Phosphatidylcholine: A Superior Protectant Against Liver Damage

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Abstract

Phosphatidylcholine (PC) is one of the most important support nutrients for the liver. PC is a phospholipid, a large biological molecule that is a universal building block for cell membranes. A cell's membranes are its essence: they regulate the vast majority of the activities that make up life. Most liver metabolism occurs on cell membranes, which occupy about 33,000 square meters in the human. More than 2 decades of clinical trials indicate that PC protects the liver against damage from alcoholism, pharmaceuticals, pollutant substances, viruses, and other toxic influences, most of which operate by damaging cell membranes.

The human liver is confronted with tens of thousands of exogenous substances. The metabolism of these xenobiotics can result in the liver's detoxicative enzymes producing reactive metabolites that attack the liver tissue. Dietary supplementation with PC (a minimum 800 mg daily, with meals) significantly speeds recovery of the liver. PC has also been shown to be effective against alcohol's liver toxicity in well-controlled studies on baboons.

PC has other qualities that enhance its usefulness as a dietary supplement. PC is safe, and is a safer means for dietary choline repletion than choline itself. PC is fully compatible with pharmaceuticals, and with other nutrients. PC is also highly bioavailable (about 90% of the administered amount is absorbed over 24 hours), and PC is an excellent emulsifier that enhances the bioavailability of nutrients with which it is co-administered. PC's diverse benefits and proven safety indicate that it is a premier liver nutrient. (*Alt Med Rev* 1996;1(4):258-274)

Phosphatidylcholine (PC) is a phospholipid nutrient that is a major building block for all known cells.[1] PC is the most abundant constituent of cell membranes, the thin and delicate yet dynamic surfaces on which cells carry out most of their activities (Fig. 1). The "workhorse" parenchymal cells that make up the liver are especially reliant on their membranes,[2] and it has been estimated that the human liver as a whole encapsulates some 33,000 square meters of cell membrane.[3] The liver's wide range of functions, as well as its capacity for ongoing renewal, hinge on its ability to make new cell membranes, which are on average 65% PC. Decades of basic and clinical research on this nutrient indicate that it is critical for optimal liver function.

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figure 1

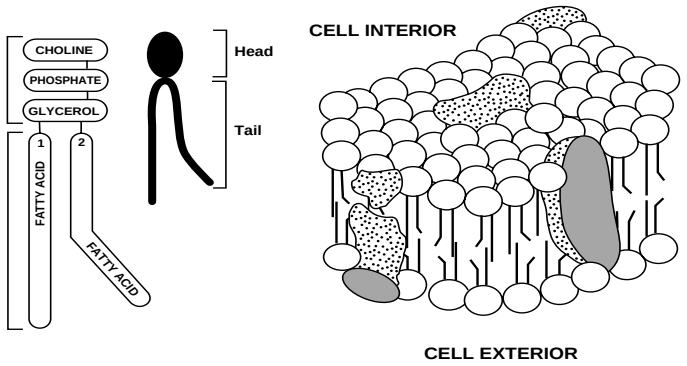

Figure 1. Phosphatidylcholine, major constituent of cell membrane systems. Left: Molecular plan of PC. Middle: PC, membrane building block. Right: the basic membrane plan, with proteins interspersed in a lipid matrix.

In its programmed efforts to rid the body of potential toxins, the liver paradoxically generates toxins that can damage the liver tissue. This can happen because evolution has been tricked: manmade foreign substances activate the liver's natural enzyme detoxification pathways, but often the metabolites that the liver generates from them via such "bioactivation" are more toxic than the starting substrates. Whether their toxicity occurs directly or following bioactivation, virtually all of the agents that damage the liver do so by way of attack on the membrane systems of the parenchymal cells.

Membrane systems are central to the survival and specialized functioning of all cells. In order to carry out its metabolic responsibilities, the liver parenchymal cells are densely packed with membranes. Given this central role of membranes in the liver's functions, the demonstrated superiority of PC in supporting the liver against damage is thoroughly consistent with the known mechanisms of liver homeostasis, toxic liver damage, and the liver's recovery processes. Out of this comes a dramatic conclusion: PC is the single most important nutrient for the liver.

The Human Liver, the Detoxification Paradox, and PC

The liver is the body's main organ for disarming and disposing of toxins, yet is itself vulnerable to toxic attack. Such toxic attack is both endogenous (from toxins generated in the liver), and exogenous (due to toxins coming from the outside). Similar metabolic mechanisms are employed to deal with the toxins coming from either source, but due to the stressful influences of modern life, toxic overload is a constant possibility.

The healthy liver is the body's largest organ and is probably also its most metabolically versatile. The liver carries out hundreds, if not thousands, of sophisticated enzymatic reactions along numerous metabolic pathways. Enzymes residing within the membranes of the parenchymal cells produce biological molecules by synthesis from smaller molecules, by the modification of preexisting metabolites or from newly-absorbed nutrients. The parenchymal cells also process hormones and many other metabolic waste products into water-soluble compounds for subsequent excretion. With the myriad of functions that it performs, the liver plays a pivotal role in maintaining homeostasis, i.e., health in all its aspects. But these routine liver functions do generate intrinsic, potentially toxic metabolites.

Normally the parenchymal cells are well equipped with protective antioxidant enzymes and with water-soluble antioxidants such as glutathione, cysteine, and taurine to neutralize endogenous toxic metabolic products. However, with the additional challenge posed to the liver's defenses by foodborne toxins and by the bioactivation products of xenobiotics, including lifestyle-related substances such as alcohol the liver's detoxification enzyme systems can be diverted to the compulsive generation of toxic metabolites that attack their maker. Last but

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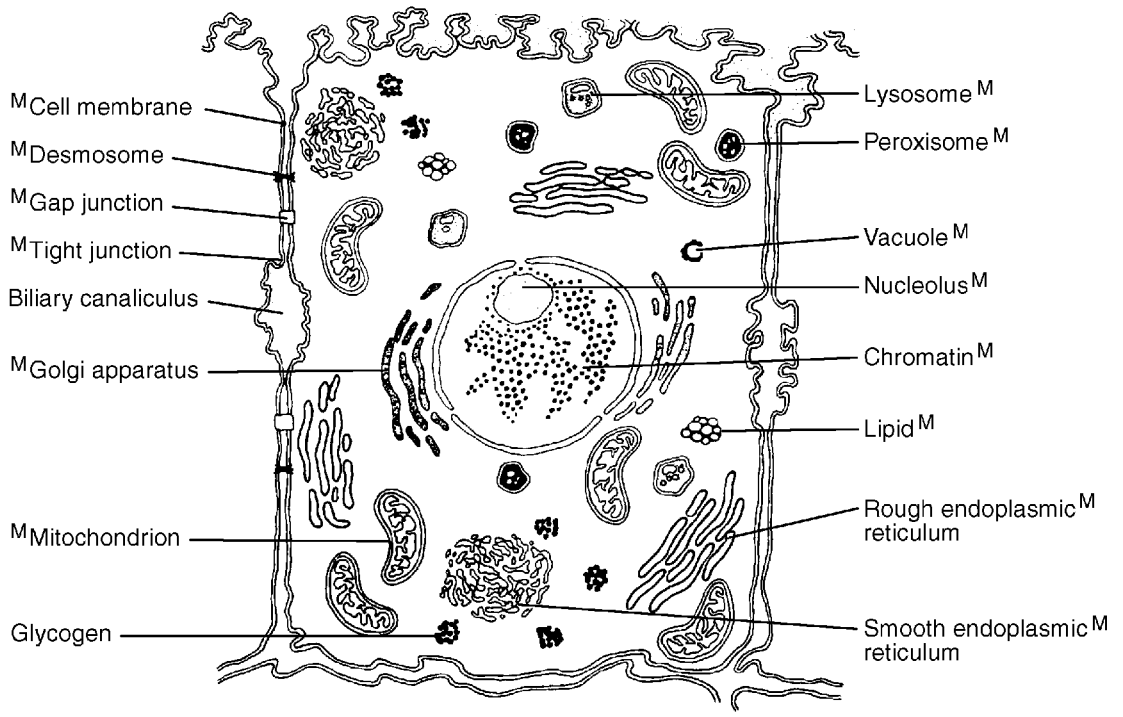
Figure 2. Schematic of the liver parenchymal cell, showing the internal functional units or organelles. Those superscripted[M] are made up of membranes or rely on membranes to function. Modified from Sherlock S, Dooley J. Diseases of the Liver and Biliary System. Oxford: Blackwell Scientific Publications; 1993.



not least, by being the first way-station for the blood draining the intestines (via the portal circulation), the liver tissue is directly exposed to preformed toxins that enter by the oral route.

It is highly doubtful that the human liver is evolutionarily equipped to cope with the tens of thousands of toxins generated by modern circumstances: pharmaceuticals, pollutants, and other toxins associated with a self-abusive lifestyle. As the liver becomes overburdened with such toxins, its stores of protective antioxidants are progressively depleted.[4] Parenchymal cells die, and cell death spreads zonally. Left unchecked, necrotic and inflammatory damage comes to threaten whole regions of the liver.

Overall Clinical Benefits of PC for the Liver

A large number of controlled clinical trials, conducted mostly in Europe, have investigated PC for the management of liver damage coming from a variety of toxic insults. In a landmark study published in 1973, Wallnoefer and Hanusch in Germany followed 650 subjects with various degrees of liver damage for at least 5 years.[6] This trial relied on biopsy, conducted in conjunction with blood analyses and clinical tests, to assess the scope and character of liver damage.[7] The subjects received PC for periods that ranged from 4 weeks to several years. The distributions of subjects, listed in groups according to approximate degree of damage severity, was as follows: fatty degeneration, n=130; acute inflammation, n=157; persistent inflammation (subacute and chronic), n=41; chronic inflammation, n=122; chronic aggressive inflammation, n=70; advanced fibrotic damage, n=130. All subjects were begun on intravenous PC (950 mg*) along with oral PC (450-700 mg*), until blood parameters began to return to normal; they were then shifted to oral PC only.

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All the groups of subjects in this study benefited from receiving PC. Of those with mild damage, more than half (51.1%) showed excellent improvement, and many subjects experienced reversal of their fatty degeneration. In the acute inflammation group, lab measures and biopsy indicated PC accelerated recovery by about 10 days. In the group with persistent inflammation, PC returned the enzyme parameters to normal after 30 days. In chronic aggressive inflammation , more than one-third (35.3%) experienced benefit and among those with advanced fibrotic damage, 17.5% benefited. In this last group with liver damage of the greatest severity, recovery was better when PC was given intravenously as well as by the oral route.

Notably, some of the subjects with persistent inflammatory damage included in this trial had failed to benefit from milk thistle extract ("silymarin") or steroid drugs, but benefited from PC. The investigators commented that for the best chance of success, the management of advanced liver damage should be continued for years rather than weeks or months; and that in their clinical experience PC proved to be the best single means for managing liver damage.

Sorrentino and collaborators (1982) studied 42 subjects with liver damage stemming from varied causes and exhibiting all degrees of severity.[8] They divided the subjects into 2 groups of 21 each, then provided conventional management (diet, B vitamins) to one group. To the other group, they gave PC (1350 mg), fortified with B1, B2, B6, B12, and E. Blood samples and clinical assessments were taken after 1 month, then at 2 months (the end of the trial). The results were subjected to a customized best-fit, least squares statistical analysis. After the first month, the data on 7 of the 8 parameters were clearly in favor of PC (5 of the 7 were 95% significant), then at month 2 the eighth parameter—SGOT—also became significant in favor of PC. In suggesting that PC can benefit the various stages of liver damage, these findings are consistent with those of Wallnoefer and Hanusch[6].

Clinical Assessment of PC In Alcoholic Liver Damage

Excessive alcohol consumption is still the single most common cause of toxic liver damage in Western societies. Alcohol damages the liver by various mechanisms.[9] First, it increases oxidative stress: the ethyl alcohol molecule becomes metabolized by the liver cell to acetaldehyde, which is a reactive oxidant ("two-electron stealer"). Acetaldehyde combines with antioxidants, often into a molecular complex (an "adduct"), thereby draining the liver cells of their antioxidant power. Acetaldehyde also reacts with enzymes and other proteins and with DNA, damaging these and sometimes causing mutations. Membrane phospholipids and their associated fatty acids also can be damaged or destroyed by the highly reactive acetaldehyde, which can do as much damage as many free radicals (technically, one-electron stealers).

Being a weak polar solvent, alcohol has a dispersive/disruptive effect on the lipids that make up the matrix of cell membranes.[9] Alcohol can literally dissolve PC and other phospholipids from the membrane, thereby inactivating the membrane proteins that depend on the lipids for activity and weakening the membrane to the point of rupture. By this means and through the acetaldehyde pathways, alcohol also attacks the mitochondria, the liver cell organelles that normally generate energy. By impairing

*Footnote: The PC preparations used in clinical trials were soy lecithins enriched in PC, sometimes also with RDA-range levels of added B vitamins and vitamin E (herein termed fortified PC). In this text the actual PC intakes are stated, as calculated and rounded to the nearest 50 milligrams (mg).

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mitochondrial function, chronic alcohol exposure robs the cell of precious energy resources needed for maintenance and for more sophisticated functions. As the cell becomes more energetically compromised, its death becomes inevitable.

Mitochondrial damage is the most likely toxic basis for the early clinical stage of alcoholic liver damage termed "fatty liver."[9,10] The mitochondria are the organelles that normally burn fats (triglycerides) to make energy for the cell. When the mitochondrial membranes become destroyed by alcohol, the parenchymal cells can no longer adequately metabolize fats. Pools of triglycerides then become deposited within hepatocytes throughout the liver tissue. It is thought that as these fatty deposits grow, they can come to occlude the important functions of the cell and cause more severe functional damage.

Clinically, the fatty liver state represents a relatively mild degree of alcoholic damage to the liver, which can often be reversed through diligent personal commitment. However, if the individual continues to consume alcohol the fat-laden parenchymal cells can begin to die off in large numbers. An inflammatory situation then develops: in response to substances exuded from dying liver cells, immune cells migrate into the liver tissue from the circulation and attempt to "mop up" the debris. However, with the liver's energetics and antioxidant adaptability now compromised, the stage is set for the inflammatory process to get out of hand and usher in a chronic inflammatory state.[9]

If liver inflammation develops from alcohol toxicity and is not controlled, as with the continuation of alcohol consumption, cells in the liver called lipocytes are transformed and begin to produce collagen, which is the primary molecular basis for connective tissue deposition and fibrosis. At first the liver may adapt, accelerating its removal of collagen to keep pace with the rate of new deposition. If the liver's functional state cannot be improved, however, the rate of collagen removal eventually falls behind the rate of collagen deposition, and progressive collagen accumulation (fibrosis, scarring) begins to obscure ever-enlarging regions of the liver. Beyond this point, the liver's many functions become seriously compromised as it develops advanced, cirrhotic damage.[10]

Clinical trials conducted with PC against alcoholic liver damage have consistently produced favorable findings. Knuechel reported in 1979 on a double blind trial conducted in Germany on 40 male subjects who had fatty deposits in the liver resulting from alcohol intake, as verified by biopsy.[11] A majority of these subjects also likely had "Stage 2" inflammatory involvement, as indicated by abnormally-elevated serum iron, elevated immunoglobulin-A (IgA), and values of SGOT and SGPT 3-5 times higher than normal.

The subjects were taken off all pharmaceuticals and randomly divided into 2 groups of 20 each. One group received a placebo and the other, 1350 mg of fortified PC per day. Liver damage was monitored at days 14, 28, and 56 after beginning the treatment, based on the levels of SGGT, SGOT, SGPT, AP, LDH, Chol, TG, and BR. In addition LAP, immunoglobulins, platelets, reticulocytes, and the blood fatty acid spectrum were measured, but only at the beginning and at the end of the trial (day 56).

In this trial, measurable benefits from PC intake were apparent at the first time point—2 weeks after the start. At 4 weeks, most of the indicators of liver damage were clearly more improved for the PC group than for the placebo group. By 8 weeks, the trial's culmination, all the main parameters of liver function were significantly improved ($p < 0.05$). The parameters LAP and IgA-IgG-IgM, measured only at the end of the trial, also were significantly improved.

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A blind clinical evaluation was conducted at the end of the trial, by a qualified investigator not informed of the randomization code. Of the PC group of 20 subjects, 6 were judged very good and 14 good. Of the placebo group, none was very good, 7 were good, 8 were moderate, and 5 showed no change. The differences were statistically highly significant in favor of the PC group. No side effects from the PC were observed. In this 2-month trial, PC definitely benefited subjects with alcoholic liver damage. It did not completely resolve the more severe inflammatory indicators, which perhaps could have been achieved had the trial gone for a longer period.

In Madrid in 1985, Schuller Perez and San Martin organized a double-blind trial.[12] They drew 20 subjects with alcohol-induced fatty liver deposits from a population and compared them with 20 matched control subjects. As in the Knuechel study just described, fortified PC was given at 1350 mg per day. The trial went for 12 weeks, and blood samples were taken at the beginning and at the end of this trial period. Initially the indicators SGGT, SGOT, SGPT, AP, and bilirubin all were higher in the PC group than in the controls, but by the trial's end they were significantly reduced and were lower than the controls. Alpha-2-globulin was also significantly increased ($p<0.01$). Clinical assessment at the trial's end determined that in the PC group 3 subjects were good, 14 were average, while 3 had not improved. In the placebo group, 0 subjects were good, 9 were average, and 11 (more than half) had experienced no benefit. The authors concluded, "it is our view that the use of highly-unsaturated phosphatidylcholine for therapy of alcohol-dependent steatoses [fatty liver] is very productive."

The above two double-trials just summarized establish the benefits of PC as an oral nutritional supplement for the earliest clinically-characterized stage of liver damage from alcohol abuse - the presence of fatty deposits in the liver. These findings are consistent with those from Buchman and collaborators (1992), who gave PC double-blind to 15 subjects with fatty liver of non-alcoholic origin as part of an intravenous feeding regimen (TPN).[13]

The next and more serious stage of liver damage by alcohol is inflammation, which if left untreated can become life-threatening. In 1990, Panoz and collaborators reported on a double-blind trial conducted in England.[14] The researchers divided 46 subjects with liver inflammation from alcohol abuse (verified by biopsy) into two groups. The PC group were placed on a high intake—about 4.6 grams daily—of fortified PC, in contrast to the placebo group, and both groups were periodically assessed for 2 years. By the end of the trial there had been deaths in both groups, but a trend was seen toward increased survival in the PC group ($p=0.086$, short of the $p<0.05$ required for statistical significance). The group that seemed to benefit the most was the intermediate stage of severity (Pugh's B classification). Tolerance of the relatively high intake of PC was good.

The findings from these and other clinical trials conducted on human subjects with alcoholic liver damage are generally consistent with a large body of data from animal experiments.

The evolutionary strategy for normal liver "detoxification" seemingly is to make potentially problematic substances water-soluble, suitable for later excretion into the bile or the urine. Therefore the healthy liver attempts to first use the P450 enzyme complexes and related pathways, to put a charge on the molecule. It then attempts to conjugate this charged, more reactive "activated" metabolite with glucuronic acid or with glutathione or other antioxidants to render it water-soluble.[4] If the first phase enzyme systems become induced, generating copious amounts of exceedingly reactive activated molecules, then the resources for conjugation

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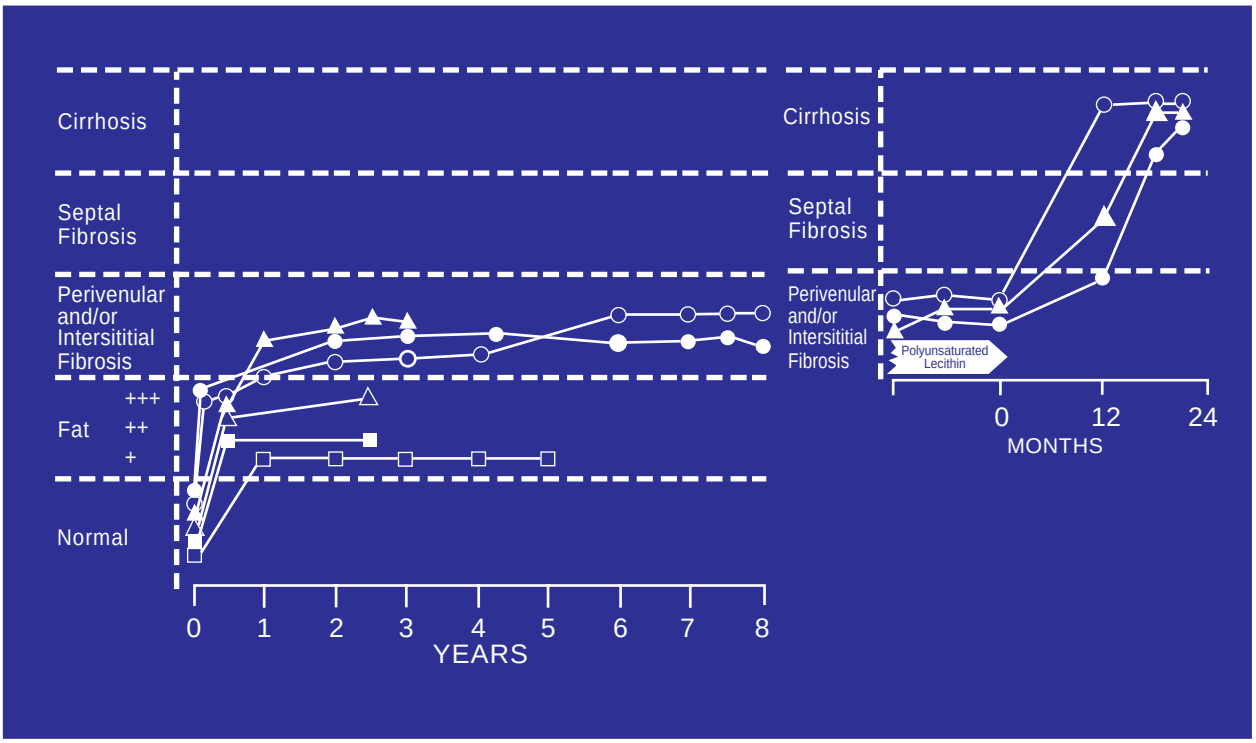
Figure 3. Inhibition of alcoholic liver damage in baboons fed an adequate diet with ethyl alcohol. Left: alcohol given daily along with PC to six baboons results in minimal fibrotic damage, stable for up to 8 years. Right: after PC is removed from the diet of three babbons, damage progresses to end-stage fibrosis ("cirrhosis") in 1-2 years. From Lieber et al.[15]



can become insufficient. When this happens, activation can still proceed but conjugation fails, and the liver tissue becomes a sitting duck for oxidative attack by the activated metabolites. Alcohol and many xenobiotics can actually induce, i.e., turn on, the Phase 1 systems, thereby racking up the potential for the system to overproduce activated metabolites. This can explain why combined intakes of alcohol and/or drugs and/or pollutants or other xenobiotics can be severely threatening to the liver's integrity.[4,9,10] In this scenario any agent that turns on Phase 1 of the detoxification system, can cause the system to concurrently convert excessive amounts of a second (or third) agent to reactive, oxidant metabolites.

The Baboon Model of Alcoholic Liver Damage

Animal studies have helped elucidate the means by which PC exerts its impressive clinical benefits against liver damage from many causes. In the case of alcohol, the most clinically relevant animal research to date has been the "baboon model" of alcoholism developed by Leiber and his colleagues at the Mount Sinai School of Medicine and the Bronx Veterans Affairs Medical Center in New York City, for more than 2 decades.[10,15,16,48] Their findings constitute compelling evidence that dietary supplementation with PC is effective against alcoholic liver damage. In early experiments they fed alcohol to rats, and found that it impaired phospholipid synthesis in the rat liver. This partially accounts for fats accumulating in the liver cells ("fatty liver"), since PC and other phospholipids are needed to metabolize triglycerides. Then, for an "experimental model" closer to the human state, they turned to research on baboon primates (Fig. 3).

Lieber and his associates placed baboons on a daily regimen of alcohol intake. Over a period of years most of the baboons developed features of alcoholic liver damage

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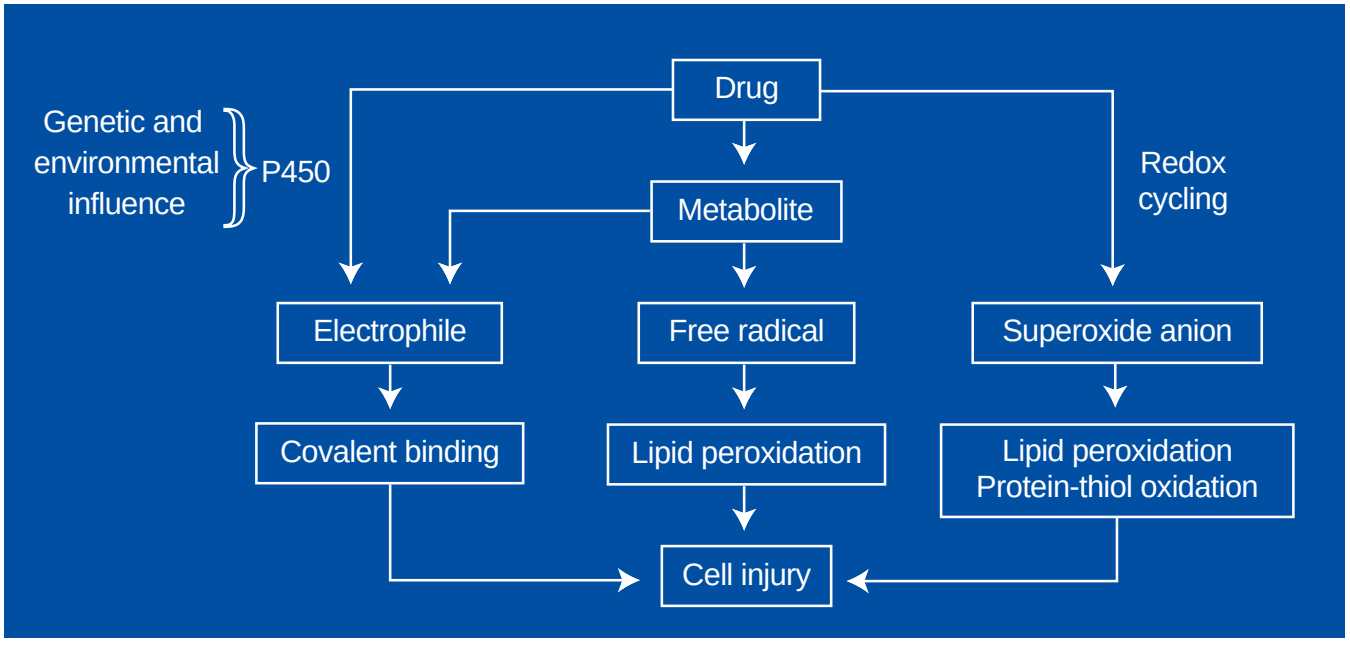
that closely resembled those seen in humans, making this is a good "animal model" for human liver disease. The researchers also developed sophisticated methods for quantitating the tissue changes seen in liver biopsy samples, and refined biochemical analyses for use on small amounts of biopsy material.

Subsequently, using a blinded trial design, they set up two main groups of baboons, one of which received alcohol along with PC, the other receiving only alcohol.[15] After running this primate trial for several years and decoding their results, Lieber's group found that the baboons fed alcohol with PC developed fatty liver and mild fibrosis, but did not progress to advanced liver damage for six years or longer. In contrast, the majority of baboons fed alcohol without PC progressed to advanced fibrosis ($p < 0.005$). While PC did not block the development of fatty liver in baboons that continued to receive alcohol, it dramatically slowed the progress to advanced disease.

Three of the baboons with fatty liver were subsequently taken off PC while continuing to be fed alcohol. These baboons rapidly progressed to extensive liver fibrosis (equivalent to advanced liver damage). From this study and a follow-up study using a similar design[17], Lieber's group were able to firmly conclude that PC is an effective means for halting (not merely slowing) the progression from early-stage alcoholic liver damage into late-stage generalized fibrosis (cirrhosis). (Figure 3) PC is unique among both nutrients and drugs, as was pointed out in a supportive peer editorial,[18] in its ability to halt the clinical progression of alcoholic liver damage.

Subsequent *in vitro* experiments by Lieber's group[16] showed that the lipocytes, the liver cells that normally store moderate amounts of fats, under the influence of alcohol become transformed to collagen-producing cells (called "transitional cells"). In the

Figure 4. Summary of the mechanisms of liver damage by drugs. Note the lipid peroxidation events that result in cell membrane damage. From Hoyumpa and Schenker.[19]



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intact, alcohol-treated liver these transitional cells intensify collagen production, but initially the liver keeps up by breaking down collagen faster (via increased collagenase enzyme activity). As alcohol damage progresses, the balance shifts: the liver's collagenase activity drops and continued collagen production by the transitional cells results in progressive collagen deposition and extensive fibrosis. This eventually deprives the liver of most of its function (the state of cirrhosis). It may well be that in the baboons fed PC along with alcohol, excessive collagen production was partially blocked by PC, and collagen breakdown was increased for a sustained period (also via increased collagenase). Ongoing dietary supplementation with PC seemingly restored normal collagen balance in the transitional cells, thereby blocking further fibrosis and protecting the baboons for several years and potentially longer.

These findings with primates strongly suggest that advanced liver damage in humans, clinically expressed as cirrhosis, may prove amenable to dietary PC. As a result of this research breakthrough by the Lieber group, excitement developed in the U.S. research community around the potential of PC to slow, to stabilize, and perhaps in some cases even to reverse, alcoholic liver damage. An editorial in the journal *Alcoholism: Clinical and Experimental Research* discussed PC as a possible "magic bullet" for this purpose.[18] The Lieber baboon studies also established that choline does not have comparable benefits to PC for the liver. The small choline molecule is actually part of the headgroup of the large PC molecule, but when free choline was added to the baboon diet it proved toxic to the alcohol-damaged liver.[48]

Benefits of PC Against Other Liver Toxins

Further clinical evidence indicates that PC supports liver cells against attack by a variety of toxic agents other than alcohol. The trials reported in this category are sparse because of the difficulties in assembling victims of toxic exposures. However, some clinical trials have been accomplished, and their findings indicate PC is also unique in its protection of the liver against toxins other than alcohol.

As discussed earlier, the liver is directly vulnerable to foreign substances ("xenobiotics") entering the body. Blood carrying newly-absorbed molecules proceeds directly to the liver from the intestines. Substances as diverse as drugs, whether legal or illegal; anesthetics; herbs, foods, and pollutants can be rendered more toxic after reaching the liver, due to bioactivation by the liver P450 and related enzyme pathways (see Fig. 4). Almost all of these substances are liver toxins because of their conversion into reactive oxidants, which deplete the antioxidants and other Phase 2 conjugation resources. This unfortunate lack of discriminative activity by the liver underlies most of the notorious liver toxicity of pharmaceuticals. Excessive intake of substances from any xenobiotic category can predispose the liver to damage in response to otherwise-reasonable intakes of substances from other categories. A classic example is alcohol intake potentiating the metabolism of pharmaceuticals.

• **Drug Xenobiotics.** Both prescription and over the counter pharmaceuticals can become activated to toxic metabolites in the liver.[4,19] The most heavily consumed among these are the painkillers acetaminophen, aspirin (acetylsalicylic acid), ibuprofen, carbamazepine, indomethacin, phenylbutazone; the antibiotic tetracycline; the anti-arrhythmic drugs amiodarone, perhexiline, and hexestrol; the blood pressure drug alpha-methyldopa; the anticlotting medication sulfinpyrazone;
the barbiturate phenobarbital; the chemotherapy drug methotrexate; the gout drug al-

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lopurinol; the anti-tuberculosis drug isoniazid (particularly in combination with rifampin); the CNS stimulant amineptine; the tricyclic antidepressant tianeptine; the anti-epileptics phenytoin and valproic acid; and the benzodiazepine sedative chlordiazepoxide. Anesthetics that are potentially toxic to the liver include halothane. Of the illicit drugs, cocaine has been extensively studied for its toxicity to the liver by bioactivation.

Marpaung and colleagues did a 1988 double-blind trial for which they assembled 101 tuberculous subjects who earlier had suffered liver damage from rifampin and 2 other anti-tuberculosis pharmaceuticals.[20] The PC group received 1350 mg of fortified PC daily, versus placebo for 3 months. Both groups showed good clinical improvement, but in the PC group SGOT and SGPT were significantly lower when compared with the group that received the placebo. Kuntz and collaborators had made a similar finding in 1979, by giving PC via the intravenous route.[21]

Long-term intakes of certain of the antiepileptic drugs, especially phenytoin, pose a high risk of liver damage. Hisanaga and collaborators (1980) in Japan followed 38 subjects who had received phenytoin and other antiepileptic drugs for an average of five years.[22] A subgroup with the highest degree of damage (assessed by SGGT enzyme elevation), after being given PC orally for 6 months, experienced remarkable benefits.

• **Other, non-Pharmaceutical Xenobiotics.** Chemicals produced by industry currently number at least sixty-five thousand. One of the chemical classes most toxic to the liver is the chlorinated and related halogenated hydrocarbons, of which carbon tetrachloride has been extensively researched as an experimental model. Included in this class is the dry cleaning solvent trichloroethylene, along with many commonly used herbicides and pesticides. In 1965 Kuntz and Neumann-Mangoldt documented an antidotal effect from PC against acute oral trichloroethylene poisoning.[23] Also, non-halogenated organic solvents, allyl alcohol, carbon disulfide, ethionine, and thioacetamide all are markedly liver-toxic, by mechanisms similar to those illustrated in Fig. 4. Numerous case histories have been published that document the benefits of PC in other types of xenobiotic toxicity.

Among plants that can be mistaken as foods, the deathcap mushroom (*Amanita phalloides*) carries toxins that are some of the most lethal agents known. Esslinger used PC, at first intravenously then also orally, to avert death in victims of deathcap poisoning.[24] In Esslinger's experience, PC worked against deathcap mushroom toxicity after milk thistle extract had failed to show benefit. He called PC "a valuable extension to therapy for this grave form of poisoning."

• **Natural plant toxins.** In addition to the deathcap mushroom, aflatoxin from moldy peanuts is also one of the most toxic natural substances, and also becomes operative via bioactivation. Constituents of herbs also can be liver-toxic by bioactivation, the most notorious of these being the pyrrolizidine alkaloids found in comfrey and at least 59 other plants.

• **Radiation exposure.** Klemm and Pabst in 1964 gave PC to 161 subjects who had previously undergone radiation treatment.[25] Radiation scattered from the head-neck area tended to damage the liver, and PC afforded partial but clinically-meaningful protection against this occurrence.

• **Other toxic insults to the liver,** such as from high galactosamine intake or partial hepatectomy (the surgical removal of liver tissue), and a variety of other sources, have proven amenable to improvement by PC in

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studies conducted with laboratory animals.

Controlled Trials with PC in Viral Liver Damage

A number of viruses can damage the liver, by precipitating widespread inflammatory breakdown which is further complicated by overactivation of the immune system (autoimmune complications). Once successfully installed in the liver parenchyma, such viruses can become chronic and very hard to dislodge. Liver viruses (here simply called LV) can wreak havoc with the liver's functions. Medical weapons for eliminating LV from the liver, or for ameliorating their progressive damage, have been limited. Controlled clinical trials have unequivocally established PC as safe and reliable nutritional support for the liver against the damage initiated by LV.

Mueting and collaborators in 1972 gave 16 subjects with chronic, aggressive LV a relatively high intake of PC (2,050 mg per day) for an average 8 months.[26] A number of clinical parameters improved, including measures of the liver's detoxification pathways that metabolize amino acids and phenols, and the authors concluded that PC was having a "normalizing" effect on the liver as a whole. From their large open study reported in 1973, over the course of which some subjects received PC for up to 5 years, Wallnoefer and Hanusch noted a success rate for chronic, aggressive LV infection of 35.3 percent.[7]

Hirayama, Yano and collaborators conducted a double-blind trial in Japan in 1978, using 124 subjects with various LV.[27,28] They gave PC (1350 mg per day) to a group of 58 subjects and placebo to 66 subjects, for twelve weeks. The PC group experienced significant reductions in SGOT and SGPT levels when compared with the placebo group; those with higher enzyme values to begin with appeared to benefit the most. A subsequent blinded biopsy assessment after 6 months confirmed that in the PC subjects, the liver parenchymal tissue had partially recovered from its earlier damage; focal necrosis/cell death was lessened in the PC group, and these subjects showed signs of liver regeneration.

In 1981, Kosina and collaborators conducted a sophisticated trial in Czechoslovakia that compared PC against drugs for the management of viral-related liver inflammation. They recruited 80 subjects with presumed acute LV infection (viruses hepatitis A and hepatitis B), and divided them into four groups of 20 subjects each.[29] The first 2 groups were drawn from subjects whose bilirubin levels were low (below 250 micromoles per liter) and were judged "moderately serious." Subjects in Group I were administered fortified PC (1350 mg) along with the "standard treatment" that involved diet, rest, vitamins, and glucose; Group II received the standard treatment only. Groups III and IV were judged "serious," with bilirubin levels above 250 micromoles per liter. Group III received fortified PC and 580 mg daily of the immunosuppressive drug prednisone (a drug option for the suspected immune system overactivation from LV); Group IV received prednisone plus the standard treatment.

PC had a clearly favorable effect in this trial. Concerning the resolution of viral damage, both Group I subjects (less severe) and Group III (more severe) had their liver tests return to normal markedly faster than the corresponding groups that did not receive PC. Subjects who did not receive PC were more likely to relapse (10% in the less severe, 25% in the severe), while no relapses occurred in the PC groups. Upset stomach, jaundice, and liver swelling, as well as the lab tests, all resolved faster in the groups treated with PC. There was a trend towards lower occurrence of the hepatitis B surface antigen (HBsAg) in the PC groups as treatment progressed.

Jenkins and collaborators at King's College, London did a double-blind trial in 1982 on 30 subjects with progressing liver

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damage from chronic LV (hepatitis B virus, negative for HBsAg), as verified by biopsy.[30] They randomly divided the subjects into two groups of 15 each, kept them on the standard immunosuppressive therapy (prednisolone or azathioprine), then gave one group PC (2,300 mg per day) and the other placebo, for 1 year. At the end of this period, the group given PC had no clinical changes, while the placebo (control) group had worsened. Biopsies revealed significant improvement of the liver structure in the PC group, versus no improvement for the controls. More of the PC subjects reported improved well-being than did the controls (62% versus 43%). In 3 of the 15 subjects given PC the viral infection was judged to be inactive at the end of the trial, while no subjects were judged inactive from the placebo group. Thus in this small controlled trial, PC halted and partly reversed chronic LV damage, improved overall well-being, and "turned off" the virus in as many as 20% of the subjects.

In 1985, Visco and collaborators assembled 60 subjects who were positive for hepatitis B virus (assessed as presence of HBsAg) and who had acute LV liver damage, and divided them into two groups.[31] Within 10 days from the onset of jaundice, on a double-blind basis the subjects were started on either fortified PC (1350 mg) or placebo capsules. Lab tests were conducted frequently, and immune evaluations and clinical exams were done at 30, 90, and 180 days (6 months, end of trial).

By the 30-day mark, the group given PC was significantly more improved than the placebo group, with 50% being negative for HBsAg versus 25% for the controls ($p<0.05$). PC improved the rate of clearance of virus antigen from the blood. The immune parameters were not significantly different, though liver enzyme tests showed trends favoring PC.

In 1990, Hantak and collaborators in Yugoslavia used PC to manage 24 subjects with LV (hepatitis B virus).[32] All the subjects were chronically infected—they all had been virus carriers for at least 6 months. Seven had viral antigens (HBeAg) which indicated a relatively high degree of active infection. The other 17 subjects had no viral antigens and had antibodies to the virus (anti-HBeAg), indicating that they were in a stage of relative viral inactivity. All subjects received 900 mg of fortified PC per day. After 4 months, the less severely affected, antibody-positive subgroup showed statistically significant improvements in SGOT, SGPT, albumins, gamma-globulins, and other biochemical measures. The subgroup that began the study with active virus had statistically significant improvements in immune measures, suggestive of clinical benefit from PC. The effects of PC in this small and not well controlled trial were judged encouraging, and might have been more dramatic had the daily intake been as high as in other trials (a minimum 1350 mg of fortified PC, rather than the 900 mg that was given).

Controlled Trials with PC Against Severe Liver Damage

This category of liver damage is characterized by extensive fibrosis, which effectively stifles whole zones of the liver. Sometimes aggressive inflammatory changes are also present. This stage can be reached as a consequence of persistent alcohol intake, persistent viral infection, or the unchecked toxic effects of any of the many other agents that can damage the liver. Given the severity of the structural and functional damage to the liver at this stage, lesser benefits are to be expected from PC supplementation than at earlier stages. Yet still PC proved beneficial.

Fassati and collaborators in 1981 in a controlled trial conducted in Prague, Czechoslovakia, studied 61 subjects with moderately severe to severe functional breakdown of the liver.[33] The degree of advanced liver damage (extensive fibrosis, inflammation, elevated en-

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zymes) was assessed by biopsy and by a wide range of blood biochemical tests. Thirty-four (34) subjects were given fortified PC (900 mg per day), and 27 subjects served as controls. The trial ran for 4 months, with each patient serving as their own control for statistical analysis.

Biochemical re-testing conducted at the end of the trial showed that except for the bilirubin values, all the other biochemical indicators were significantly improved ($p<0.01$). These included the albumin/globulin ratio, albumin, bromsulfalein (BSP) clearance, SGPT, and SGOT. The number of subjects positive for HBsAg in the blood moved from 8 of 34 to 3 of 34 in the PC group; that of the controls moved from 7 of 27 to 6 of 27. The trend apparent in the PC group was not statistically significant due to the small numbers of HBsAg-positive subjects in both groups from the beginning of the trial. The investigators commented that fortified PC was the only intervention they were aware of that seemed to bring down viral antigen levels, and they urged further investigation of this possible benefit with larger groups of subjects.

In 1991, Ilic and Begic-Janev conducted a randomized, double-blind, placebo-controlled trial.[34] They recruited 50 subjects, all positive for HBsAg (hepatitis B virus antigen) who had extremely severe liver damage as verified by biopsy and immunologic testing. The test group was administered 1350 mg of fortified PC, and the control group received a placebo. Both groups were followed for 1 year, with periodic sampling for lab assessments, then at the end of the 12 months they were biopsied again.

After 12 months the subjects given PC had experienced considerably greater benefit, as assessed both from the structural biopsy findings and from the lab findings ($p <0.001$). Among the PC group, 20 of 25 were judged good to moderately good, versus 6 of 25 being moderately improved in the placebo group. Six of the 25 in the PC group also lost the HBsAg viral antigen, versus only 3 of 25 for the placebo group. Such "seroconversion" indicated marked clinical improvement for these fortunate subjects. A number of cell-structural, biochemical, immunologic, and hematologic parameters were significantly improved in the PC group as compared with the placebo group. Improvement in the PC group continued well past the end of the trial.

As a rule, researchers working with such severely affected subjects obtained better results by maintaining the subjects on combined intravenous PC and oral supplementation until substantial improvement had begun.

Other trials with severe liver damage, though not controlled, are worthy of note. Wallnoefer and Hanusch in their pioneering study administered PC both intravenously and orally to 130 subjects with advanced, fibrotic liver damage.[7] Once the clinical indicators began returning to normal, they switched to purely oral administration at relatively low intakes (450-700 mg), which was continued for months to years as necessary. PC produced benefits for 17.5% of these subjects, as confirmed from normalized enzyme levels and improved tissue structure on biopsy. Using a similar strategy, they achieved benefit for 35.3 percent of their subjects with chronic viral infection of a kind that was positive for viral antigen and has an aggressive tendency to progress to severe liver damage. Kuntz reported in 1989 on 10 subjects to whom he gave PC intravenously at 2,800 mg per day.[3] Improvements were seen as early as the seventh day, and at the end of the 28-day trial period 3 subjects showed "dramatic, life-saving" improvement, 2 had "increasingly rapid improvement," 2 had gradual improvement, 2 had no change; and 1 of the 10 subjects had died.

Kalab and Cervinka worked with 30 subjects who had advanced liver damage for which pharmaceutical treatments had failed.[35] Orally administered fortified PC (1350 mg daily) produced clinical improvement after 6

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months, with favorable effects on the usual enzyme indicators of liver damage.

In summary, the experiences from the clinical trials discussed above concur with findings from others[36-40] to paint a clear picture of PC as an effective and safe nutrient for liver damage of all degrees of severity.

PC Benefits the Liver Primarily Through Cell Membranes

The efficacy of PC in protecting the liver against toxic attack can be attributed to its important role in cell membranes. The membrane systems are among the cell constituents most vulnerable to toxic attack, and the diverse array of hepatotoxic substances operates through common pathways: free radical or other oxidative attack that depletes antioxidants, leading to oxidative overload and subsequent peroxidative damage to the cell's membranes.[4] The ultimate consequence is the death of the cell.

The phospholipids of cell membranes are partially unsaturated, and by being packed tightly next to each other in the membrane they are highly vulnerable to oxidative attack from free radicals and other highly reactive, oxidant toxins. Under excessive or sustained attack, the membrane phospholipids become degraded ("peroxidized"), mainly through their fatty acid tails. As the phospholipids peroxidize, membrane continuity is interrupted. Holes begin to develop in the cell's outer membrane, resulting in loss of control over internal conditions. Enzymes and other larger bio-molecules begin to leak out, homeostasis fails, and the death of the cell becomes imminent.

Viral attack on the liver follows a model similar to chemical attack: viral invasion of the parenchymal cells initiates release of pro-inflammatory, oxidizing substances. Immune cells arrive in the area and begin releasing more oxidants via their "respiratory burst." These activities initiate cascades of peroxidative membrane damage to the liver cell membranes, and the damage spreads to neighboring zones within the tissue.

PC plays crucial roles in supporting the membrane-based structure and functions of the liver's parenchymal cells. When orally administered to experimental animals, in quantities usually equivalent to 1-3 grams per day for the human, PC had the following liver-protective effects:

- Leakage of "indicator" enzymes from the liver tissue was lessened
- Lipid peroxidation from free radical/oxidant insult was lessened
- Membrane damage was slowed, membrane integrity was conserved
- Cell death, fibrosis, and fatty infiltration of the liver tissue were diminished
- Cell synthesis of RNA and protein increased, suggesting regeneration
- Liver metabolism improved

This documented range of benefits from PC is consistent with its functions at the cell membrane. PC is required for the structural integrity of all the body's cell membrane systems, and is essential to their functionality.[41-45] PC is crucial both for the internal membranes to do their housekeeping and specialized functions, and for the cell's "master switch"—its outer membrane. The outer membrane interfaces with both the external environment and the internal environment of the cell; PC supports the membrane receptors that "hear" these molecular messages and carry them across the membranes in both directions. This outer membrane is also the cells' reservoir for the eicosanoids and other phospholipid derivatives that act as outgoing vocabulary, speaking the language of that cell to others.

The accumulated findings from decades of research are that PC is an important protective nutrient for the liver, primarily through being a building block for cell mem-

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branes. PC is essential for the liver's baseline homeostatic housekeeping functions, for the liver's recovery following toxic damage, and not least to support the sophisticated liver metabolism that determines the individual's level of health and freedom from disease.

PC is highly bioavailable (about 90% of the administered amount is absorbed over 24 hours),[46] and PC represents a far more pleasant means for dietary choline repletion than choline itself. Lastly, even as the PC molecule is efficiently absorbed, it also is an excellent emulsifier that enhances the bioavailability of nutrients with which it is co-administered. Antioxidant nutrients and especially the flavonoids are likely to be better absorbed in combination with PC,[47] as are B vitamins, minerals, and numerous other nutrients.

Conclusion:

From the many controlled clinical studies conducted on thousands of human subjects to date, PC's confirmed clinical benefits include:

- Successful improvement of specific indicators of liver damage
- Faster functional and structural recovery of the liver tissue
- Accelerated restoration of subjects' overall well-being

In the trials cited in this review, PC was very well tolerated at oral intakes that ranged up to 4.6 grams per day, and was found to be more effective the earlier it was administered. Subjects who are started on PC after their liver is already severely damaged are more likely to benefit from higher oral intakes of PC (up to or exceeding 4.6 grams per day). The most severe cases are likely to thrive with the help of intravenous PC, administered in combination with a high oral dose.

Lieber and colleagues' elegant studies with baboons as a primate model of alcoholic liver damage have established that PC can stave off steadily-worsening damage from chronic alcohol consumption; improvement from PC is far more likely if the subject's alcohol consumption is ceased. The small choline molecule is actually part of the headgroup of the large PC molecule, but when free choline was added to the baboon diet it proved toxic to the alcohol-damaged liver. Phosphatidylcholine is a highly bioavailable form of choline; it is also the most biologically significant and (for damaged livers, at least) the safest source of choline.

PC is undoubtedly a critically important nutrient for the liver, both because it is the primary cell membrane building block and because the liver is so functionally dependent on its estimated 33,000 square meters of membrane surface. Whether the liver has been damaged by alcohol, by other toxic chemicals, by pharmaceuticals, or by viruses, dietary supplementation with PC significantly speeds recovery. The clinical studies demonstrate that dietary PC in sufficient amounts revitalizes whole zones of cells in the recovering liver.

PC has other qualities that further enhance its remarkable usefulness as a dietary supplement. PC is well documented as safe to take, and seems fully compatible with pharmaceutical regimens and with other nutrients. The PC molecule enhances the bioavailability of nutrients with which it is co-administered, is highly bioavailable and represents a far better means for dietary choline repletion than choline itself.

The jury is still out on whether PC is truly a "magic bullet" for alcoholic liver disease, but its benefits against various severities of liver damage and its proven safety indicate that for the liver it is a nutrient of major importance.

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