell. Among those cell functions which the cell membrane controls are:

- Entry of nutrients into the cell, and the exit of waste products
- Movements of charged atoms (ions) into and out of the cell
- Passage of molecular messages from outside the cell to its interior
- Cell movement, shape changes, flattening or expansion
- Cell-to-cell communication and other associations

The membrane-based ion pumps, transport molecules, enzymes, and receptors which manage these master-switch activities are proteins, but all depend on the phospholipid membrane matrix for their full functional capacity and for their coordinated activity. PS seemingly has the specialized function of helping to anchor many of these proteins in the matrix. Also, PS carries a negatively charged amino head group which tends to associate preferentially with ATPases, kinases, receptors, and other key membrane proteins. These specific PS-protein associations may be the ultimate key to the remarkable global effects of PS on the brain as a whole (Pepeu et al, 1996).



Left: Molecular organization of Phosphatidylserine (PS). Right: PS is preferentially distributed in the bi-layer portion of the cell membrane that faces the cells interior. PS associates with key membrane proteins.

The influences of PS at the level of the individual membrane proteins amount to essential contributions at a 'micro-level' of the cell membrane. PS therefore facilitates an array of cell functions that build on membrane functions. As examples:

- Maintenance of the cell's internal environment: PS in the cell membrane is essential for the ATPase enzymes that regulate cellular sodium-potassium AND calcium-magnesium balance (see Toffano, 1987). Due to their constant electrical activity, generated by ion movements across their membranes, nerve cells rely heavily on the ATPase enzymes. In cell membrane preparations isolated from the brains of aged rats treated with PS, the cholesterol/phospholipid ratio and ATPase activities were found to be reversed towards values characteristic of younger rats.

- Signal transduction: The many different receptors on cell membranes, and the enzymes within the membrane to which they are closely linked, rely heavily on membrane phospholipids for their activities. PS is known to regulate the binding of opiates and glutamate to their receptors, to enhance olfactory bulb sensitivity in turtles, and to restore prolactin receptor density in aging rats. PS also has a potent activation effect that is important for protein kinase C, a major signal transduction complex, and for adenylate cyclase signal transduction activity in the rat hypothalamus (see Zanotti et al, 1987).
- Secretory vesicle release: Most cells secrete hormones, nerve transmitters, or other materials to the outside environment by way of membrane-coated micro-packages called secretory vesicles. In fact, vesicle secretion is the major means by which nerve transmitters are released from the nerve cell axon endings. PS may help prepare the cell membrane and/or the vesicle membrane for the two to fuse with each other and thereby release the secretory packet to the outside (see Nishizuka, 1984). PS also seems to revitalize acetylcholine stores in the brains of aged rats (see Pepeu et al, 1996).
- Cell-to-cell communication: PS is the key to a unique mechanism for cell-to-cell communication that involves release of part of the PS head group as a "lyso-PS" (see Toffano, 1987).
- Cell-to-cell recognition: PS helps anchor and stabilize antigens and receptors linked to the cell membrane. Enzymes (amino-PL translocases) can ‘flip’ PS from the inner half of the bilayer to the outer half. PS accumulating in this location apparently signals that this particular cell has become ‘old’ and should be ‘recycled’ (Schlegel et al, 1996). Immune cells then recognize this signal and eliminate the worn-out cell. Such ‘flip-flopping’ of PS may also be important for nerve cell receptor function. In animal experiments, age-related receptor abnormalities were partially normalized by dietary PS.
- Cell growth regulation: Growth factors are small molecules, usually proteins that pass between cells and regulate cell proliferation and renewal. The growth factors usually operate

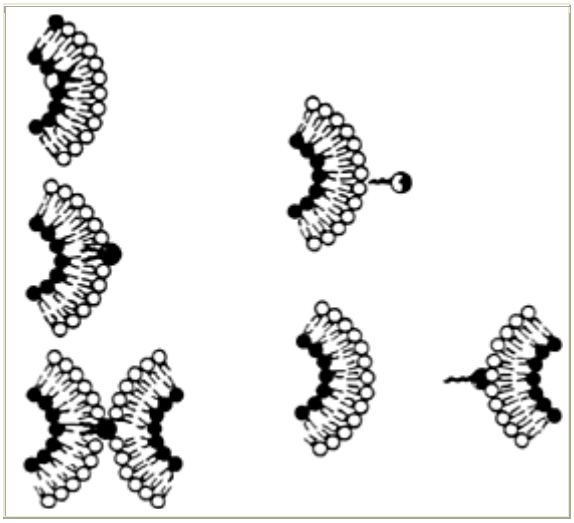
by turning on or off specific cell membrane receptors. Nerve growth factor (NGF) is one of the most important growth factors for nerve tissue. In animal studies PS partially blocked NGF receptor decline related to aging, and in "test tube" experiments PS stimulated NGF synthesis and release from cultured PC12 nerve cells (see Nunzi, 1990).

In vitro ('test tube') experiments indicated that PS could confer protection on nerve cells from toxic attack (Latorraca et al, 1993). The authors suggested PS had antioxidant effects, but their data also seem consistent with enhanced cellular detoxification capacity linked to improvements in membrane-based cell functions.

Numerous experimental studies have been conducted with PS in animals, as reviewed in Toffano (1987). The results with PS in animals overwhelmingly support the clinical conclusions drawn from the human studies. In the rat brain, PS stimulated acetylcholine output from the cerebral cortex; stimulated dopamine synthesis by strongly activating tyrosine hydroxylase, and induced dopamine release from dopaminergic neurons; and, in aged rats, reset lagging circadian and estrus rhythms and reversed fading EEG signals that correlated with fading memory function (see Aporti et al, 1986). Structurally, PS protected the hippocampus (a major memory center) from the loss of dendrite connections that normally occurs with aging (see Nunzi et al, 1987). This constellation of benefits from PS to animal brains at the biochemical level correlated with improvements in spatial memory and passive avoidance seen in aged rats, as well as their capacities to cope with stress (reviewed in Pepeu et al, 1996).

Nunzi and co-workers (1992) found that in the rat hippocampus, a fall-off in nerve growth factor receptor density occurs with aging. PS reversed this receptor density decline and seemed to enhance NGF production.

The above described array of anti-aging effects demonstrated with PS on animal models of brain decline are unique to the PS molecule - other phospholipids did not effectively substitute for PS in such experiments, nor did the amino acid serine (reviewed in Toffano, 1987).



Phosphatidylserine, vesicle secretion, and cell-to-cell communication.

Left: in the healthy cell, PS is confined to the inner leaflet of the cell membrane (upper); exposed at the outer face of a secretory vesicle (middle), PS can promote membrane-membrane fusion and release of the vesicle (bottom). Right: the lyso head of PS can be released from the cell (top) and act as a primary messenger to nearby cells (bottom).

Safety and Bioavailability

A relatively large number of clinical trials have been conducted with PS (minimum of 34 published, of which 17 were conducted double blind). PS has emerged from this extensive clinical examination with an excellent safety record.

Cenacchi and collaborators (1987) reviewed laboratory findings from 130 subjects given 300mg of PS daily for up to 60 days during clinical trials. They found lowering of uric acid levels and (liver) SGPT, which, though statistically significant, were clinically negligible. Side

effects from the clinical trials also were negligible; Cenacchi et al, (1993) reported from their large six-month trial with 425 subjects that 'adverse events' were very few, and clinically unimportant.

These observations are remarkable in the light of the large number of subjects enrolled in this study, who represent a sample of the geriatric population commonly encountered in clinical practice. For the course of the trial, these elderly subjects were allowed to stay on the wide range of pharmaceutical medications common to their population and no adverse interactions with PS became evident.

No danger is evident from long-term intake of PS. Preclinical toxicological studies on rats and dogs indicated PS was safe when taken by the oral route (Heywood et al, 1987). Dogs survived 70 grams per day of PS for one year without apparent damage at the histological level. No reproductive studies appear to be available.

Phosphatidylserine has good bioavailability by the oral route. Following oral dosing to rats, radioactively labeled PS appears in the blood at about 30 minutes. After a few more minutes uptake begins into the liver and, later, the brain.

In the brain PS can be enzymatically converted to PE (phosphatidylethanolamine) and seemingly serves as a backup reservoir for this other important cell membrane phospholipid. PE in its turn can be enzymatically converted to PC (phosphatidylcholine). PS gets into the mitochondria, which are the cells' energy producing compartments. There PS serves as a ready source of PE, which is known to be centrally involved in the inner membranes that regulate the production of chemical and electrical energy.

One possible basis for the versatile biological actions of PS administered orally is that the fatty acid at Tail 2 is subject to being shuffled, either:

(a) During the course of absorption,

(b) While the molecule is in an intestinal cell,

(c) After its delivery to an organ.

The tails of PS are shuffled to suit the needs of the cell as they change over time, or as the PS 'parent molecule' are transported from tissue to tissue, cell to cell, or perhaps even from spot to spot within a membrane. Enzymes (hydrolases, acyltransferases) that remove or replace Tail 2 are present in the digestive juices, in the intestinal lining cells, and in the membranes of all the other cells of the body. The acyltransferases are used to remove fatty acids from PS (or other phospholipids), and replace them with other fatty acids, depending on the functional needs of the cell.

The odds are infinitely small that the fatty acid of Tail 2 on a PS molecule is going to stay in position all the way from oral administration until the parent molecule reaches a nerve cell. Removal of Tail 2 may facilitate passage across the blood-brain barrier, and the evidence indicates that the nerve cell membranes re-mold the tails of the PS parent molecules to suit their functional needs.

However, PS is known to enhance the effect of heparin, a very strong prescription blood thinner. It is possible that combined use of PS and any drug or supplement that thins the blood could interfere with normal blood clotting enough to cause problems. Some medications and supplements to consider include warfarin (Coumadin), aspirin, pentoxifylline (Trental), clopidogrel (Plavix), ticlopidine (Ticlid), garlic, ginkgo, and vitamin E.

Conclusion: PS Can Boost Multiple Brain Functions

After a quarter century of research with PS on human subjects, laboratory animals, cells in culture and molecules in the test tube, it is clear that this nutrient has profound value to the human brain. PS has been intensively studied for cognitive decline. Substantial amounts of mechanistic, experimental and clinical data are available on PS, and

the findings overwhelmingly indicate PS is highly effective and is safe to take. The fact that PS is an orthomolecule, i.e., intrinsic to all the body's cells, is predictive of its safety for both short-term and long-term use.

A reasonable supplementation strategy with PS is to begin at 300 mg per day with meals for a month, then go into a maintenance mode at a lower level of intake (100 to 200 mg daily). There is no indication of potential problems from long-term supplementation with PS.

As a general rule, because PS is so safe the more severe the subject's problems the more aggressive can be the supplementation strategy. Patients with severe memory problems can be kept on all their other supplements and medications, and be given PS with their meals at 300 to 500 mg per day on an ongoing basis. Subjects afflicted with motor problems may respond better at 500 mg per day. Mood problems may require a starting dose of 400 mg per day. For age-related cognitive decline (ARCD), a daily intake of 300 mg may be appropriate.

PS is far more abundant in the brain than in the other organs, and to date has the most clinical significance as a brain nutrient. Nerve cell homeostasis, renewal, and specialized functions all involve membrane-based processes that rely on Phosphatidylserine. Dietary supplementation with PS can benefit brain functions from the most basic to the most sophisticated. PS can slow the loss of brain functions, and in some cases partially rejuvenate them (Crook et al, 1991).

One effect that PS manifests as an orthomolecule is that it works to keep the brain's processes within normal limits, raising them when they are low and lowering them when they are high. Thus PS boosts the weak stress response in the elderly person, and calms down exaggerated stress response in the healthy young person. PS may also benefit children as evidenced by findings from a pilot study on ADD (Attention Deficit Disorder).

The fight-or-flight response is a basic, universal response to stress of any kind, and occurs in response to physical as well as mental stress. Stressful conditions typically cause cortisol, ACTH (adreno-cortico-trophic-hormone) and other stress hormones to be released into the circulation, even in the young and healthy. Thus young men who vigorously ride stationary bicycles in the laboratory show a surge of ACTH and cortisol release as a result of their strenuous exercise. PS given to these athletes prior to starting exercise produced an impressive degree of down-regulation of the stress hormones. PS may have the capacity to 'normalize' the stress-induced activation of the hypothalamic-pituitary-adrenal axis, and so improve athletic training capacity (Monteleone et al, 1992).

The clinical findings consistently indicate that supplementation with PS can benefit memory, learning, concentration, semantic skills, and control over mood.

Dr. Thomas Crook and the Memory Assessment Clinics developed tests for cognitive function that are currently the state of the art; their findings indicate ARCD-Age-Related Cognitive Decline-is well underway in otherwise-healthy persons by the fifth decade of life. Crook et al's 1991 double-blind trial established that PS could turn back the clock on brain aging: on name-face recall PS reversed more than 12 years worth of cognitive decline. This solid clinical finding suggests that if supplementation with PS can be started during the fifth decade, the chances for ameliorating further progressive loss of the brain's higher functions will be markedly improved.

While PS appears to be the best single means currently available for conserving the intellect, its membrane-based action mechanisms make it compatible with other nutrient classes like the antioxidants, the B vitamins, and the minerals. PS also has proven compatibility with many of the pharmaceuticals that are in common use by the elderly (Cenacchi et al, 1993); as an orthomolecule it is unlikely to interfere with the actions of the few pharmaceuticals available for

cognitive decline, and as a pro-homeostatic nutrient it should actually complement their actions.

As a safe and effective dietary supplement, particularly when employed in conjunction with exercise and lifestyle revision PS has proven potential to improve the quality of life for the young, the middle aged, and the elderly. With benefits so diverse they are unmatched or exceeded by any other known intervention, PS is indispensable for conserving (and sometimes for restoring) memory, learning, concentration, and other higher mental capacities threatened by the wear and tear of modern life.

Phosphatidylserine is a nutritional supplement, not a drug; as such, it is more widely known in alternative than in conventional medicinal circles. In short, it is a fatty substance that may halt memory declines and even bring memory improvements (at least among those who have already suffered some decline).

Counter Point

Therapeutic Uses

Meaningful evidence from numerous double-blind studies suggests that animal-source PS is an effective treatment for Alzheimer's disease and other forms of age-related mental decline. Vegetable-derived PS has little supporting evidence.

PS is widely marketed as a treatment for ordinary age-related memory loss as well. While there is little direct evidence that it works, in studies of severe mental decline, PS appears to have been equally effective whether the cause was Alzheimer's disease or something entirely unrelated, such as multiple small strokes.

This certainly suggests that PS may have a positive impact on the brain that is not specific to any one condition. From this observation, it is not a great leap to suspect that it might be useful for much less severe problems with memory and mental function, such as those that seem

to occur in nearly all of us who are older than 40. Indeed, one double-blind study did find that animal-source Phosphatidylserine could improve mental function in individuals with relatively mild age-related memory loss. However, two studies failed to find plant-source PS effective for this condition. PS has also been proposed for enhancing mental function in young people, but there is no direct evidence at all that any form is effective. Animal-source PS has also shown a slight bit of promise for depression.

Recently, PS has become popular among athletes who hope it can help them build muscle more efficiently. This use is based on weak evidence that PS slows the release of cortisol following heavy exercise. Cortisol is a hormone that causes muscle tissue to break down. For reasons that are unclear, the body produces increased levels of cortisol after heavy exercise. Strength athletes believe that this natural cortisol release works against their efforts to rapidly build muscle mass and hope that PS will help them advance more quickly. However, only two double-blind placebo-controlled studies of PS as a sports supplement have been reported, and neither one found effects on cortisol levels. Of these small trials, one found a possible ergogenic benefit, and the other did not.

Interestingly, PS has also been advocated as an aid to recovery from heavy exercise, according to the theory that use of PS would help reduce muscle soreness. This would seem to contradict the proposed effects on cortisol, as cortisol has anti-inflammatory properties. Nonetheless, researchers performed a double-blind study to evaluate whether 750 mg daily of soya-source PS would reduce muscle soreness following downhill racing; no benefits were seen.

One study found preliminary evidence that a combination of soya-based PS and lecithin may moderate the body's reaction to mental stress. Another study evaluated use of phosphatidylserine for reducing stress in golfers, but the benefits seen had failed to reach statistical significance.