Pantothenic Acid

Gregory S. Kelly, ND

Description

Pantothenic acid (vitamin B_5) is a water-soluble B-complex vitamin that was identified in 1933, isolated and extracted from liver in 1938, and first synthesized in 1940.[1] R. J. Williams is credited with coining the name from the Greek word *panthos*, which translates as "from everywhere." It was given this name because of its widespread presence in food.[2]

Most vitamin B_5, and its derivatives or precursors, added to foods and beverages, or used in dietary supplements, is made by chemical synthesis.[2,3] Only the Dextrorotatory (D) isomer of pantothenic acid – D-pantothenic acid – possesses biologic activity. Pure D-pantothenic acid can be used as a dietary supplement: it is water-soluble, viscous, and yellow in color. Because D-pantothenic acid is relatively unstable – it can be destroyed by heat and acid and alkaline conditions – the more stable calcium pantothenate is the form of vitamin B_5 usually found in dietary supplements. It is water-soluble, crystalline, and white in color. Ten mg of calcium pantothenate is approximately equivalent to 9.2 mg of pure D-pantothenic acid.[2]

[Note: A monograph on pantethine was published in volume 15 of *Alternative Medicine Review* in 2010.[5]]

The disulphide form of pantothenic acid – pantethine – is also available as a dietary supplement. This is considered to be the most active form of vitamin B_5 because it contains the sulfhydryl-group needed for biological activity in Coenzyme A (CoA).[4]

A liquid form of vitamin B_5 – dexpanthenol, D-pantothenyl alcohol, D-panthenol, or panthenol – is also available. This is an alcohol pro-vitamin of vitamin B_5 (i.e., it is converted into pantothenic acid in the body), which is used primarily as a topical or injected form for cosmetic purposes or wound healing.[6]

Unless otherwise specified, the supplemental form of vitamin B_5 used in studies referenced in this monograph is calcium pantothenate.

Dietary Sources and Intake

Foods that are considered to be exceptionally good dietary sources of pantothenic acid include peanut butter (5-8 mg/100 g), liver (5-7 mg/100 g), kidney (4-6 mg/100 g), peanuts (2-3 mg/100 g), almonds (2-3 mg/100 g), wheat bran (2-3 mg/100 g), cheese (1.5 mg/100 g), and lobster (1.5 mg/100 g). The vast majority of vitamin B_5 in foods is found already incorporated into Coenzyme A (CoA) and as phosphopantetheine.[2] Refining, freezing, canning and cooking food causes losses of pantothenic acid, so a modern processed food diet would be expected to have lower amounts of vitamin B_5 than a whole foods diet.[2]

The Dietary Reference Intake (DRI) is 5 mg/d of pantothenic acid for males and females 14 years old and over, 6 mg/d during pregnancy, and 7 mg/d during lactation.[7] A 1981 study estimated that the average American diet contains about 5.8 mg/d of pantothenic acid.[8] A 2010 population study conducted in Japan, using data from the Nation Health and Nutrition Survey, estimated a daily intake of 4.52 mg/d of pantothenic acid.[9]

While the average intake appears to approximate the DRI, subsets of the population might be at higher risk for insufficient intake. A dietary analysis of healthy adolescents reported that 49 percent of the females and 15 percent of the males consumed less than 4 mg/day of pantothenic acid in their diet.[10] A study of Hispanic children, considered to be of low socioeconomic status, conducted in Houston, Texas, indicated that pantothenic acid intake was extremely variable and below recommended intake for many of the studied subjects.[11] The diet of residents of a

Gregory S. Kelly, ND – Senior editor for *Alternative Medicine Review*; consultant for Lifestrive; co-owner of Health Coach; author of the book *Shape Shift*.
Email: gkelly@altmedrev.com

Keywords: pantothenic acid, vitamin B5, B5, acne, adrenal, aldehydes, alopecia, anti-aging, celiac, chemicals, ergogenic, hyperlipidemia, lifespan, lupus, obesity, osteoarthritis, rheumatoid arthritis, SLE, stress, ulcerative colitis, wounds

northern Utah nursing home had a mean daily pantothenic acid content of 3.75 mg.[12] A study conducted at a long-term care facility for the aged affiliated with the University of Toronto's Medical School reported that neither of the two most commonly fed diet types – unrestricted diet and lactose-free diet – supplied sufficient quantities of pantothenic acid.[13] A study conducted in 100 free-living elderly individuals in Greece reported that their Mediterranean-style diet was insufficient in pantothenic acid.[14]

Other circumstances might also be risk factors for insufficiency. A study reported that pantothenic acid levels were significantly lower in females using oral contraceptives compared with females who were not.[15] The daily mean dietary intake of pregnant women was estimated as 2.75 mg/1,000 kcal.[16] This would supply an inadequate amount of pantothenic acid for pregnant women consuming the low-to-moderate range of recommended calories during pregnancy. The mean pantothenic acid intake of lactating women was estimated as 7.6 mg/d over a 6-month period,[17] which exceeds their DRI.[7]

To elicit severe signs of pantothenic acid deficiency in mice, treatment with an antibiotic is necessary. Presumably this occurs because sufficient pantothenic acid to ward off signs of severe deficiency is produced by intestinal bacteria.[18] It's possible that intestinal flora contributes to overall vitamin B_5 status in humans; however, this area has not been investigated.

Biochemistry

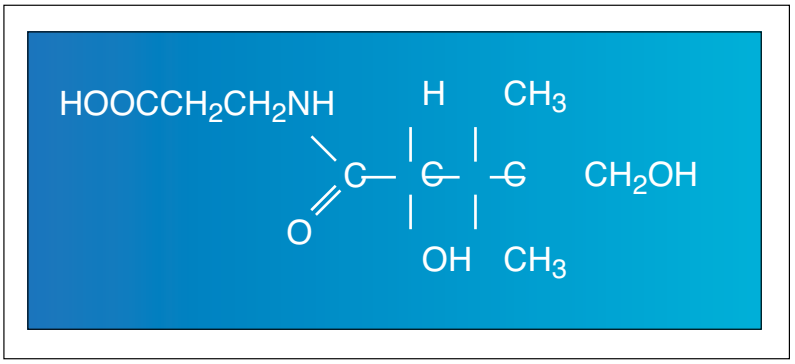
Pantothenic acid is used in CoA and acyl carrier proteins (ACP), which carry and transfer acetyl and acyl groups, respectively. *In vivo* effects of pantothenic acid are generally thought to be a result of its incorporation into these molecules.[2]

CoA is an essential cofactor in fatty acid oxidation, lipid elongation, and fatty acid synthesis. It is involved in the production of many secondary metabolites such as polyisoprenoid-containing compounds (e.g., dolichol, ubiquinone [CoQ10], squalene, and cholesterol), steroid molecules (e.g., steroid hormones, vitamin D and bile acids), acetylated compounds (e.g., acetylated derivatives of amino sugars [e.g., N-acetylglucosamine], acetylated neurotransmitters [e.g., N-acetylserotonin, acetylcholine]), and prostaglandins and prostaglandin-like compounds. Biosynthesis of phospholipids (e.g., phosphatidylcholine, -ethanolamine, -serine, -inositol, -cardiolipin), as well as plasmalogen, sphingenin, and ceramide, require CoA. Directly or indirectly, CoA is involved in the breakdown of the carbon skeleton of most of the amino acids. The breakdown of the pyrimidine bases, cytosine, uracil, and thymine, is also dependent on CoA.[2]

ACP is involved in fatty acid synthases, polyketide synthases, lysine synthesis, and nonribosomal peptide synthetases.[2]

Most plants and microorganisms accomplish biosynthesis of pantothenic acid by enzymatically combining pantoic acid with ß-alanine. Mammals lack the enzyme for this synthetic step, so are unable to synthesize pantothenic acid.[3]

In mammals, endogenous synthesis of CoA and ACP can begin with pantothenic acid. The biosynthetic pathway begins with a phosphorylation reaction catalyzed by a magnesium-dependent enzyme – pantothenate kinase (also called pantothenic acid kinase) – resulting in the formation of 4'-phosphopantothenic acid (4'-PPA).[2,3,19] This step is considered the most important control step in the biosynthesis of pantothenic acid-dependent enzymes.[2] The next step is a condensation reaction with cysteine, producing 4'-phosphopantothenoyl cysteine. In the absence of cysteine, 4'-PPA will accumulate, suggesting that the absence of cysteine as a substrate is a limiting factor in the biosynthesis of pantothenic acid's down-line metabolites. 4'-Phosphopantetheine (4'-PP) is then formed by a decarboxylation reaction.[2,3] The reaction rate of this enzymatic step is also increased by the availability of protein-sulfhydryl compounds such as cysteine.[20] The final two steps in the synthesis of CoA involve the addition of an adenosyl group derived from ATP and the phosphorylation of this molecule. Both of these enzymatic reactions require magnesium as a cofactor.[2,3]



While CoA accounts for a large proportion of cellular pantothenic acid, ACP also contains the pantothenic acid molecule. The synthesis of ACP is not completely elaborated; however, as in CoA, 4'-PP has been identified as the prosthetic group.[21]

Bioavailability and Pharmacokinetics

Existing evidence suggests that the bioavailability of pantothenic acid is in the range of 40-63 percent.[8,22] Pantothenic acid appears to be absorbed rapidly following an oral dose, resulting in increased tissue levels of CoA and other pantothenic acid metabolites within six hours.[23] Content of CoA and pantothenic acid increases significantly in leukocytes and urine 6-24 hours after oral administration.[23]

In mice, pantothenic acid absorption occurs in the small intestine, and is sodium-dependent and saturable. Varying the dietary intake of pantothenic acid – low, normal, or high doses – has no physiologically significant effect on small intestinal uptake.[18]

After pantothenic acid is absorbed and transported into cells, it can be converted to CoA or ACP by the series of enzymatic reactions previously described. In animals, pantothenic acid appears to concentrate in the liver,[24,25] muscles, and blood.[24] Animal experiments suggest that pantothenic acid can enter and leave the brain and cerebral spinal fluid by saturable transport systems.[26]

Pantothenic acid is found in the breast milk of lactating women. Amounts found correlate to the amount of pantothenic acid in the diet of the mother the day preceding milk collection.[17]

The amount of pantothenic acid found in a 24-hour urine sample appears to accurately reflect intake during the past several days in humans.[10,22,29] Blood pantothenic acid levels respond less readily to intake than levels found in urine and are not considered as reliable an indicator.[22] Levels of pantothenic acid in erythrocytes correlate with dietary intake and urinary excretion.[10]

Deficiency

Outright deficiency of pantothenic acid does not appear to occur under usual circumstances. Presumably this is a result of (1) pantothenic acid being found in a wide variety of foods in adequate amounts to prevent deficiency, and (2) other vitamin deficiencies being limiting factors in persons eating nutritionally poor diets (i.e., signs and symptoms of other nutrient deficiencies are produced before pantothenic acid deficiency is evident).[2]

To produce a deficiency in animal experiments, semisynthetic diets free of pantothenic acid have been used, often in combination with drugs that act as pantothenic acid antagonists. Antibiotics have also been used in some experiments to inhibit gut microflora-produced pantothenic acid.[2,18]

Early nutritional research indicated that pantothenic acid deficiency produced a loss of fur color in brown and black rats and dermatitis in chickens. This led to pantothenic acid being thought of as an "anti-gray" and "anti-dermatitis" factor.[28] While graying of fur can occur, it does not occur in all animals. Even in a single type of animal, it does not occur consistently in all animals subjected to the same degree of deficiency.[30] Other outwardly visible effects of deficiency in mice include weight loss (or reduced growth), poor grooming, hair loss, exudation around the eyes, diarrhea, and hind leg paralysis.[18,30]

One of the consistent findings in animal experiments of pantothenic acid deficiency has been a progressive morphological and functional change to the adrenal glands. In early deficiency, the adrenal gland hypertrophies.[29,31] The adrenal cortex, specifically, becomes enlarged and there is a progressive depletion of ketosteroids from the zona reticularis and fasciculata.[31,32] The eventual result of deficiency is adrenal hypofunction, with an inability to respond appropriately to stress.[29,33,34] In late-stage deficiency, the adrenals atrophy and morphological damage occurs.[33,35] If pantothenic acid is supplied early enough after deficiency is induced (i.e., before adrenal exhaustion occurs), the response to stress can be improved and morphological changes to the adrenals can be reversed. After adrenal exhaustion has occurred, pantothenic acid administration is no longer effective for these purposes.[29]

Deficiency causes the thymus of mice to atrophy[31,36] and the spleen to enlarge.[18,31] Lymphopenia followed by lymphocytosis can occur.[31] The ability to produce antibody titers against various infectious agents can also be reduced.[36]

In male rats, a pantothenic acid deficiency results in increased weight of the testes, reductions in sperm motility, and decreased plasma concentrations of testosterone and corticosterone.[37]

An increase in triglycerides might be a nonspecific sign of mild deficiency. In rats, a mild deficiency produced by a diet low, but not devoid of, pantothenic acid significantly increased serum triglycerides.[38]

Knowledge about pantothenic acid deficiency in humans comes from several sources – prisoners of

war, controlled deficiency experiments, and the unintentional side effects produced by a pantothenic acid antagonist drug.

Malnourished prisoners of war during World War II reported numbness and burning sensations in their feet, which was remedied with pantothenic acid supplementation.[39]

The most extensive investigations of human pantothenic acid deficiency took place in the mid-to-late 1950s.[40-43] A diet low in pantothenic acid, generally in combination with the drug omega-methyl pantothenate (a pantothenate kinase inhibitor), was used to produce pantothenic acid deficiency in healthy subjects. A severe depletion of pantothenic acid for approximately six weeks was required before clear signs and symptoms of deficiency – many of which mirror the effects of deficiency in animals – were produced.[40] The triad of fatigue (including apathy and malaise), headache, and weakness was the most consistent finding. Other common effects included gastrointestinal disturbances (nausea, abdominal cramps, occasional vomiting, increased flatulence, and epigastric burning sensations); sleep disturbances; and personality changes and emotional disorders. A less regular occurrence was signs of cardiovascular instability (tachycardia and lability of arterial blood pressure, with a tendency to orthostatic hypotension). Paresthesias, burning sensations of the hands and feet, and muscle cramps and weakness occurred in several subjects. Impaired motor coordination also occurred in some subjects, and was accompanied by a peculiar gait. In some deficiency experiments, infections were common; in others they were not. Several biochemical abnormalities were reported. A loss of the normal eosinopenic response to adrenocorticotropic hormone (ACTH) was the most consistent lab finding. Less consistent lab findings among studies of pantothenic acid deficiency include a reduction in the degree of urinary acetylated para-aminobenzoic acid (PABA) and 17-ketosteroids, abnormal glucose tolerance, increased sensitivity to insulin, reduced secretion of gastric hydrochloric acid and pepsin, decreased and increased cholesterol, and hypokalemia.[40-43] Administration of pantothenic acid was followed by improvement of the paresthesias and muscle weakness, but fatigue and some degree of irritability persisted. There was also a prompt correction of the impaired eosinopenic response to ACTH and most of the other clinical symptoms when pantothenic acid was supplied.[40]

One of the key findings remarked upon by the researchers was that the deficiency results produced were inconsistent between individuals and from experiment to experiment. The same was true for prompt and complete recovery from all symptoms, which did not always follow pantothenic acid administration. They suspected biochemical individuality, unrecognized variations in the composition of the diet, the activity of, or response to, a drug antagonist of pantothenic acid, or possible other factors might be involved in producing these inconsistencies. Whatever the reason(s), there was a wide variation in normal persons in response to their attempts to induce pantothenic acid deficiency and to corrective doses of pantothenic acid.[40]

The last mechanism for producing pantothenic acid deficiency in humans was the administration of calcium hopantenate (also called homopantothenate; a pantothenic acid antagonist). Cases of reversible encephalopathy, hepatic steatosis, and a Reye-like syndrome were reported in persons receiving this drug. It has been suggested that these outcomes might have been produced by a medication-induced pantothenic acid deficiency.[44]

Clinical Indications/Mechanisms

Acne vulgaris

One hundred cases of acne – 45 males and 55 females of Chinese descent – were treated with high-dose pantothenic acid. Participants were between the ages of 10-30 years of age with most (80 percent) between the ages of 13-23. A total of 10 g/d of pantothenic acid was given in four divided doses. Participants were also asked to apply a cream to the affected area 4-6 times daily; the cream contained 20 percent by weight pantothenic acid. The face became noticeably less oily and a decrease in facial sebum secretion occurred usually within 2-3 days after initiation of therapy. Within two weeks, facial pore size had become noticeably smaller, existing acne lesions had begun to heal, and the rate of new acne eruptions had slowed. By eight weeks, acne was usually controlled – most acne lesions were gone and new eruptions only occurred occasionally – in cases of moderate severity. In the participants with severe acne, treatment for six months or longer was occasionally needed to control acne. The author noted that in some of the severe cases, daily doses of 15-20 g/d of pantothenic acid would produce a faster response. Thirty-five patients were monitored for 18 months; the maintenance dose needed to control acne ranged from 1 to 5 g/d of pantothenic acid.[45]

A single study suggested that a 5-percent dexpanthenol cream could help treat mucocutaneous adverse reactions caused by isotretinoin treatment for acne.[46]

Alopecia

A case study from the early 1950s reported benefits of using the alcohol pro-vitamin form of pantothenic acid (dexpanthenol) topically for hair loss.[47]

The only study that used oral pantothenic acid as a sole intervention for diffuse alopecia in women reported that there was no clear evidence of benefit. The dose used was 100 mg/d for 4-5 months.[48]

Two studies reported that use of a proprietary product containing pantothenic acid (60 mg/capsule), vitamin B_1, yeast, L-cystine, keratin, and PABA improved hair quality and slowed hair loss after four months of use in persons with diffuse effluvium capillorum and agnogenic structural alterations of hair.[49,5]

Celiac Disease

A letter to the editor of the *British Medical Journal* in 1972 suggested the hypothesis that patients with celiac disease who respond only partially to a gluten-free diet might potentially benefit from the administration of pantothenic acid. No clinical evidence in support of this hypothesis was provided in this letter (i.e., the author did not mention results of any cases of giving pantothenic acid to persons with celiac disease).[51]

Chemical Exposure to Aldehydes and Phenols

Abstracts from untranslated Russian research have suggested that pantothenic acid might play a role in protecting against exposure to certain chemicals. Pantothenic acid and its derivatives decreased the acute toxicity of acetaldehyde, as well as the duration of the narcotic action of ethanol, in mice and rats.[52] In animals, a combination of vitamins including pantothenic acid helped protect against poisoning from phenol vapors.[53] In humans, pantothenic acid combined with vitamin B_1 protected workers engaged in manufacturing of phenol-formaldehyde resins.[54]

Ergogenic Aid (Exercise Performance)

Existing evidence is not supportive of pantothenic acid supplementation improving exercise performance. While a study reported that 2 g/d of pantothenic acid for two weeks decreased blood lactate levels and decreased oxygen consumption during prolonged exercise at 75-percent VO^2max in highly trained endurance runners,[55] a dose of 1 g/d for two weeks failed to increase run time to exhaustion in highly trained distance runners.[56] A combination of vitamin B_1 and pantothenic acid (1.8 g/d of a 55%/45% pantethine/pantothenic acid mix) or placebo was given to highly trained cyclists for seven days. No significant differences were observed in cycling performance.[57]

Hepatitis A

An abstract of an untranslated Russian study suggested that both calcium pantothenate (300-600 mg) and pantethine (90-180 mg) could be useful additions to therapy for viral hepatitis A. The abstract noted that benefits with calcium pantothenate were not as pronounced as with pantethine.[58]

Hyperlipidemia

The pantethine form of vitamin B_5 has been reported to have lipid-lowering effects, with supplementation capable of reducing cholesterol and triglyceride levels.[59] No studies have investigated whether pantothenic acid has lipid-lowering effects.

Inflammatory Bowel Disease

Three patients with ulcerative colitis were administered dexpanthenol (1,000 mg) as part of an enema. The treatment was not considered effective.[60]

Lifespan Extension (Anti-Aging)

Several old studies suggested that pantothenic acid supplementation extends the lifespan of animals. Royal jelly was reported to extend the lifespan of *Drosophila melanogaster* (common fruit fly); pantothenic acid was the primary anti-aging factor isolated from royal jelly.[61] The combination of pyridoxine, biotin, and sodium yeast nucleate extended the lifespan of *Drosophila melanogaster*; addition of pantothenic acid further increased lifespan.[62] A dose of 300 mcg/d (approximately 10 mg/kg/d) of calcium pantothenate extended the lifespan of black mice by 19 percent.[63]

Lupus Erythematosus

Several reports exist on the use of pantothenic acid for persons with lupus erythematosus from the 1950s. One indicated that pantothenic acid (10-15 g/d), when taken together with vitamin E (1,500-3,000 IU/d) for up to 19 months, showed

efficacy.[64] Another reported that the combination of oral pantothenic acid and topical dexpanthenol was not effective.[65]

Obesity

Aurothioglucose injection into the hypothalamus is used as a means to induce hypothalamic obesity – an increase in food intake, weight gain primarily as body fat, and blood sugar and lipid increases – in animal experiments. Pantothenic acid and several of its derivatives – phosphopantothenate, pantethine, dexpanthenol – countered hypothalamic obesity after injection of aurothioglucose. The effects with dexpanthenol were more pronounced than with the other forms of pantothenic acid used.[66]

One hundred individuals of Chinese descent, all following a calorie-restricted diet that only provided 1,000 calories/d, were supplemented with 10 g/d of pantothenic acid in four divided doses. Average weight loss was reported to be 1.2 kg (2.6 lbs) per week. Ketone bodies in urine were either absent or detected in trace amounts. Dieters did not complain of hunger or weakness. A maintenance dose of 1-3 g/d, along with continued adherence to a strict diet, was needed to maintain weight loss. The author claimed that no side effects were observed with this protocol.[67]

A product containing pantothenic acid, *Garcinia cambogia*, *Matricaria chamomilla*, *Rosa damascena*, *Lavandula officinalis* and *Cananga odorata* was reported to produce an average weight loss of 4.67 percent after 60 days of supplementation.[68]

Osteoarthritis and Rheumatoid Arthritis

A double-blind trial compared taking the combination of pantothenic acid and L-cysteine against placebo in the treatment of osteoarthrosis of the knees. No difference was observed either subjectively or objectively between the two groups.[69]

A double-blind study of persons with rheumatoid arthritis patients, who had not responded to previous drug treatment with salicylates, compared the addition of pantothenic acid (500 mg/d initially, increasing to 500 mg four times daily by the 10th day) with placebo. A significant reduction in morning stiffness, degree of disability, and severity of pain was reported for persons taking pantothenic acid.[70]

Stress

Animal and human evidence suggests that pantothenic acid is needed for adrenal function and might be involved in the adrenal response to stress.

As mentioned in the section on deficiency, a progressive morphological and functional change occurs to the adrenal glands when there is a pantothenic acid deficiency. The eventual result of deficiency is adrenal hypofunction, with an inability to respond appropriately to stress. If pantothenic acid is supplied early enough after deficiency has been induced (i.e., before adrenal exhaustion occurs), the response to stress can be improved.[29,31-35]

Supplementation of pantothenic acid when the diet is adequate in pantothenic acid also appears to impact adrenal function. In male rats, adding pantothenic acid (0.03%) to drinking water for nine weeks increased adrenal gland weight, basal plasma levels of corticosterone, and the release of corticosterone in response to ACTH.[71] Supplementation also increases urinary excretion of 17,21-dihydroxy-20-ketosteroids – a sign of functional activation of the adrenal gland.[72]

Results of several animal studies suggest that providing supplemental pantothenic acid might improve the response to certain types of stress. Supplementing the diet of rats with 43.6 mg of calcium pantothenate per 100 g of chow increased adrenal weight significantly in response to surgical stress. In unstressed animals supplementation of pantothenic acid had no effect on adrenal weight.[73] Since adrenal hypertrophy in response to stress is believed to be an adaptive response,[74] this suggests that pantothenic acid supplementation improved the stress response. Exposure to gamma radiation reduces blood levels of pantothenic acid and its derivatives by about 80 percent. It also produces a significant increase in oxidative stress – lipid peroxidation increases and liver levels of CoA and reduced glutathione decrease. Administration of dexpanthenol, in amounts sufficient to increase blood pantothenic acid levels significantly above control (non-irradiated) levels, normalized these markers of oxidative stress.[75]

Pantothenic acid appears to be involved in optimizing the response to cold stress. A deficiency of pantothenic acid increases the sensitivity of undernourished rats to cold.[76] Deficiency also significantly decreases average survival time of rats exposed to cold stress.[77] Supplementing the combination of calcium pantothenate and a small amount of hydrocortisone prolonged survival of cold-stressed, adrenalectomized rats.[78] Supplementation of pantothenic acid allowed rats that had undergone removal of the adrenals to swim in cold water for as long as rats with intact adrenals.[79] In rats with intact

adrenals, supplementation with large amounts of pantothenic acid doubled the length of time they were able to swim in, and survive in, cold water.[80] Men receiving pantothenic acid (10 g/d for six weeks) had a less pronounced drop in white blood cell counts and vitamin C levels subsequent to cold-water immersion stress, compared to pre-supplementation values.[81]

A report indicated that a high proportion of schizophrenic patients had impaired adrenal function. When pantothenic acid was given to these patients, adrenal function improved.[82]

Wound Healing

In animal research, oral and topical pantothenic acid have been associated with accelerated closure of skin wounds and increased strength of scar tissue; however, no significant benefits were observed with wound healing in a randomized, double-blind study of humans who took 200 mg of pantothenic acid and 1,000 mg of vitamin C by mouth during recovery from surgical tattoo removal.[83]

Drug-Nutrient Interactions

Pantothenic acid helps prevent cisplatin-induced deafness in guinea pigs when both drugs are administered jointly. When deafness has been previously produced by cisplatin, recovery can sometimes occur after the administration of pantothenic acid.[84]

Animal experiments suggest that pantothenic acid might help prevent some side effects of valproic acid (VPA). *In utero* exposure to VPA during pregnancy is associated with an increased risk of neural tube defects (NTDs) in animals. Pretreatment of pregnant mice with pantothenic acid protects against VPA-induced NTDs.[85] Hepatic failure is a rare, but possible, side effect of VPA. Presumably this side effect is in part related to a VPA-induced depletion of CoA, which results in abnormalities in CoA-dependent liver processes. In developing mice, the combination of pantothenic acid and carnitine helped prevent this side effect.[86]

A single study reports that a 5-percent dexpanthenol cream can help treat mucocutaneous adverse reactions caused by using isotretinoin for acne.[46]

A theoretical concern exists that pantothenic acid, since it is involved in the biosynthesis of acetylcholine, might increase the effects of acetylcholinesterase inhibitor drugs (i.e., drugs that inhibit the cholinesterase enzyme and so prevent the breakdown of acetylcholine).

As mentioned in the section on deficiency, two drugs – omega-methyl pantothenate (a pantothenate kinase inhibitor) and calcium hopantenate (a pantothenic acid antagonist) – can produce deficiencies in pantothenic acid. Neither of these medications is currently an FDA-approved drug product for human use.[87]

Animal research on adrenal function suggests that pantothenic acid supplementation might augment the response to corticosteroids.[71,78,79]

A study reported that pantothenic acid levels were significantly lower in females using oral contraceptives compared with females who were not.[15]

Pantothenic acid has been reported to have no estrogenic action itself, but enhanced the action of estradiol in rats.[88]

Experimental work from the 1950s suggested that pantothenic acid might interfere with the ability of some antibiotics – aureomycin,[89] erythromycin,[90] and streptomycin[91] – to inhibit the growth of certain microorganisms under *in vitro* conditions. It has been speculated that this might be because these antibiotics inhibit enzymes involved in the biosynthesis of pantothenic acid or its downstream coenzymes (CoA or ACP); supplying pantothenic acid overcomes this enzyme inhibition.[91] *In vivo* research, also conducted in the 1950s, did not indicate a decrease in clinical efficacy when streptomycin was combined with pantothenic acid.[92-94] Vestibular ototoxicity – nausea, vomiting, and vertigo – is an established side effect of streptomycin. A report indicated that administration of 50 mg pantothenic acid three times daily improved symptoms of vestibular ototoxicity caused by streptomycin in 30 out of 31 persons.[94] However, another report indicated that adding 150 mg/d of pantothenic acid to the combination of streptomycin and isoniazid failed to prevent symptoms of vestibular ototoxicity.[92]

Analogs of pantothenic acid – N-substituted pantothenamide (pantothenamides), and anti-metabolites such as N-pentylpantothenamide and N-heptylpantothenamide – have antibiotic activity and are under investigation as potential novel antibiotics. These anti-metabolites compete for and use enzymes involved in the biosynthesis of CoA and/or ACP, producing biologically inactive analogs. The result is an inhibition of bacterial growth. Extracellular availability of pantothenic acid does not appear to prevent the bacterial growth inhibition of pantothenamides under test conditions.[95-99] The effects of exogenous supplementation of pantothenic acid on pantothenamides has not been investigated.

Sulfonamides reduced the fecal elimination of pantothenic acid and produced marked reductions of pantothenic acid concentrations in the liver of rats.[100] However, young men did not have a reduction in pantothenic acid excretion when given the sulfonamide, phthalylsulfathiozole.[101]

There have been anecdotal reports that dexpanthenol may increase bleeding time. These reports have not been substantiated and increased risk of bleeding is not regarded as a serious potential risk. Nevertheless, because of this, it has been recommended that pantothenic acid be used with caution in persons taking anticoagulants or other medicines capable of prolonging bleeding time.[6]

Nutrient-Nutrient Interactions

Ascorbic acid appears to have a pantothenic acid-sparing effect in rats. The addition of ascorbic acid (2 percent of the diet) to a rat diet deficient in pantothenic acid allowed many of the animals to grow normally and prevented signs of deficiency.[102,103] Augmenting a pantothenic acid-deficient diet with ascorbic acid (2 percent of the diet) in female rats resulted in offspring with significantly higher blood, hepatic and tissue pantothenic acid levels compared with the offspring of females fed a diet deficient in pantothenic acid without added ascorbic acid. Ascorbic acid also prevented some of the histochemical differences in the adrenals of the offspring.[104]

In vitro evidence suggests that biotin and pantothenic acid use the same sodium-dependent, specialized carrier-mediated system for uptake in colonic epithelial cells. In this experiment, pantothenic acid caused a concentration-dependent competitive inhibition in biotin uptake.[105] This has led to speculation that high doses of pantothenic acid might inhibit the absorption of biotin in the large intestine;[6] however, whether competitive inhibition occurs under *in vivo* conditions has not been investigated.

Side Effects and Toxicity Data

Acute oral LD_{50} values for pantothenic acid are 10,000 mg/kg in mice and rats, with lethal doses producing death by respiratory failure.[106]

Chronic administration for 6 months produced no toxic signs, weight loss, or histopathological changes in rats (dose up to 2,000 mg/kg, dogs (50 mg/kg), and monkeys (200-250 mg/kg).[106]

Calcium pantothenate at 3 percent of the diet was the lowest-observed-adverse-effect-level (LOAEL) in rats, with enlargement of the testes, diarrhea, and hair damage observed, and the amount of weight increase and the food intake less than those of controls. The no-observed-adverse-effect-level (NOAEL) was 1 percent of the diet comprised of calcium pantothenate.[107] Although it is not possible to derive a numerical upper limit for pantothenic acid in humans, evidence available from clinical studies using high doses of pantothenic acid indicates that intakes considerably in excess of current DRI do not represent a health risk for the general population.[106,109]

The existing clinical studies on pantothenic acid were not designed to monitor and assess side effects, so information of adverse effects on humans is limited. The most commonly reported side effect is mild transient gastrointestinal disturbance such as nausea, heartburn, and diarrhea. Adverse effects typically do not occur until doses exceed 1 gram daily.[6,109-111]

There is one reported case of eosinophilic pleuropericardial effusion (fluid around the heart and lungs) in a patient taking 300 mg/d of pantothenic acid in combination with 10 mg/d of biotin for 2 months. The condition resolved after the vitamins were stopped.[112]

There are reported cases of contact urticaria[113] and dermatitis[114] occurring with the use of hair lotions and conditioners containing dexpanthenol.

Pantothenic acid has an FDA Pregnancy category A rating for doses at or below the DRI level. What this means is that well-controlled studies have failed to demonstrate a risk to the fetus in the first trimester of pregnancy (and there is no evidence of risk in later trimesters) for doses at or below the DRI level. Pantothenic acid has a Pregnancy category C rating when dosed above the DRI (i.e., animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks).[108]

Dosing

The Dietary Reference Intake (DRI) established by the Institute of Medicine for pantothenic acid is as follows:[7,108]

- 1–3 years old: 2 mg/d
- 4–8 years old: 3 mg/d
- 9–13 years old: 4 mg/d
- 14 years old and over: 5 mg/d
- Pregnancy: 6 mg/d
- Lactation: 7 mg/d

Oral supplementation of pantothenic acid has been significantly in excess of the DRI for several months or longer. In clinical studies the dose used has varied significantly. The low end of dosing has generally been 100 mg/d. The high end has been 10 g/d. At higher doses, the existing studies have often used 3-4 divided doses a day. High potency pantothenic acid supplements are generally in the range of 250-1,000 mg per capsule/tablet. Dosing at the highest levels – 10 g/d – can present adherence issues, because of the number of tablets or capsules required to achieve the dose.

References

1. Williams RJ. Pantothenic acid – a vitamin. *Science* 1939;89:486.
2. Rucker RB, Bauerly K. Pantothenic acid. In: Zempleni J, Rucker RB, McCormick DB, Suttie JW, eds. *Handbook of Vitamins*. New York, NY: CRC Press; 2007:289-305.
3. Webb ME, Smith AG, Abell C. Biosynthesis of pantothenate. *Nat Prod Rep* 2004;21:695-721.
4. Khomich TI . Pantethine and the biosynthetic regulation of the coenzyme of acetylation. *Eksp Med (Riga)* 1991;27:112-118. [Article in Russian]
5. No authors listed. Pantethine: Monograph. *Altern Med Rev* 2010;15:279-282.
6. http://www.drugs.com/npp/pantothenic-acid.html [Accessed August 1, 2011]
7. http://iom.edu/Activities/Nutrition/SummaryDRIs/~/media/Files/Activity%20Files/Nutrition/DRIs/RDA%20and%20AIs_Vitamin%20and%20Elements.pdf [Accessed July 29, 2011]
8. Tarr JB, Tamura T, Stokstad EL. Availability of vitamin B6 and pantothenate in an average American diet in man. *Am J Clin Nutr* 1981;34:1328-1337.
9. Watanabe T, Suemura K, Taniguchi A, et al. Dietary intake of seven B vitamins based on a total diet study in Japan. *J Nutr Sci Vitaminol (Tokyo)* 2010;56:279-286.
10. Eissenstat BR, Wyse BW, Hansen RG. Pantothenic acid status of adolescents. *Am J Clin Nutr* 1986;44:931-937.
11. Wilson TA, Adolph AL, Butte NF. Nutrient adequacy and diet quality in non-overweight and overweight Hispanic children of low socioeconomic status: the Viva la Familia Study. *J Am Diet Assoc* 2009;109:1012-1021.
12. Walsh JH, Wyse BW, Hansen RG. Pantothenic acid content of a nursing home diet 1,2. *Ann Nutr Metab* 1981;25:178-181.
13. Wendland BE, Greenwood CE, Weinberg I, Young KW. Malnutrition in institutionalized seniors: the iatrogenic component. *J Am Geriatr Soc* 2003;51:85-90.
14. Grammatikopoulou MG, Papadopoulou SK, Zakas A, et al. Dietary intake of free-living elderly in northern Greece. *J Nutr Elder* 2006;26:131-146.
15. Lewis CM, King JC. Effect of oral contraceptives agents on thiamin, riboflavin, and pantothenic acid status in young women. *Am J Clin Nutr* 1980;33:832-838.
16. Song WO, Wyse BW, Hansen RG. Pantothenic acid status of pregnant and lactating women. *J Am Diet Assoc* 1985;85:192-198
17. Johnston L, Vaughan L, Fox HM. Pantothenic acid content of human milk. *Am J Clin Nutr* 1981;34:2205-2209.
18. Stein ED, Diamond JM. Do dietary levels of pantothenic acid regulate its intestinal uptake in mice? *J Nutr* 1989;119:1973-1983.
19. Fisher MN, Robishaw JD, Neely JR. The properties and regulation of pantothenate kinase from rat heart. *J Biol Chem* 1985;260:15745-15751.
20. Scandura R, Barboni E, Granata F, et al. Pantothenoylcysteine-4'-phospate decarboxylase from horse liver. *Eur J Biochem* 1974;49:1-9.
21. Tahiliani AG, Beinlich CJ. Pantothenic acid in health and disease. *Vitam Horm* 1991;46:165-228.
22. Fry PC, Fox HM, Tao HG. Metabolic response to a pantothenic acid deficient diet in humans. *J Nutr Sci Vitaminol (Tokyo)* 1976;22:339-346.
23. Moiseenok AG, Tsverbaum EA, Rybalko MA. Pantothenic acid biotransformation in human vitamin deficiency. *Vopr Med Khim* 1981;27:780-784. [Article in Russian]
24. Böhmer BM, Roth-Maier DA. Effects of high-level dietary B-vitamins on performance, body composition and tissue vitamin contents of growing/finishing pigs. *J Anim Physiol Anim Nutr (Berl)* 2007;91:6-10.
25. Gurinovich VA, Moiseenok AG. Metabolism of pantothenic acid and its derivatives in animals deficient in this enzyme. *Ukr Biokhim Zh* 1987;59:60-66. [Article in Russian]
26. Spector R. Pantothenic acid transport and metabolism in the central nervous system. *Am J Physiol* 1986;250:R292-R297.
27. Tsuji T, Fukuwatari T, Sasaki S, Shibata K. Urinary excretion of vitamin B1, B2, B6, niacin, pantothenic acid, folate, and vitamin C correlates with dietary intakes of free-living elderly, female Japanese. *Nutr Res* 2010;30:171-178.
28. Bender DA. Optimum nutrition: thiamin, biotin and pantothenate. *Proc Nutr Soc* 1999;58:427-433.
29. Hurley LS, Morgan AF. Carbohydrate metabolism and adrenal cortical function in the pantothenic acid-deficient rat. *J Biol Chem* 1952;195:583-590.
30. Kuo YM, Hayflick SJ, Gitschier J. Deprivation of pantothenic acid elicits a movement disorder and azoospermia in a mouse model of pantothenate kinase-associated neurodegeneration. *J Inherit Metab Dis* 2007;30:310-317.
31. Melampy RM, Cheng DW, Northrop LC. Effect of pantothenic acid deficiency upon adrenal cortex, thymus, spleen, and circulating lymphocytes in mice. *Proc Soc Exp Biol Med* 1951;76:24-27.
32. Deane HW, McKibbin JM. The chemical cytology of the rat's adrenal cortex in pantothenic acid deficiency. *Endocrinology* 1946;38:385-400.
33. Ashburn LL, Daft FS, Faulkner RR. Hematopoiesis in pantothenic acid-deficient rats. *Blood* 1947;2:451-462.
34. Taylor DW. Effects of deficiency of pantothenic acid on oxygen poisoning in the rat. *Nature* 1959;183:257.

35. Morgan AF, Simms HD. Adrenal atrophy and senescence produced by a vitamin deficiency. *Science* 1939;89:565-566.
36. Mahboob S. Thymic weight in pantothenic acid deficiency. *Nutr Metab* 1976;20:272-277.
37. Yamamoto T, Jaroenporn S, Pan L, et al. Effects of pantothenic acid on testicular function in male rats. *J Vet Med Sci* 2009;71:1427-1432.
38. Wittwer CT, Beck S, Peterson M, et al. Mild pantothenate deficiency in rats elevates serum triglyceride and free fatty acid levels. *J Nutr* 1990;120:719-725.
39. Davenport RE, Spaide J, Hodges RE. An evaluation of various survival rations. *Am J Clin Nutr* 1971;24:513-523.
40. Hodges RE, Ohlson MA, Bean WB. Pantothenic acid deficiency in man. *J Clin Invest* 1958;37:1642-1657.
41. Hodges RE, Bean WB , Ohlson MA, Bleiler R. Human pantothenic acid deficiency produced by omega-methyl pantothenic acid. *J Clin Invest* 1959;38:1421-1425.
42. Thornton GH, Bean WB, Hodges RE. The effect of pantothenic acid deficiency of gastric secretion and motility. *J Clin Invest* 1955;34:1085-1091.
43. Bean WB, Hodges RE, Daum K. Pantothenic acid deficiency induced in human subjects. *J Clin Invest* 1955;34:1073-1084.
44. Noda S, Umezaki H, Yamamoto K, et al. Reye-like syndrome following treatment with the pantothenic acid antagonist, calcium hopantenate. *J Neurol Neurosurg Psychiatry* 1988;51:582-585.
45. Leung LH. Pantothenic acid deficiency as the pathogenesis of acne vulgaris. *Med Hypotheses* 1995;44:490-492.
46. Romiti R, Romiti N. Dexpanthenol cream significantly improves mucocutaneous side effects associated with isotretinoin therapy. *Pediatr Dermatol* 2002;19:368.
47. Abirached IA. Case of baldness treated with pantothenic acid alcohol. *Folha Med* 1951;32:121-122.
48. Brzezińska-Wcisło L. Evaluation of vitamin B6 and calcium pantothenate effectiveness on hair growth from clinical and trichographic aspects for treatment of diffuse alopecia in women. *Wiad Lek* 2001;54:11-18. [Article in Polish]
49. Petri H, Pierchalla P, Tronnier H. The efficacy of drug therapy in structural lesions of the hair and in diffuse effluvium – comparative double blind study. *Schweiz Rundsch Med Prax* 1990;79:1457-1462. [Article in German]
50. Budde J, Tronnier H, Rahlfs VW, Frei-Kleiner S. Systemic therapy of diffuse effluvium and hair structure damage. *Hautarzt* 1993;44:380-384. [Article in German]
51. Monro J. Pantothenic acid and coeliac disease. *Br Med J* 1972;4:112-113.
52. Moiseenok AG, Dorofeev BF, Omel'ianchik SN. The protective effect of pantothenic acid derivatives and changes in the system of acetyl CoA metabolism in acute ethanol poisoning. *Farmakol Toksikol* 1988;51:82-86. [Article in Russian]
53. Skvortsova RI, Pozniakovskiĭ VM, Agarkova IA. Role of the vitamin factor in preventing phenol poisoning. *Vopr Pitan* 1981:32-35. [Article in Russian]
54. Skvortsova RI, Pozniakovskiĭ VM. Effect of a therapeutic and prophylactic diet enriched with thiamine and calcium pantothenate on the acetylating capacity of the body of workers engaged in the manufacture of phenol-formaldehyde resins. *Vopr Pitan* 1977:40-42. [Article in Russian]
55. Litoff D, Scherzer H, Harrison J. Effects of pantothenic acid supplementation on human exercise. *Med Sci Sports Exerc* 1985;17:287.
56. Nice C, Reeves AG, Brinck-Johnsen T, Noll W. The effects of pantothenic acid on human exercise capacity. *J Sports Med* 1984;24:26-29.
57. Webster MJ. Physiological and performance responses to supplementation with thiamin and pantothenic acid derivatives. *Eur J Appl Physiol Occup Physiol* 1998;77:486-491.
58. Komar VI. The use of pantothenic acid preparations in treating patients with viral hepatitis A. *Ter Arkh* 1991;63:58-60. [Article in Russian]
59. McRae MP. Treatment of hyperlipoproteinemia with pantethine: a review and analysis of efficacy and tolerability. *Nutr Res* 2005;25:319-333.
60. Loftus EV Jr, Tremaine WJ, Nelson RA, et al. Dexpanthenol enemas in ulcerative colitis: a pilot study. *Mayo Clin Proc* 1997;72:616-620.
61. Gardner TS. The use of *Drosophila melanogaster* as a screening agent for longevity factors; pantothenic acid as a longevity factor in royal jelly. *J Gerontol* 1948;3:1-8.
62. Gardner TS. The use of *Drosophila melanogaster* as a screening agent for longevity factors; the effects of biotin, pyridoxine, sodium yeast nucleate, and pantothenic acid on the life span of the fruit fly. *J Gerontol* 1948;3:9-13.
63. Pelton RB, Williams RJ. Effect of pantothenic acid on the longevity of mice. *Proc Soc Exp Biol Med* 1958;99:632-633.
64. Welsh AL. Lupus erythematosus: treatment by combined use of massive amounts of pantothenic acid and vitamin E. *AMA Arch Derm Syphilol* 1954;70:181-198.
65. Cochrane T, Leslie G. The treatment of lupus erythematosus with calcium pantothenate and panthenol. *J Invest Dermatol* 1952;18:365-367.
66. Naruta E, Buko V. Hypolipidemic effect of pantothenic acid derivatives in mice with hypothalamic obesity induced by aurothioglucose. *Exp Toxicol Pathol* 2001;53:393-398.
67. Leung LH. Pantothenic acid as a weight-reducing agent: fasting without hunger, weakness and ketosis. *Med Hypotheses* 1995;44:403-405.
68. Toromanyan E, Aslanyan G, Amroyan E, et al. Efficacy of Slim339 in reducing body weight of overweight and obese human subjects. *Phytother Res* 2007;21:1177-1181.
69. Haslock DI, Wright V. Pantothenic acid in the treatment of osteoarthrosis. *Rheumatol Phys Med* 1971;11:10-13.

70. Tufts M, Bunde CA. Therapeutic advantages of the addition of calcium pantothenate to salicylates in the oral treatment of rheumatoid arthritis. *Am Pract Dig Treat* 1953;4:755-756.
71. Jaroenporn S, Yamamoto T, Itabashi A, et al. Effects of pantothenic acid supplementation on adrenal steroid secretion from male rats. *Biol Pharm Bull* 2008;31:1205-1208.
72. Fidanza A. Therapeutic action of pantothenic acid. *Int J Vitam Nutr Res Suppl* 1983;24:53-67.
73. Dumm ME, Laken B, Ralli EP. Factors influencing adrenal weight and adrenal cholesterol in rats following stress. *J Nutr* 1955;56:517-531.
74. Selye H. The general-adaptation-syndrome. *Annu Rev Med* 1951;2:327-342.
75. Slyshenkov VS, Omelyanchik SN, Moiseenok AG, et al. Pantothenol protects rats against some deleterious effects of gamma radiation. *Free Radic Biol Med* 1998;24:894-899.
76. Weiss B. Thermal behavior of the subnourished and pantothenic-acid-deprived rat. *J Comp Physiol Psychol* 1957;50:481-485.
77. Ershoff BF. Comparative effects of pantothenic acid deficiency and inanition on resistance to cold stress in the rat. *J Nutr* 1953;49:373-385.
78. De Bias DA, Paschkis KE, Cantarow A, Friedler G. The effects of various metabolites and autonomic blocking agents in combating stress. *Exp Med Surg* 1957;15:30-46.
79. Dumm ME, Ralli EP. Factors influencing the response of adrenalectomized rats to stress. *Metabolism* 1953;2:153-164.
80. Ralli EP, Dumm ME. Relation of pantothenic acid to adrenal cortical function. *Vitam Horm* 1953;11:133-158.
81. Ralli EP, Kuhk WJ Jr, Gershberg H, et al. Effects of vitamin supplementation of the diet on reaction to short-term cold stress in normal young male adults. *Metabolism* 1956;5:170-196.
82. Monro J. Pantothenic acid in schizophrenia. *Lancet* 1973;1:262-263.
83. Vaxman F, Olender S, Lambert A, et al. Effect of pantothenic acid and ascorbic acid supplementation on human skin wound healing process. A double-blind, prospective and randomized trial. *Eur Surg Res* 1995;27:158-166.
84. Ciges M, Fernández-Cervilla F, Crespo PV, Campos A. Pantothenic acid and coenzyme A in experimental cisplatin-induced ototoxia. *Acta Otolaryngol* 1996;116:263-268.
85. Dawson JE, Raymond AM, Winn LM. Folic acid and pantothenic acid protection against valproic acid-induced neural tube defects in CD-1 mice. *Toxicol Appl Pharmacol* 2006;211:124-132.
86. Thurston JH, Hauhart RE. Amelioration of adverse effects of valproic acid on ketogenesis and liver coenzyme A metabolism by cotreatment with pantothenate and carnitine in developing mice: possible clinical significance. *Pediatr Res* 1992;31:419-423.
87. http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm [Accessed August 5, 2011]
88. Sharaf A, Gomaa N. Interrelationship between vitamins of the B-complex group and oestradiol. *J Endocrinol* 1974;62:241-244.
89. Foster JW, Pittillo RF. Metabolite reversal of antibiotic inhibition, especially reversal of aureomycin inhibition by riboflavin. *J Bacteriol* 1953;66:478-486.
90. Brown RG, Emerson GA. *In vitro* antagonism of pantothenic acid, ß-alanine and l-carnosine to inhibitory effects of erythromycin on growth of *Corynebacterium diphtheriae*. *Fed Proc* 1953;12:304-305.
91. Lichstein HC, Gilfillan RF. Inhibition of pantothenate synthesis by streptomycin. *Proc Soc Exp Biol Med* 1951;77:459-461.
92. Johnston RN, Smith DH, Ritchie RT, Lockhart W. Prolonged streptomycin and isoniazid for pulmonary tuberculosis. *Brit Med J* 1964;1:1679-1683.
93. LaCaille RA, Prigot A. The clinical trial of streptomycin pantothenate in the treatment of soft tissue infections. *Am J Surg* 1958;95:963-966.
94. Penman AC, Dickson I, Miller JS. Neurotoxic symptoms in streptomycin therapy: a pilot trial of treatment with pantothenic acid. *Tubercle* 1957;38:422-424.
95. Clifton G, Bryant SR, Skinner CG. N′-(substituted) pantothenamides, antimetabolites of pantothenic acid. *Arch Biochem Biophys* 1970;137:523-528.
96. Strauss E, Begley TP. The antibiotic activity of N-pentylpantothenamide results from its conversion to ethyldethia-coenzyme A, a coenzyme A antimetabolite. *J Biol Chem* 2002;277:48205-48209.
97. Thomas J, Cronan JE. Antibacterial activity of N-pentylpantothenamide is due to inhibition of coenzyme A synthesis. *Antimicrob Agents Chemother* 2010;54:1374-1377.
98. Virga KG, Zhang YM, Leonardi R, et al. Structure-activity relationships and enzyme inhibition of pantothenamide-type pantothenate kinase inhibitors. *Bioorg Med Chem* 2006;14:1007-1020.
99. Zhang YM, Frank MW, Virga KG, et al. Acyl carrier protein is a cellular target for the antibacterial action of the pantothenamide class of pantothenate antimetabolites. *J Biol Chem* 2004;279:50969-50975.
100. Wright LD, Skeggs HR. Succinylsulfathiazole in the nutrition of the rat. *Am J Med Sci* 1946;212:312-314.
101. Grundy WE, Freed M, Johnson HC, et al. The effect of phthalylsulfathiazole (sulfathalidine) on the excretion of B-vitamins by normal adults. *Arch Biochem* 1947;15:187-194.
102. Daft FS. Effect of vitamin C on pantothenic-deficient rats. *Fed Proc* 1951;10:380.
103. Daft FS, Schwarz K. Prevention of certain B vitamin deficiencies with ascorbic acid or antibiotics. *Fed Proc* 1952;11:200.
104. Everson G, Northrop L, Chung NY, Getty R. Effect of ascorbic acid on rats deprived of pantothenic acid during pregnancy. *J Nutr* 1954;54:305-311.
105. Said HM, Ortiz A, McCloud E, et al. Biotin uptake by human colonic epithelial NCM460 cells: a carrier-mediated process shared with pantothenic acid. *Am J Physiol* 1998;275:C1365-C1371.

106. Scientific Committee on Food: Opinion of the Scientific Committee on Food on the tolerable upper intake level of pantothenic acid. Report of the European Commission: Health and consumer protection directorate-general 2002SCF/CS/NUT/UPPLEV/61 Final:1-6 (http://ec.europa.eu/food/fs/sc/scf/out80k_en.pdf) [Accessed July 27, 2011]
107. Shibata K, Takahashi C, Fukuwatari T, Sasaki R. Effects of excess pantothenic acid administration on the other water-soluble vitamin metabolisms in rats. *J Nutr Sci Vitaminol (Tokyo)* 2005;51:385-391.
108. Institute of Medicine. *Dietary Reference Intakes for Thiamin, Riboflavin, Niacin, Vitamin B6, Folate, Vitamin B12, Pantothenic Acid, Biotin, and Choline*. Washington, DC: National Academy Press; 1998:367-368.
109. Cosmetic Ingredient Review. Final report on the safety assessment of panthenol and pantothenic acid. *J Am Coll Toxicol* 1987;6:139-162.
110. Fox HM. Pantothenic acid. In: Machlin LJ, ed. *Handbook of Vitamins, Nutritional, Biochemical and Clinical Aspects*. New York, NY: Dekker; 1984:437-458.
111. Unna K, Greslin JG. Studies on the toxicity and pharmacology of pantothenic acid. *J Pharmacol Exp Ther* 1941;73:85-90.
112. Debourdeau PM, Djezzar S, Estival JL, et al. Life-threatening eosinophilic pleuropericardial effusion related to vitamins B5 and H. *Ann Pharmacother* 2001;35:424-426.
113. Schalock PC, Storrs FJ, Morrison L. Contact urticaria from panthenol in hair conditioner. *Contact Dermatitis* 2000;43:223.
114. van Ketel WG. Hair lotion dermatitis with sensitization to d-panthenyl ethyl ether. *Contact Dermatitis* 1984;10:48.