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Invited Review

Curcumin: An Atoxic Antioxidant and Natural NF-~B, Cyclooxygenase-2, Lipooxygenase, and Inducible Nitric Oxide Synthase Inhibitor: A Shield Against Acute and Chronic Diseases

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Chronic diseases (ChD) constitute a fast-increasing burden to society. The World Health Organization estimates that 46% of global disease burden and 59% of global mortality is due to ChD; 35 million individuals die each year from ChD, and the numbers are increasing steadily.

The painful increase in costs for health care in recent decades is expected to continue and to accelerate. This is not only because the numbers of patients with ChD is increasing but also because treatments are becoming more sophisticated and thereby more expensive. For example, the costs of diabetes doubled during the past 5 years. If these trends continue, most healthcare systems, socialized or private, will be in great trouble, and dramatic and painful cuts in privileges will be unavoidable. In 2002, $1.6 trillion was spent in the US on health care, about $5440 for every person, an expense expected to double by 2011.[1] In order to prevent a total collapse of the system, preventive measures will be increasingly necessary.

The cost of medication is a large and growing part of health expenditure. This is one of many reasons why inexpensive alternatives to standard pharmaceuticals for prevention and treatment of disease, methods which have been successfully practiced for centuries in countries such as India and China, are increasingly attractive. Agents with the documented ability to boost resistance and decrease vulnerability to disease, often referred to as chemopreventive agents, will have an important role to play. These substances are not only inexpensive, they are also easily available and have limited or no toxicity. Among these chemopreventive agents are a series of phenolic and other compounds believed to reduced aging and prevent degenerative malfunctions of organs: isothiocyanates in cruciferous vegetables, epigallocatechin-3-gallate (EGCG) in green tea, caffeic acid in coffee, capsaicin in hot chili peppers, chalcones in apples, euginol in cloves, gallic acid in rhubarb, hisperitin in citrus fruits, naringenin in citrus fruits, kaempferol in white cabbage, myricetin in berries, quercetin in apples and onions, resveratrol and other procyanidin dimers in red wine, and various curcumenoids found in turmeric (TU) curry.

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Curcumin (CU): A Promising Tool

Interest in polyphenols, and especially in CU as a chemoproctive agent, has dramatically increased in recent years. CU, the most explored of the curmenoids, has received increasing interest in recent years. The majority of studies reported thus far are experimental and few clinical studies have been published. This review is intended to provide a comprehensive description of the experimental and clinical effects of treatment with CU.

The nuclear factor NF-~B plays a critical role in several signal transduction pathways involved in chronic inflammatory diseases [2] such as asthma and arthritis and various cancers.[3] Activation of NF-~B is linked with apoptotic cell death, either promoting or inhibiting apoptosis, depending on cell type and condition. The expression of several genes such as cyclooxygenase-2 (COX-2), matrix mettaloproteinase-9 (MMP-9), inducible nitric oxide synthase (iNOS), tumor necrosis factor (TNF), interleukin-8 (IL-8), eotaxin, cell surface adhesion molecules, and antiapoptotic proteins are regulated by NF-~B.[4] The cyclooxygenases are responsible for prostaglandin synthesis. Although COX-1 is constitutive and required for normal "housekeeping" functions, COX-2 is inducible and barely detectable under normal physiologic conditions. It is rapidly but transiently induced as an early response to proinflammatory mediators and mitogenic stimuli, including cytokines, endotoxins, growth factors, oncogenes, and phorbol esters. COX-1 is responsible for protection of mucosal surfaces, maintenance of renal function, and platelet activity and stability. COX-2 synthesizes series-2 prostaglandins (PGE2, PGF2-~), which contribute to inflammation, swelling, and pain. Among the functions of PGE2 are promotion of IL-10, an immunosuppressive cytokine, and suppression of

IL-12.[5] Another enzyme that plays a pivotal role in mediating inflammation is iNOS. iNOS is activated by NF-~B and acts in synergy with COX-2 to promote the inflammatory reaction.

TU: An Approved Food Additive

CU, 1,7-bis(4-hydroxy-3-methoxyphenol)-1,6heptadiene-3,5-dione), is a polyphenol found in the dietary spice TU, derived from dried rhizozomes of the perennial herb *Curcuma longa* Linn, a member of the ginger family. It is a lipophilic molecule with phenolic groups and conjugated double bonds. Its molecule resembles ubiquinols and other phenols known to possess strong antioxidant activities. Its bioavailability from oral administration is low but can be improved by dissolution in ambivalent solvents (glycerol, ethanol, DMSO).[6] Its bioavailability has been reported to be increased by coingestion of peperine (a component of pepper), a finding that has been demonstrated in both experimental animals and humans.[7] TU is mainly known for its ability to preserve food and is approved as a food additive in most Western countries. It is produced in several Asian and South American countries. In India alone, about 500,000 metric tons are produced each year, of which about half is exported. It has been used for generations in traditional medicine for the treatment of inflammatory conditions such as arthritis, colitis, and hepatitis. Several studies have demonstrated that CU is nontoxic, even in very high doses.[8,9] Treatment of humans during 3 months with 8000 mg CU per day showed no side effects.[9] It is estimated that most adult Indians consume 80–200 mg CU per day.[10] A common therapeutic dose is 400–600 mg CU 3 times daily, corresponding to up to 60 g fresh TU root or about 15 g TU powder. The content of CU in TU is usually 4%–5%.

CU Controls Stress -Induced Overinflammation

CU inhibits COX-2 and iNOS inhibits arachidonic acid metabolism, modulates cellular signal pathways, and inhibits certain hormonal, growth factor, and oncogene activities. It is also a potent inducer of cytoprotective heat shock proteins (HSP).[12,13] CU inhibits lipooxygenases (LOX) and leukotreines such as LBT4 and 5HETE,[14] especially when bound to phosphatidylcholine micelles.[15] It is reported to inhibit cytochrome P450 isoenzymes and thereby activation of carcinogens.[16] CU can intercept and neutralize potent prooxidants and carcinogens, both ROS (superoxide, peroxyl, hydroxyl radicals) and NOS (nitric oxide, NO; peroxynitrite).[17] It is also a potent inhibitor of TGF-~ and fibrogenesis,[18] which may explain its positive effects in diseases such as kidney fibrosis, lung fibrosis, liver cirrhosis and Crohn's disease, and in prevention of the formation of tissue adhesions.[19] It has been suggested that CU is effective in Th1-mediated immune diseases.[20]

Many medicinal herbs and pharmaceutical drugs are therapeutic at one dose and toxic at another. Interactions between herbs and drugs, even if structurally unrelated, may increase or decrease the pharmacologic and toxicological effects of either component.[21,22] It is suggested that CU may increase the bioavailability of vitamins such as vitamin E and decrease cholesterol. In experimental studies, CU significantly raises the concentration of ~-tocopherol in lung tissues and decreases plasma cholesterol.[23] Polyphenols, isothiocyanates such as CU and flavonoids such as resveratrol, are all made accessible for absorption into the intestinal epithelial cells and the rest of the body by digestion/fermentation in the intestine by microbial flora.[24] CU binds to albumin, by hydrophobic interactions, and may thereby be transported to appropriate target cells, where it elicits its pharmacologic effects.[25] It is also reported to form intracellular conjugates with glutathione.[26]

CU to Prevent and Treat Diseases

Atherosclerosis. Hyperhomocysteinemia, an expression of increased prooxidant activity in the body, is generally regarded as a cardiovascular risk factor, equivalent to hypercholesterolemia.[27] High intake of antioxidants and vitamins, particularly B-vitamin-rich foods, and folate, is known to be associated with reduced total plasma homocysteine (tHcy) and lower incidence of cardiovascular disease.[28,29] A strong inverse association has been reported among plasma concentrations of vitamin E, plasma cholesterol, and presence of carotid arteriosclerosis.[30] CU may prevent lipid peroxidation, stabilize cellular membranes, inhibit proliferation of vascular smooth muscle cells, and inhibit platelet aggregation, all important ingredients in the pathogenesis of arteriosclerosis. When the ability of CU, quercetin, capsaicin, and a defined antioxidant butylated hydroxy anisole (BHA) were compared with inhibit the initiation and propagation phases of low-density lipoprotein LDL oxidation, CU was found to be the most effective and quercetin the least.[31] Cellular membranes, such as those of erythro- AQ: 3 cytes, with excess cholesterol content show reduced fluidity and become fragile. CU, capsaicin, and garlic (allecin), fed to rats receiving a cholesterol-enriched diet, prevented both the increase in membrane cholesterol and the increased erythrocyte fragility.[32] Dietary CUoids have been reported to increase hepatic acyl-CoA and prevent high-fat diet–induced accumulation in the liver and adipose tissues in rats.[33] CU was reported to prevent the early atherosclerotic lesions in the thoracic and abdominal aorta, in parallel with significant increases in plasma concentrations of coenzyme Q, retinol, and ~-tocopherol and reductions in LDL-conjugated dienes and TBARS (thiobarbituric acid–reactive substances), which were observed in rabbits fed an atherogenic diet for 30 days.[34]

Diabetes. Insulin resistance syndrome is associated with elevated tHcy and increased lipid oxidation.[35] TU (1 g/kg body weight) or CU (0.08 g/kg body weight) was supplied daily for 3 weeks to rats with alloxan-induced diabetes (AID). Then, healthy controls (CO) were compared with diabetic animals (AID) and with animals treated with CU.[36] Significant improvements were observed in blood glucose (mg/dL CO 88.3, AID 204.4, TU 142.7, CU 140.1), hemoglobin (gm/dL CO 14.7, AID 10.8, TU 13.6, CU 13.1), and glycosylated hemoglobin (gm/dL CO 2.8, AID 11.2, TU 9.0, CU 7.8). Significant

differences were also observed in TBARS in liver tissue icantly inhibited elevations in alkaline phosphatases (nmol/g tissue CO 43.0, AID 54.0, TU 34.0, CU 29.0), (ALP): CO 85.88, high fat diet (AO) 239.56, CU 177.41 TBARS in plasma (nmol/mL CO 3.8, AID 7.3, TU 5.3, and PCU 149.15; and in ~-glutamyl transferase (GGT): CU 4.6), glutathione in liver (~g/mg CO 23.4, AID 11.2, CO 0.60, AO 2.51, CU 1.43, PCU 1.15. Similar benefi-TU 16.6, CU 20.9), and glutathione in plasma (mg/dL cial effects were observed on histology in various tis-CO 22.4, AID 14.2, TU 18.4, CU 20.1). Activity of sues and in hepatic content of cholesterol, triglycersorbitol dehydrogenase (SDH), which catalyzes the ides, free fatty acids, and phospholipids. Rats in conversion of sorbitol to fructose, was significantly low- another study were fed for 4 weeks with fish oil and ered by treatment with both TU and CU. ethanol (FE), which resulted in hepatic lesions consist-

Respiratory diseases. As mentioned above, CU is a ing in fatty liver, necrosis, and inflammation. CU in a potent inhibitor of TGF-~ and fibrogenesis[18] and may daily dose of 75 mg/kg/d to these rats prevented the have positive effects in fibrotic diseases in kidneys, histologic lesions.[43] CU suppressed NF-~B-dependent liver, intestine (Crohn's disease), body cavities (preven- genes, blocked endotoxin-mediated activation of tion of fibrous adhesions),[19] and lung fibrosis, including NF-~B, and suppressed the expression of cytokines, cystic fibrosis. The latter is of special interest as it has chemokines, COX-2, and iNOS in Kupffer cells. Similar been linked to glutathione deficiency. The effect of CU effects were also observed in carbon tetrachloride– upon amiodarone-induced lung fibrosis was recently induced injuries. Pretreatment for 4 days (100 mg/kg/d studied in rats.[37] Significant inhibition of LDH activ- body weight) with CU before intraperitoneal injection ity, infiltration of neutrophils, eosinophils and macro- of CCl_4 prevented significantly subsequent increases in phages in lung tissue, LPS-stimulated TNF-~ release, TBARS: CO 274, CCl_4 556, CU 374, alanine aminophorbol myristate acetate (PMA)-stimulated superox- transferase (ALT): CO 46, $CCL_4$182, CU 97 and asparide generation, myeloperoxidase (MPO) activity, tate aminotransferase (AST): CO 97, CCl_4 330, CU 211 TGF-~1 activity, lung hydroxyproline content and and in hydroxyproline (~g/g liver tissue): CO 281, CCl_4 expression of type I collagen and c-Jun protein were 777, CU 373.[44]
observed when CU was supplemented (200 mg/kg body *Pancreatic diseases.* The effect of CU was studied in 2 weight) in parallel with intratracheal instillation of different models of pancreatitis: cerulein-induced and 6.25 mg/kg body weight of amiodarone. CU exhibits ethanol CCK–induced .[45] CU was administered IV in structural similarities to isoflavonoid compounds that parallel with induction of pancreatitis. A total of 200 are thought to bind directly to the cystic fibrosis trans- mg/kg/d weight was administered during the treatmembrane conductance regulator (CFTR) protein and ment period of 6 hours. CU treatment significantly alter its channel properties.[38] Egan et al, [39] who had reduced histologic injuries of the pancreatic tissue (acipreviously observed that CU inhibits a calcium pump nar cell vacuolization and neutrophil infiltration), in endoplasmic reticulum, thought that reducing cal- intrapancreatic activation of trypsin, hyperamycium levels might liberate the mutant CFTR and lasemia, hyperlipasemia, pancreatic activation of increase its odds of reaching the cell surface (see also NF-~B, I~B degradation, activation of activator protein Zeitlin[40]). The ~F508 mutation, the most common (AP)-1, and inflammatory molecules such as IL-6, cause of cystic fibrosis, will induce a misprocess in the TNF-~, chemokine KC, iNOS, and acidic ribosomal endoplasmic reticulum of a mutant CFTR gene. A dra-phosphoprotein (ARP). CU in both models also stimumatic increase in survival rate and in normal cAMP- lated pancreatic activation of caspase-3, a mediator of mediated chloride transport across nasal and gastroin-apoptosis.
testinal epithelia was observed in gene-targeted mice *Gastric diseases.* Both a methanol extract of TU and homozygous for the ~F508 when supplemented CU.[38] pure CU were tested *in vitro* against 19 different *Hel-*
No human studies are yet reported, and it too early to *icobacter pylori* strains, including 5 cagA~ strains (cag know if this treatment will be able to halt or reverse A is the strain-specific *H pylori* gene linked to prema-the decline in lung function also found in patients with lignant and malignant lesions). Both treatments were cystic fibrosis. An eventual antiasthmatic effect of CU equally effective and both significantly reduced growth was recently tested in guinea-pigs sensitized with of all strains tested.[46] Subsequent studies demonstrate ovalbumin. Significant reductions were observed both that CU inhibits the infection and inflammation of in airway constriction and airway hyperactivity to gastric mucosal cells by inhibiting activation of NF-~B, histamine .[41] degradation of I~B~, NF-~B binding to DNA, and activity

Liver diseases. Ethanol-induced steatosis is known to of I~B kinases ~ and ~. No CU–induced effects were be further aggravated by supply of PUFA-rich vegeta-observed on mitogen-activated protein kinases (MAPK), ble oils that have been thermally oxidized. Rats fed by extracellular signal regulating kinases 1 and 2(ERK1/2), gavage for 45 days with a diet containing 20% ethanol and p38. However, the *H pylori*–induced mitogenic and 15% sunflower oil, heated to 180°C for 30 minutes response was blocked by CU .[47] Significant antifungal (AO), showed extensive histopathological changes, properties against various fungal organisms, especially with focal and feathery degeneration, micronecroses phytopathogenic, by CU have also been reported.[48] and extensive steatosis in the liver, and extensive con- *Intestinal diseases.* Inflammatory bowel disease is gestion and fatty infiltration in the kidneys. These associated with overproduction of NO, induced by changes were largely prevented by administration of increased expression of the iNOS. Various attempts to CU, particularly photo-irradiated CU (PCU, CU kept reduce this expression have been made .[49] Pretreatment in bright sunshine for 5 hours) .[42] Both products were during 10 days with CU at 50 mg/kg/d before induction supplied in a dose of 80 mg/kg/d. Both products of trinitrobenzene sulfonic acid (TNBS) coli-

tis resulted in a significant reduction of histologic tissue injury, neutrophil infiltration (measured as decreased myeloperoxidase activity), and lipid peroxidation (measured as decreased malondialdehyde activity) in the inflamed colon and in decreased serin protease activity.[50] A significant reduction in NF-~B activation, reduced levels of NO, and marked suppression of Th1 functions (IFN~ and IL-12p40 mRNA) were also observed. In another similar study, CU was added to the diet 5 days before induction of TNBS colitis, resulting in a significant reduction in myeloperoxidase and attenuation of the TNBS-induced message for IL-1~ on semiquantitative RT-PCR.[51] Western blotting revealed a significant attenuation of the activation of p38 MAPK. CU was supplied in combination with caffeic acid phenethyl ester (CAPE) to animals treated with cytostatic drugs (arabinose cytosine, Ara-C, and methotrexate, MTX).[51] The treatment inhibited the NF-~B-induced mucosal barrier injury and increased the *in vitro* susceptibility of the nontransformed small intestinal rat epithelial cell, IEC-6, to the cytostatic agents.

Cancer. Cancer is a group of ~100 different diseases, which manifest themselves in uncontrolled cellular reproduction, tissue invasion, and distant metastases.[52] Behind the development of these diseases is often exposure to carcinogens, which produce genetic damage and irreversible mutations if not repaired. During the last 50 years, attempts have been made to find or produce substances that could prevent these processes, so-called chemopreventive agents. Cancers are generally less frequent in the developing world, associated both with less exposure to environmental carcinogens and a richer supply of natural chemopreventive agents. The incidence per 100,000 population in the USA is considerably higher than in India for the following diseases: prostatic cancer (23 times), melanoma of the skin (male 14 times, female 9 times), colorectal cancer (male,11 times, female 10 times), endometrial cancer (9 times), lung cancer (male 7 times, female 17 times), bladder cancer (male 7 times, female 8 times), breast cancer (5 times), and renal cancer (male 9 times, female 12 times).[53] These differences are even greater when compared with China for some diseases, such as breast cancer and prostatic cancer. Consumption of saturated fat and sugary foods is much less common in the Asian countries, but equally important, consumption of plants with high content of chemopreventive substances is significantly higher in these countries. As an example, the consumption of CU has for centuries been about 100 mg/d in these Asian countries.[54] CU induces *in vitro* apoptosis of various tumor cell lines: breast cancer cells,[54,55] lung cancer cells,[56] human melanoma cells,[57] human myeloma cells,[58] human leukemia cell lines,[59] human neuroblastoma cells,[60] oral cancer cells,[61] prostatic cancer cells.[62–65] CU has inhibited intrahepatic metastases in experimental models.[66]

Few *in vivo* experimental studies and no clinical controlled trials are concluded thus far. However, a recent phase I study reported histologic improvement of precancerous lesions in 1 of 2 patients with recently resected bladder cancer, 2 of 7 patients of oral leukoplakia, 1 of 6 patients of intestinal metaplasia of the stomach, and 2 of 6 patients with Bowen's disease.[67] This was a small study, but its main purpose was to document that CU is not toxic to humans up to 8000 mg/d when taken by mouth for 3 months. Improvement of lesions was an incidental but highly suggestive finding.

Neurodegenerative diseases. A growing body of evidence implicates free radical toxicity, radical induced mutations, oxidative enzyme impairment and mitochondrial dysfunction in neurodegenerative diseases (NDD). Significant oxidative damage is observed all NDDs, which in the case of Alzheimer's disease (AD) leads to extracellular deposition of ~-amyloid (A~) as senile plaques. Nonsteroidal anti-inflammatory drugs (NSAIDs) like ibuprofen have proven effective in prevention of the progress of AD in animal models.[68] Gastrointestinal and occasional liver and kidney toxicity induced by inhibition of COX-1 precludes widespread chronic use of such drugs.[69] Use of antioxidants such as vitamin E (~-tocopherol) hasproven unsuccessful even when high doses were used.[70] Vitamin E, ~-tocopherol, is in contrast to ~-tocopherol a poor scavenger of NO-based free radicals. CU is a several times more potent scavenger than vitamin E[71]and is also a specific scavenger of NO-based radicals.[72] When used in a transgenic mouse model of AD, a modest dose of CU (24 mg/kg body weight), but not a much higher dose (750 mg/kg), significantly reduced oxidative damage and amyloid deposition.[73] Similar observations, reductions in both A~ deposits and in memory deficits, have also been noted in Sprague-Dawley rats.[74] The age-adjusted prevalence of both AD[75] and Parkinson's disease (PD) in India,[76] with its significantly higher intake of TU, is much lower than in Western countries. However, the preventive effects of consumption of TU can also be achieved with other polyphenol-rich fruits and vegetables if consumed in enough quantities. Blueberries, strawberries, and spinach in doses of 18.6, 14.8, and 9.1 g of dried extract/kg body weight were effective in reversing age-related deficits in both neuronal and behavioral parameters.[77] A study from 1999 is of special interest. Rats on chronic ethanol were randomized to 80 mg/kg body weight of CU.[78] Nonintoxicated normal rats (NI) were compared with rats given ethanol without CU (NI) and with CU-treated rats (CU). The degree of histopathological changes, the levels of TBARS (NI 1.29, CO 2.98, CU 2.41), cholesterol (NI 1531.9, CO 2031.1, CU 1658.2), phospholipids (NI 1845.5, CO 2795.1, CU 2011. 5), and free fatty acids (NI 26.7, CO 53.1, CU 39.9) in brain tissue were all significantly improved after CU treatment.

Ocular opacities. Cataract, an opacity of the eye lens, is the leading cause of blindness worldwide and is responsible for the blindness of almost 20 million people in the world.[79] Nutrition deficiencies, especially lack of consumption of antioxidants, diabetes, excessive sunlight, smoking, and other environmental factors are known to increase the risk of cataracts.[80] The age-adjusted prevalence of cataract in India is, however, 3 times that of the United States.[81] Despite that, 3 different experimental studies have reported signifi-

cant preventive effects of CU against cataracts induced by naphthalene,[82] galactose,[83] and selenium.[84]

Tobacco/cigarette smoke (CS)-induced injuries. CS is suggested to cause 20% of all deaths and about 30% of all deaths from cancer. CS contains thousands of compounds of which about 100 are known carcinogens, cocarcinogens, mutagens, or tumor promoters. Each puff of smoke contains ~10 trillion free radicals. Antioxidant levels in blood are significantly reduced in smokers. Activation of NF-~B has been implicated in chemical carcinogenesis and tumorigenesis through activation of several genes such as COX-2, iNOS, MMP-9, IL-8, cell surface adhesion molecules, antiapoptotic proteins, and others. A recent study reported that CU suppresses activation of NF-~B, which correlates with down-regulation of COX-2, MMP-9, and cyclin D1 in human lung epithelial cells.[85]

Other Studies

Increasing evidence suggests that saturated fat in the diet increases and plant fiber intake reduces inflammatory reaction in the body.[86] A high fat/low fiber diet is apparently associated with many chronic diseases.[87] Fruit and vegetable intake is associated with a reduction in the incidence of chronic diseases.[88] Focus is increasingly turning from fiber *per se* to active ingredients in plants, such as CU in TU. The only active ingredients to be reasonably explored with regard to their potential to enhance human health are those in the soya bean and more recently in TU. However, other compounds, including resveratrol in red wine and peanuts and quercetin in apples and onions and others, might prove equally powerful. This assumption is supported by a recent study using PC-SPES, a partially extracted composition of 8 herbs, all different from those mentioned above.[89] PC-SPES inhibited LPS induced production of murine macrophages and decreased their production of proinflammatory cytokines, including TNF~, IL-1~, and IL-6 and the inducible enzymes COX-2 and iNOS. Furthermore, PC-SPEC rescued C57BL/6 mice from death by LPS induced septic shock in conjunction with decreased levels of TNF~ and IL-1~.[89] PC-SPES has also been shown to inhibit growth of and induce apoptosis of various human cancer cells.[90–92]

One of the negative characteristics of CU is its low absorption and low availability in certain tissues such as the liver.[93] However, the efficacy of CU can m ost likely be improved both by modification of the C U molecule,[42] and production of new synthetic analogs.[94]

CONCLUSIONS

The use of medicinal plants and their active components is becoming an increasingly attractive approach for the treatment of various inflammatory disorders among patients unresponsive or unwilling to take standard medicines. Food derivates have the advantage of being relatively nontoxic. This is certainly so for TU and CU. If one chooses to supply CU together with its fiber (eg, as TU), the effects from the intake of fiber and from the active chemopreventive agent, CU and other curcumenoids, may be potentiated.

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