

Raynaud's Syndrome

Raynaud's syndrome (RS) can be a debilitating condition that causes periods of severely restricted blood flow to the fingers and toes (and sometimes to other parts of the body such as the nose or ears). In the worst case scenario, this can result in amputation of the damaged digits.

The causes of RS remain a mystery in many cases. The disease causes significant free-radical nerve damage in the affected tissues. This damage leads to local endothelial dysfunction, thickening of the arterial walls, and the formation of scar tissue, or fibrosis (Simonini G et al 2000). RS is closely associated with more serious diseases (especially scleroderma, a connective tissue disorder). Many scientists believe that RS may be the initial diagnosis, before the actual diagnosis of scleroderma is recognized. Other diseases associated with RS include systemic lupus erythematosus and arthritis. In each case, RS may contribute to the more serious disease by encouraging the formation of scar tissue in the connective tissue and through damage to arteries. Therefore, it is crucial that patients who have RS pursue aggressive antioxidant therapy to lower their risk of developing a more serious condition.

RS typically affects the small blood vessels in the fingers and toes but can affect those in the ears, nose, and tip of the tongue as well (Adee AC 1993; Awami M et al 2004a,b; NIAMS 2001). During episodes of RS, the affected area may become painful and turn blue (NIAMS 2001).

RS that occurs in the absence of another disease is referred to as primary RS (also sometimes called Raynaud's disease or Raynaud's syndrome). It is thought to involve a localized defect in the arteries and arterioles that deliver blood to the extremities. Because RS is associated with conditions, such as migraine headaches and angina, caused by spasms of blood vessels (vasospasm), it may have a similar vasospastic mechanism.

RS that occurs in the presence of other diseases is called secondary RS. Occupational RS is a common form of secondary RS that results from using vibrating tools such as jackhammers (NIAMS 2001). Drugs or treatments used to treat high blood pressure (beta blockers), migraine headaches (ergotamine-containing drugs), and cancer (chemotherapy) have been known to cause RS (Merck 2005; NIAMS 2001).

OXIDATIVE DAMAGE: RS'S LASTING EFFECT

In normal healthy tissue, blood flow to the skin is regulated by a complex system that includes neural signals, hormones, and mediators released from circulating cells and blood vessels. Under normal circumstances, when a person is exposed to cold or is under emotional stress, arterioles constrict to return blood flow to the core of the body, for warmth and protection (NIAMS 2001). This reaction is regulated by vasoconstrictive agents such as endothelin 1 (Nakamura H et al 2003; Rajagopalan S et al 2003a) and factors that impair production of nitric oxide, a potent vasodilator (Generini S et al 2005).

In individuals with RS, the normal reaction is exaggerated—blood circulation in the arterioles is greatly restricted, resulting in a visible progression of symptoms as blood flow to the affected areas drops. Skin first turns white as it is deprived of blood, then turns blue (cyanosis) because of the lack of blood and oxygen, and then has localized red flushing as the blood returns to the affected area (Browne BJ et al 1995). This progression may be accompanied at first by a loss of sensation in the affected extremities, followed by a prickling, throbbing, or tingling sensation as circulation returns (NIAMS 2001).

Skin changes may migrate, moving from one finger to the next, sometimes even involving the thumb (Pistorius MA et al 1995). The tip of the nose, the earlobes, and (rarely) the cheeks or chin can also be affected (Adee AC 1993). The characteristic skin changes can occur in as little as 3 minutes. An episode can last from a few minutes to several hours (NIAMS 2001), although episodes may last longer in people who have connective tissue disorders such as scleroderma (Dziankowska-Bartkowiak B et al 2004).

Researchers are working to discover the underlying mechanism in RS and have found that certain receptors, called alpha 2–adrenergic receptors, are hypersensitive in people who have RS. Alpha-receptors are located on the membranes of vascular smooth muscle cells and help regulate vasoconstriction and smooth muscle contraction in blood vessel walls (Freedman RR et al 1995). Studies have found that blocking certain alpha-2 receptors reduced the number of vasospastic attacks in the fingers (Freedman RR et al 1995; Furspan PB et al 2004).

No matter what the underlying cause is, it is known that episodes of RS trigger significant free-radical nerve damage in affected tissues. During RS, the blood flow is restricted, then restored. This causes ischemic reperfusion injury, the same type of injury that can occur after a stroke, when the returning blood flow to the brain causes additional damage. In RS, the ischemic reperfusion injury

(which generates high levels of free radicals that attack the endothelium in arteries and surrounding tissue) causes scar tissue to form in the connective tissue (Simonini G et al 2000).

This may help explain why RS is frequently associated with autoimmune connective tissue disorders such as scleroderma, lupus, and arthritis (Ziegler S et al 2003). In about 20 percent of cases, RS is the first indication of a more serious connective tissue disorder such as scleroderma, lupus, or arthritis, which means that the conditions of patients who have RS should be closely monitored for these conditions (Grassi W et al 1998; Ho M et al 1998; Ziegler S et al 2003).

Episodes of RS are unpredictable and difficult to reproduce accurately in a clinical setting (Bornmyr S et al 2001). RS can remain dormant for years, only to resurface suddenly in response to infection, fatigue, or stress. If RS progresses, permanently decreased blood flow to the affected area can cause fingers to become thin and tapered, with smooth shiny skin and slow-growing nails. Often the most serious consequence is loss of sensitivity in the affected extremity. However, more severe cases of secondary RS can result in tissue death, finger deformity, skin ulceration, or gangrene (Lavery JP et al 1992). RS can also affect the lungs. When the lungs are affected, breathing cold air triggers a coughing attack (ISN 2005). Vasospasm may also affect the heart, lungs, and kidneys (Ho M et al 1998).

RS is also infrequently associated with hypothyroidism, alone or associated with scleroderma (Grassi W et al 1998). Treatment with supplemental thyroid hormones (such as those used to treat hypothyroidism) has been shown to resolve RS in extremely rare cases (Shagan BP et al 1976).

DIAGNOSING RS

Diagnosing RS is complicated because it can be mistaken for other conditions such as carpal tunnel syndrome, vascular disease, or thoracic outlet syndrome (Lavery JP et al 1992). Therefore, physicians diagnose RS based on the presence of some of the following factors (NIAMS 2001):

- Periodic attacks of cyanosis
- A negative antinuclear antibody test result, which demonstrates the absence of lupus
- A normal erythrocyte sedimentation rate, which demonstrates the absence of major systemic inflammation

Although it is difficult to cause an attack of RS in a doctor's office (Bornmyr S et al 2001), submerging the patient's hands in ice, recording the time it takes for normal color to return to the hands, and performing a vascular assessment may determine the severity of RS.

Because RS may be an important marker of more serious disease conditions, a full blood laboratory panel should be performed to rule out underlying autoimmune disorders, malignancies, kidney or liver dysfunction, and syndromes that affect the blood or circulation (Lavery JP et al 1992). In particular, an antinuclear antibody test and erythrocyte sedimentation rate should be performed to assess potential autoimmune conditions. Diagnosis of secondary RS includes periodic episodes of cyanosis, a positive antinuclear antibody test result, and an abnormal erythrocyte sedimentation rate (NIAMS 2001).

CONVENTIONAL TREATMENT OF RS

Treatment of RS is determined by type. In primary RS, conventional treatment is often conservative, using self-help strategies such as preventing attacks and reducing symptoms. Pharmacological treatment is rarely required and, unfortunately, antioxidant therapy is rarely recommended. When necessary, calcium channel blockers are considered the safest and most effective drugs. They relax smooth muscle and dilate small blood vessels, reducing the frequency and severity of attacks in primary and secondary RS (NIAMS 2001).

Treatment of secondary RS focuses on the underlying condition, such as scleroderma or lupus (NIAMS 2001). In addition to treatment of the underlying condition, a number of drugs may be prescribed to control the episodes of RS (ISN 2005):

- **Calcium channel blockers.** Calcium channel blockers are traditionally first-choice prescription medications to treat RS. These drugs block calcium channels in the smooth muscle of vessel walls, thereby preventing contraction. Nifedipine is considered the standard for treatment. Adverse effects of the various calcium channel blockers are frequent and include abnormal heart rhythm, flushing, swelling, and headache. These effects may subside over time, and long-acting preparations may minimize them. Diltiazem has fewer side effects but may be less effective. Calcium channel-blocking drugs improve symptoms only moderately in the treatment of secondary RS (Thompson AE et al 2001).
- **Vasodilators.** Cilostazol, a relatively new vasodilator, has shown promise in the treatment of RS (Rajagopalan S et al 2003b). Sildenafil has also been used with some effectiveness.
- **Prostaglandin E1.** Transdermal patches containing prostaglandin E1 improved blood flow to skin capillaries and reduced the number of episodes of RS in subjects who had RS secondary to scleroderma (Schlez A et al 2003).

In addition to pharmaceutical treatments, a number of other therapies are used in treating RS:

- **Paraffin.** Regular paraffin (hot wax) treatment may be helpful, although it must be used with caution. Use only physician-prescribed hot wax units because wax that is too hot may damage fragile blood vessels. Never heat wax on a stove or in an electric cooking pot (such as a Crock-Pot). A physical or occupational hand therapist can provide training in the proper procedure (ISN 2005).
- **LASER irradiation.** Low-level LASER treatment has been shown to reduce the frequency and severity of RS attacks. The conditions of people who had primary and secondary RS improved with LASER irradiation (Awami M et al 2004a; Hirschl M et al 2004). Patients with RS who received low-level LASER treatment experienced less response to cold (Awami M et al 2004a). Those who had a decreased threshold for vasospasm experienced the greatest benefit (Hirschl M et al 2004).
- **Surgery.** In selective cases of severe RS, doctors may recommend surgery to reestablish blood flow to an affected area by interrupting nerve pathways. In cervical sympathectomy, nerve pathways that may be contributing to the symptoms of RS are interrupted. Early studies of this procedure show mixed results. There is little evidence that the benefits of surgery are long standing. In localized digital sympathectomy, nerve pathways to specific digits or an area affected by RS (usually the fingers) are interrupted. The surgeon makes small incisions in the affected area and cuts nerves around blood vessels. This type of surgery is usually performed only on individuals who have failed to benefit from conservative medical treatment and continue to experience poor blood flow to affected areas, or on individuals who have severe RS or tissue-threatening RS (more common in secondary RS) (Flatt AE 1980).

NUTRITIONAL APPROACHES TO RS

Although the causes of RS have remained mysterious, researchers understand the damage cascade that RS can touch off. During episodes of RS, high levels of free radicals are generated that damage the inner lining of arteries (endothelium) and surrounding tissue. The use of antioxidants in treating RS is based on research studies that showed that levels of important antioxidants (such as vitamin E, vitamin C, and selenium) are depleted in patients who have RS.

Vitamin E. Vitamin E is a key antioxidant, protecting polyunsaturated fatty acids from oxidation (Traber MG 1999). It has been found to have therapeutic effects in certain forms of RS. A clinical trial has shown that the alpha-tocopherol form of vitamin E was beneficial in treating occupational RS (Matoba T et al 1977).

Vitamin C. Vitamin C is important for the synthesis of collagen, a key component of blood vessel walls. Studies have demonstrated that administering vitamin C improves blood flow. For example, in patients who have atherosclerosis of the coronary arteries, the ascorbic acid form of vitamin C improved blood vessel vasoconstriction, thus improving blood flow through the arteries (Gocke N et al 1999). A deficiency of ascorbic acid and selenium has been found to raise the risk of scleroderma in people with RS (Herrick AL et al 1994).

Niacin. An experimental evaluation of the usefulness of no-flush niacin in treating RS concluded that it produced beneficial therapeutic effects on the microcirculation, not only through vasodilation, but also through mechanisms such as an enhanced ability to break up clots (fibrinolysis) and lowering of lipids (fats) in the blood. Compared to standard drug treatment, few adverse effects were noted (Holti G 1979). Another study found that long-term supplementation with nicotinate acid derivatives may improve peripheral circulation through a different effect than the one detected by short-term studies (Ring EF et al 1977). Niacin has also resulted in a significant improvement in the symptoms of RS and a reduction in the frequency of RS attacks (Murphy R 1985).

Magnesium. Magnesium is essential to maintain relaxation of the smooth muscle of the small arteries affected by RS (Shils ME 1999). Requirements for magnesium increase with physical stress, which is a trigger associated with initiating RS episodes (Golf SW et al 1998). Red blood cell levels of magnesium were found to vary seasonally in women who had primary RS. Magnesium levels were significantly lower in winter than in summer (Leppert J et al 1994).

Essential Fatty Acids. Omega-3 and gamma-linoleic acid (an omega-6 fatty acid found in evening primrose oil and borage oil) are anti-inflammatories that have been shown to help relieve symptoms of RS. One study found that taking evening primrose oil dramatically decreased the number of attacks of RS with the onset of cold weather, although there was no change in blood flow to the hands (Belch JJ et al 1985). A clinical study found that ingesting fish oil increased the median time before onset of RS after exposure to cold (especially in people who had primary RS). Fish oil also improved tolerance to cold exposure, as evidenced by significantly increased blood pressure in the fingers. Almost half of the people who ingested fish oil did not exhibit symptoms of RS in response to a cold water bath (DiGiacomo RA et al 1989).

L-Arginine. L-arginine has been shown to reverse tissue damage caused by RS and improve symptoms in subsequent attacks (Rembold C et al 2003). It stimulates production of nitric oxide, thus helping to keep arteries open and relaxed (Rembold C et al 2003). Studies on L-arginine are mixed, with some showing efficacy and others showing no effectiveness.

Ginkgo Biloba. Ginkgo biloba is a well-tolerated plant extract. In one study, Ginkgo biloba reduced the frequency of RS attacks

per week by 56 percent (Muir AH et al 2002).

Estrogens. Estrogen and related compounds increase nitric oxide synthesis, which in turn relaxes vascular smooth muscle and dilates arteries. Estrogen has been shown to reduce endothelial dysfunction in secondary RS (Generini S et al 2005). The phytoestrogen genistein has been documented in the laboratory to inhibit cold-induced vasoconstriction in the arterioles of patients who have RS (Furspan PB et al 2004).

N-Acetylcysteine (NAC). NAC is a powerful antioxidant itself, and it also replenishes natural antioxidant molecules such as glutathione, which is active in preventing or reducing endothelial dysfunction in people who have RS. In two recent studies, intravenous NAC reduced the frequency and severity of RS attacks in patients who had scleroderma (Sambo P et al 2001) and also enhanced global perfusion of the hands (Salsano F et al 2005).

STRATEGIES TO REDUCE ATTACKS OF RS

A first line of defense against RS, whether primary or secondary, is to protect the extremities from common triggers of attacks such as cold or emotional and physical stress.

Protect Your Body. Extreme changes in temperature are worse than cold alone. If you have RS:

- Keep your head and torso warm to enable blood to flow more freely to your hands and feet (AF 2004).
- Wear socks to bed.
- Use an electric blanket to warm the sheets before getting into bed.
- Dress in loose layers of blended fabrics, including a sweater.
- Wear long underwear made of silk to protect against chills without overheating the body.
- Wear a warm hat and earmuffs to prevent heat loss through the head when outside.
- Use chemical-pack heaters inside socks and mittens.
- Warm body parts by using tubes of fabric filled with grain that can be warmed in a microwave and then applied to affected areas.
- Cover exposed skin (including nose and cheeks) in cold, windy weather.
- Avoid getting the skin wet or perspiring in cold weather. Moisture cools the skin as it evaporates.
- Wear an under layer of clothing in a material that wicks away moisture.
- Be prepared for temperature changes by having extra clothing available in your car or at work.
- Drink warm beverages.
- Carry an insulated hot water bottle with you on car trips.

Protect Your Hands. Damp cold is more likely to precipitate an attack. Take the following steps to protect your hands from cold temperatures:

- Wear mittens and wristlets outside in cold weather. Mittens warm hands more effectively than gloves because they pool heat from the entire hand. Wristlets keep cold air out of the gap between sleeves and mittens.
- Wear mittens to bed.
- Wear mittens when handling cold or frozen foods (NIAMS 2001).
- Never clean vegetables under cool, running water; use warm water. Or use already-prepared vegetables from the produce department.
- Run bath or shower water ahead of time to avoid touching cold water.
- Avoid touching the cold water from garden hoses.
- Do not hang wet clothes outside.
- Do not shovel snow.
- Do not hold cold beverages. Use insulated cup holders and straws.

Protect Your Skin. People who have RS should take precautions with skin care because minor cuts and scrapes take longer to heal and are more susceptible to infection:

- Take care not to injure skin, particularly areas affected by RS.
- Wear gloves when using detergents or harsh chemicals.
- Wear gloves when gardening.
- Treat injuries without delay.
- Consult a healthcare provider if infection or skin ulcers develop.
- Use creams to keep skin soft. Rough, dry skin is more likely to tear (Cleveland Clinic 2005).

Rewarm Affected Areas. A prolonged attack of RS can lead to tissue death, gangrene, and possibly amputation. Consider each attack an emergency and respond immediately. Try to remain calm when an attack begins (AF 2004). Gently rewarm fingers and toes as soon as possible. The sooner rewarming is started, the easier it will be to restore circulation and lessen the chance of damage. Try moving the affected part right away, which may avert the need for further measures. If moving the affected body part does not result in the alleviation of symptoms of RS, try applying moist heat. Become familiar with the following rewarming strategies (AF 2004):

- Do not clap your hands together or rub them vigorously. Doing so can damage blood vessels.

- Place your hands under your armpits or between your legs.
- Cup your hands to your mouth and breathe on your fingers.
- Have another person hold (but not rub) your hands.
- Wiggle your fingers and toes.
- Walk (or otherwise move) around.
- Twirl your arms around in the air in large circles until circulation returns. Avoid twirling your arms, however, if scleroderma has damaged your blood vessels.
- Run warm (but not hot) water over the affected body parts until normal color returns.
- Do not overheat hands to avoid constricting blood vessels and prolonging an attack.

Avoid Vasoconstrictive Substances. Try not to consume food or medications, or be around substances, that can constrict blood vessels:

- Do not smoke. Smoking constricts peripheral blood vessels (AS 2005) and reduces the blood concentration of antioxidants such as ascorbic acid (Herrick AL et al 1994; Yale 2004).
- Avoid breathing second-hand smoke.
- Cut down on your intake of caffeine-containing foods, beverages, and drugs. Caffeine, a vasoconstrictor, can be found in chocolate and some aspirin preparations, teas, and medications (ISN 2005).
- Do not use birth-control pills (Yale 2004).
- Avoid taking most over-the-counter decongestants, cold remedies, and diet pills (NIAMS 2001).
- Have your doctor monitor your condition closely if you take medications for migraines, high blood pressure, or heart problems. Some migraine headache, blood pressure, and heart medications can cause symptoms of RS (NIAMS 2001).

Avoid Precipitating Activities. Attacks of RS may be initiated by operating vibrating equipment such as chain saws, jackhammers, or drills (NIAMS 2001). When using a vacuum cleaner, try wearing oven mitts to reduce the effect of the vibrations. Symptoms of RS can also be brought on by repetitive hand motions (such as those used while typing, playing the piano or guitar, sewing, and chopping or dicing food). Do not carry heavy shopping bags with handles that restrict blood flow to fingers.

Use Biofeedback. Blood vessels can be trained to relax using biofeedback (NIAMS 2001). In one form of biofeedback, you “think” that your hands are warm. In another form of biofeedback, you place your hands in a bowl of warm water (in a warm room) for 5 minutes, then move to a cold room or cold environment. Then you again place your hands in warm water, this time for 10 minutes. Repeat the procedure several times a day for as many days as necessary to produce a conditioned reflex that is the opposite of the normal one: that is, when exposed to cold, the blood vessels in the fingers will dilate rather than constrict (without the aid of warm water). The success of biofeedback has been documented by studies. Biofeedback subjects showed significant elevations in blood flow to, and temperature of, the fingers and in skin conductance level beyond what could be explained by other differences in the study groups (Freedman RR 1989). Improvement in symptoms was maintained 9 weeks, 1 year, and 2 years in RS and 8 years in RS secondary to systemic lupus erythematosus (Freedman RR et al 1988; Keefe FJ et al 1980; Sappington JT et al 1985). Biofeedback is generally not as effective in treating secondary RS as it is in treating primary RS. It may also not work as well for warming the feet.

LIFE EXTENSION FOUNDATION RECOMMENDATIONS

In addition to making lifestyle changes and treating any underlying conditions, a number of the following nutrients have been shown to reduce the severity and frequency of attacks of RS:

- **Vitamin E (alpha-tocopherol)**—400 International Units (IU)
- **Gamma E tocopherols**—At least 359 milligrams (mg) of gamma E–mixed tocopherols daily
- **Vitamin C**—2500 mg/day
- **Niacin**—750 mg/day or less. Use the lowest dose of niacin that relieves symptoms of RS. If you cannot tolerate the niacin flush, take 1500 to 4000 mg of inositol hexanicotinate (which does not cause flushing) in three divided doses.
- **Magnesium**—1000 mg/day along with 1000 mg of elemental calcium
- **Gamma linolenic acid**—900 mg/day of borage oil
- **L-arginine**—900 mg/day
- **Eicosapentaenoic acid (EPA) and docosahexaenoic (DHA)**—1400 mg of EPA and 1000 mg of DHA
- **Ginkgo biloba extract**—120 mg/day
- **Selenium**—200 micrograms (mcg) daily
- **NAC**—600 mg/day

In addition to these supplements, hormone replacement therapy (with estrogen or phytoestrogen compounds) may be considered.

Estrogen therapy should only be undertaken after blood tests have been performed and under the guidance of a qualified physician. Studies have shown that unopposed estrogen therapy can raise the risk of certain cancers. For more information on bioidentical hormonal therapy and on hormonal testing, call 1-800-544-4440.

RAYNAUD'S SYNDROME SAFETY CAVEATS

An aggressive program of dietary supplementation should not be launched without the supervision of a qualified physician. Several of the nutrients suggested in this protocol may have adverse effects. These include:

EPA/DHA

- Consult your doctor before taking EPA/DHA if you take warfarin (Coumadin). Taking EPA/DHA with warfarin may increase the risk of bleeding.
- Discontinue using EPA/DHA 2 weeks before any surgical procedure.

Ginkgo biloba

- Individuals with a known risk factor for intracranial hemorrhage, systematic arterial hypertension, diabetes, or seizures should avoid ginkgo.
- Do not use prior to or after surgery.
- Avoid concomitant use of ginkgo with NSAIDS, blood thinners, diuretics, or SSRI's.
- Gastrointestinal symptoms (nausea and diarrhea) may occur.
- Allergic skin reactions may occur.
- Elevations in blood pressure may occur.

GLA

- Consult your doctor before taking GLA if you take warfarin (Coumadin). Taking GLA with warfarin may increase the risk of bleeding.
- Discontinue using GLA 2 weeks before any surgical procedure.
- GLA can cause gastrointestinal symptoms such as nausea and diarrhea.

L-Arginine

- Do not take L-arginine if you have the rare genetic disorder argininemia.
- Consult your doctor before taking L-arginine if you have cancer. L-arginine can stimulate growth hormone.
- Consult your doctor before taking L-arginine if you have kidney failure or liver failure.
- Consult your doctor before taking L-arginine if you have herpes simplex. L-arginine may increase the possibility of recurrence.

Magnesium

- Do not take magnesium if you have kidney failure or myasthenia gravis.

NAC

- NAC clearance is reduced in people who have chronic liver disease.
- Do not take NAC if you have a history of kidney stones (particularly cystine stones).
- NAC can produce a false-positive result in the nitroprusside test for ketone bodies used to detect diabetes.
- Consult your doctor before taking NAC if you have a history of peptic ulcer disease. Mucolytic agents may disrupt the gastric mucosal barrier.
- NAC can cause headache (especially when used along with nitrates) and gastrointestinal symptoms such as nausea and diarrhea.

Niacin (nicotinic acid)

- Do not take high doses of nicotinic acid (1.5 to 5 grams daily or more) if you have liver dysfunction, an unexplained elevation in your serum aminotransferase (transaminase) level, active peptic ulcer disease, arterial bleeding, or if you consume large

amounts of alcohol.

- Consult your doctor before taking high doses of nicotinic acid if you have a history of jaundice, peptic ulcer disease, gastritis, disease of the liver or bile ducts, gout, kidney dysfunction, or cardiovascular disease (especially acute myocardial infarction or unstable angina).
- Consult your doctor before taking high doses of nicotinic acid if you have diabetes. High doses of nicotinic acid can negatively affect glucose tolerance. Monitor your serum glucose level frequently if you take nicotinic acid and have diabetes.
- Have your doctor monitor your serum aminotransferase level if you take high-doses of nicotinic acid.
- Nicotinic acid may cause flushing, principally of the face, neck, and chest. This flushing is thought to be prostaglandin-prostacyclin mediated. Histamine may also play a role in the flushing.
- Nicotinic acid can cause dizziness, palpitations, rapid heartbeat, shortness of breath, sweating, chills, insomnia, nausea, vomiting, abdominal pain, and muscle pain.
- High doses of nicotinic acid can cause blurred vision, macular edema, toxic amblyopia, and cystic maculopathy.

Selenium

- High doses of selenium (1000 micrograms or more daily) for prolonged periods may cause adverse reactions.
- High doses of selenium taken for prolonged periods may cause chronic selenium poisoning. Symptoms include loss of hair and nails or brittle hair and nails.
- Selenium can cause rash, breath that smells like garlic, fatigue, irritability, and nausea and vomiting.

Vitamin C

- Do not take vitamin C if you have a history of kidney stones or of kidney insufficiency (defined as having a serum creatine level greater than 2 milligrams per deciliter and/or a creatinine clearance less than 30 milliliters per minute).
- Consult your doctor before taking large amounts of vitamin C if you have hemochromatosis, thalassemia, sideroblastic anemia, sickle cell anemia, or erythrocyte glucose-6-phosphate dehydrogenase (G6PD) deficiency. You can experience iron overload if you have one of these conditions and use large amounts of vitamin C.

Vitamin E

- Consult your doctor before taking vitamin E if you take warfarin (Coumadin).
- Consult your doctor before taking high doses of vitamin E if you have a vitamin K deficiency or a history of liver failure.
- Consult your doctor before taking vitamin E if you have a history of any bleeding disorder such as peptic ulcers, hemorrhagic stroke, or hemophilia.
- Discontinue using vitamin E 1 month before any surgical procedure.

For more information see the Safety Appendix

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