

Influenza

Influenza (commonly known as the flu) is one of the most feared and deadly infectious diseases (Dolin R 2004; Hilleman MR 2002; Nicholson KG et al 2003). In the 20th century alone, there were seven influenza epidemics or pandemics. The most devastating (1918 to 1919) was the Spanish flu, which killed 40 to 50 million people (Nicholson KG et al 2003). From 2005 to 2006, newspapers were full of headlines about the avian flu, or H5N1. This particularly deadly strain has been found in Asia and Eastern Europe, where it is noted for its lethality. Although H5N1 has jumped from its host species (birds) to humans, it has not yet been found to be transmitted person to person. Total deaths caused by the virus have been very low (around 200 people as of this writing), although the mortality rate of people who have been infected is extremely high, around 80 percent (Wong SS et al 2006).

Even when the flu does not reach pandemic proportions, it is the source of misery, illness, and death every flu season, which runs roughly through the fall and early winter months in North America. Since the early 1970s, researchers estimate that influenza has caused more than 40,000 deaths in the United States every year (Dushoff J et al 2006). It is estimated that flu outbreaks cost about \$12 billion annually in the United States (Kasper DL et al 2004).

Everyone is susceptible to infection with the flu virus, which is usually spread by direct contact with contaminated secretions (Nicholson KG et al 2003). It can also be spread when the virus is sneezed or coughed into the air, although influenza is not typically spread by aerosol (being dissolved in air), as are other respiratory viruses (Bridges CB et al 2003; Goldmann DA 2000). This means that the flu can spread only short distances between people—simply being in a room with someone who has the flu is not a major risk factor. The severity of the infection and the duration of the illness, however, depend on several factors, including:

- Resistance of the respiratory tract to oxidative stress associated with influenza infection, as well as its ability to mount a local immune/inflammatory response and its ability to manufacture and secrete antibodies (Beck MA et al 1998; Mileva M et al 2002b; Muller F et al 2000; Nicholson KG et al 2003).
- Level of immunity against that particular strain of influenza (Dolin R 2004; Glezen WP 2004; Nicholson KG et al 2003; Wareing MD et al 2002; Zambon MC 2001).
- Overall health of the person's immune system (Brandtzaeg P 2003; Chandra S et al 1986; Nicholson KG et al 2003).
- Antioxidant status (Hennet T et al 1992).
- Overall nutritional and general health status.

Nutrition has recently been singled out as the most important factor in resistance to influenza infection (Beck MA et al 2004).

INFECTION: THE FLU VIRUS AT WORK

There are two main types of flu viruses: influenza A and influenza B. The most serious and deadly flu outbreaks are caused by influenza A because of its ability to genetically shift into new forms against which no person has developed immunity. H5N1, the avian flu, is caused by an influenza A virus. Influenza B generally causes less severe infection. Outbreaks of influenza B commonly occur in schools and military camps, where many people live or work in close contact.

Infection with the flu begins with exposure of the upper respiratory tract to the virus. In infected cells, viral replication occurs 4 to 6 hours after infection, after which time the infected cell bursts, spreading the virus to nearby cells. The cycle then repeats, infecting more and more cells each time. This accounts for the incubation period for the flu, which ranges from about 18 to 72 hours, depending on the strain and the effectiveness of the body's immune response. The more virulent the strain, and/or the weaker the host's immunity, the sooner the cycle of cell death and viral spread produces noticeable symptoms. People who have weak immune systems, such as the elderly, sick people, or young children, can therefore be quickly overwhelmed by strong strains of the virus.

The immune response to the flu is complex and comprehensive. Almost immediately after sensing the virus, the body mounts a response that calls upon all facets of the immune system. This includes natural immune responses, such as the release of proinflammatory cytokines and enhanced natural killer cell activity, which includes the release of antiviral interferons. White blood cells called neutrophils and macrophages also flood the site of infection, producing yet more proinflammatory and fever-causing cytokines. This rapid, indiscriminate immune response is responsible for the sudden onset and continuation of symptoms, which usually peak by the second day of infection (Wright PF et al 2001; Yuen KY et al 2005).

At the same time that this nonspecific response is occurring, the body is creating specific antibodies to recognize and destroy that particular strain of flu virus in the future. The body's immune system relies on T-cells and B-cells, which are coded to identify specific antigens (invaders) and stimulate a more effective and rapid immune response in the event of future infection. In the case of

the influenza virus, antibodies against the flu are detected in the second week after primary infection. These antibodies will help protect against similar strains of the flu in the future. New strains, such as those created by genetic shifting, retain their full power. For more information on a healthy immune system, please see the chapter "Immune System Enhancement."

Ideally, the best approach to the flu is to avoid getting sick in the first place. This may mean using a vaccine to help bolster the immune response against specific strains, or taking nutrients such as lactoferrin that have been shown to enhance the immune system.

Once infection has occurred, the goal of flu therapy is to stop the virus before it replicates enough to cause illness. Flu vaccines, which contain dead or inactivated flu viruses, help people ward off illness by enabling their bodies to recognize and fight a specific strain of flu virus early in the infection process. Every year, doctors try to determine which variety of the flu is likely to cause an outbreak, then vaccines against that particular strain are manufactured. Vaccination against influenza is often recommended for at-risk populations, especially the elderly (Cox RJ et al 2004; Glezen WP 2004; Kilbourne ED 2004; Langley JM et al 2004; Munoz FM 2003; Nicholson KG et al 2003; Pfliegerer M et al 2001; Sandhu SK et al 2001; Wareing MD et al 2002). Additionally, animal studies suggest that supplementing with dehydroepiandrosterone (DHEA) may restore the aging immune system sufficiently to allow normal response to the vaccine (Daynes RA et al 1994).

In many cases of flu infection, the onset of symptoms is so abrupt that people can pinpoint the hour when they began to feel ill. Body temperature rises rapidly, and can reach 100°F to 106°F within the first 24 hours; a sharp headache may occur (Dolin R 2004). These symptoms are not characteristic of other, less serious, respiratory infections such as the common cold, so they are reliable indicators that the person is infected with the flu. Respiratory symptoms, such as coughing and congestion, appear later in the illness. In the absence of complications, influenza symptoms typically resolve within a week, although, in a significant number of elderly people, general weakness and fatigue may persist for several weeks (Dolin R 2004).

The most common and dangerous complication of influenza is pneumonia, which can affect people of all ages and may be life-threatening. The people most commonly affected by complications of influenza are 65 years or older or those who have chronic disorders such as diabetes. Newborn infants, like the elderly, are at increased risk of serious complications because of their incompletely developed immune systems. These complications include pneumonia and other lung conditions, as well as occasional heart diseases such as myocarditis. Minor complications of influenza in infants and young children can include ear infections, while the fever itself may be responsible for febrile convulsions in children 6 months to 6 years.

You Should Get a Flu Vaccine If You ...

- Are age 65 or older.
- Have a chronic medical condition, such as a cardiovascular, pulmonary, metabolic, or renal disease.
- Have a weak immune system.
- Are a pregnant woman in her second or third trimester (Cox RJ et al 2004).
- Smoke.
- Are a health-care provider or a volunteer in a health-care setting.

CONVENTIONAL ANTIVIRAL DRUGS

Although good nutrition and flu vaccines are first-line treatments for the prevention of the flu, antiviral drugs also may be given to prevent infection or reduce the severity of illness. If given quickly enough, antiviral drugs have been shown to reduce the duration of symptoms by about 50 percent, although some people experience unpleasant side effects of the central nervous system with these drugs. Some of the adverse effects from using these drugs can include nervousness, jitters, insomnia, or difficulty concentrating (Kasper DL et al 2004). Everyone (including people who have been vaccinated against the flu) can receive antiviral drugs.

Common antiviral drugs include:

- **Amantadine and rimantadine.** In the United States, amantadine and rimantadine are approved by the US Food and Drug Administration (FDA) for treatment of influenza infection. Amantadine is approved for prevention and treatment in adults and in children older than 1 year; rimantadine is approved for prevention and treatment in adults and for prevention in children (Jefferson T et al 2004). The effectiveness of amantadine in the treatment of influenza in people who are at high risk of complications has not been proved in clinical trials. Also, influenza A rapidly develops resistance to amantadine (Dolin R 2004; Nicholson KG et al 2003).
- **Oseltamivir.** In October 1999, the antiviral drug oseltamivir (Tamiflu) was approved in the United States for treatment of uncomplicated influenza in adults. People who take oseltamivir usually recover 1.3 days (30 percent) faster than those who do not. The most common adverse effects are mild to moderate transient nausea or vomiting. Other side effects include bronchitis, insomnia, and vertigo. Less than 1 percent of people who take oseltamivir in clinical trials discontinued the drug

early because of nausea or vomiting (McClellan K et al 2001; Treanor JJ et al 2000).

In 2000, oseltamivir was approved for prevention of influenza in people who have been exposed to the virus. It is up to 92 percent effective in preventing influenza when taken once daily (Peters PH Jr et al 2001). In one clinical trial involving 548 patients (276 taking oseltamivir, 272 taking placebo), a daily dose of 1.75 milligrams (mg) of oseltamivir was given for up to 42 days to a group of elderly nursing home residents. In the placebo group, oseltamivir reduced the incidence of influenza from 4.4 to 0.4 percent (Peters PH Jr et al 2001). Oseltamivir shortened the duration of influenza by 1.5 days (26 percent) in children age 1 to 12 years when given within 2 days of symptom onset (Whitley RJ et al 2001).

- **Zanamivir.** The antiviral zanamivir (Relenza) is delivered through an inhaler. In the United States, zanamivir is approved only for prevention of influenza. Several clinical trials have demonstrated efficacy comparable to that of oseltamivir. Seasonal prevention with 10 mg of zanamivir daily in unvaccinated healthy subjects reduced the incidence of influenza from 69 to 81 percent (Nicholson KG et al 2003).

What You Have Learned So Far

- The flu is one of the deadliest infectious diseases in the world, and is responsible for more than 40,000 deaths each year in the United States alone.
- Flu infection is spread by exposure to the virus through contact with an infected person's secretions.
- The flu virus begins to replicate within hours of the host's exposure to the virus. The incubation period (the time before the illness manifests itself) is generally between 18 and 72 hours.
- Symptoms of influenza (a high fever and sharp headache) often come on suddenly. The severity of these symptoms often peaks by the second day. After that, the fever usually subsides and symptoms begin to appear in the respiratory tract.
- People who have weak immune systems, such as the elderly and young children, are at risk of having a more severe influenza infection.
- Flu vaccines, which contain dead viruses or inactivated viruses, may help prevent flu infection.
- The immune response against the flu employs both natural and acquired immune weapons. After exposure to one form of flu virus, the body produces antibodies that recognize that particular virus again. The ability of influenza A virus to shift its genotype enables it to evade recognition by the immune system, and allows rapid spread.

THE LIFE EXTENSION FOUNDATION FLU PROGRAM

The Life Extension Foundation's approach to the flu is based on the idea of preemption. At the first sign of infection, consider taking the following supplements. This program is not meant for long-term consumption because of the high doses. Only follow these recommendations for a few days.

Vitamin C. Megadoses of vitamin C (1000 mg every hour for the first 6 hours and three times daily thereafter) administered during or after influenza infection decreased influenza symptoms in a large group of students (Gorton HC et al 1999).

Vitamin E. Both human and animal studies have shown that vitamin E, a powerful antioxidant, can help fight influenza infection by boosting the immune system (Gay R et al 2004; Hara M et al 2005). Animal studies have shown that vitamin E, in conjunction with other antioxidants, can help protect against the flu by reducing the oxidative damage associated with the virus:

- After being infected with the influenza virus, aged mice fed a diet supplemented with vitamin E had significantly lower pulmonary viral levels and maintained their body weight, unlike control mice or mice fed with other antioxidants. Levels of pro-inflammatory cytokines, including interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-alpha), were lowest in the group supplemented with vitamin E (Han SN et al 2000).
- Vitamin E was shown to reduce the viral activity in the lungs of middle-aged mice after exposure to influenza (Meydani M 1999).
- Supplementation with vitamin E before infection helped protect the lungs of the mice against lipid peroxidation (Mileva M et al 2002a).

Selenium and zinc. A combination supplement containing selenium and zinc can reduce the severity of flu infection:

- In one study, seniors who received an experimental formula of zinc, selenium, fermentable oligosaccharides (a kind of sugar that enhances beneficial bacteria), and structured triacylglycerides for 183 days showed signs of enhanced immune function and had fewer days of upper respiratory symptoms (Langkamp-Henken B et al 2004).
- A 2-year supplementation program of vitamins and micronutrients showed that selenium and zinc significantly reduced infections in elderly residents of nursing homes (Gironon F et al 1997) and enhanced the immune response of the residents

to influenza vaccination (Girodon F et al 1999).

Mice that are deficient in selenium are more susceptible to influenza infection (Beck MA 2001). In selenium-deficient mice, the proinflammatory response is stronger and the immune response is weaker than in mice that have an adequate level of selenium (Beck MA et al 2003). Moreover, the genome of viruses in selenium-deficient mice shifts toward more virulent, resistant strains (Beck MA et al 2004).

Zinc has also been studied extensively for its ability to inhibit the viruses (such as the rhinovirus) that cause the common cold (Hulisz D 2004; Marshall S 1998; Mossad SB et al 1996; Prasad AS et al 2000).

Lactoferrin. Lactoferrin is a subfraction of whey and has antiviral, antimicrobial, anticancer, and immune-enhancing effects. Lactoferrin is concentrated in the saliva, where it comes into direct contact with pathogens and kills or suppresses them through a variety of mechanisms (Kawasaki Y et al 1993; Schoen P et al 1997). Lactoferrin may stimulate macrophages, which in turn may help induce cell-mediated immunity (Zimecki M et al 2002). Lactoferrin is present naturally in many mucous membrane secretions, suggesting an innate antimicrobial function (Nishiya K et al 1982; Zimecki M et al 2002). A recent study showed that lactoferrin inhibits viral infection by interfering with the ability of certain viruses to bind to cell receptor sites (Waarts BL et al 2005).

Elderberry extract. Studies show that a black elderberry extract (Sambucol) has antiviral properties against 10 strains of influenza virus. In a double-blind, placebo-controlled, randomized study, elderberry extract reduced the duration of influenza symptoms by 1 to 2 days (Barak V et al 2001; Zakay-Rones Z et al 1995).

Green tea. Green tea has been shown to inhibit bacteria and viruses and stimulate the immune system (Imanishi N et al 2002). Black tea and extracted components, such as catechin and saponins (Hayashi K et al 2000), inhibit influenza virus growth, infectivity, and symptoms (Iwata M et al 1997b; Iwata M et al 1997a). In a cell culture study, the active ingredients in green tea were found to be powerful inhibitors of all varieties of influenza virus (Song JM et al 2005).

Garlic. Garlic has been valued for centuries for its medicinal properties. Garlic, and its active component, allicin, has a wide spectrum of antifungal, antibacterial, and antiviral action. It benefits the immune system by increasing the number of natural killer cells and the killer activities of spleen cells (Harris JC et al 2001; Kyo E et al 2001). One recent study tested an allicin-containing garlic supplement on a group of 146 volunteers from November through February. Half the group took one garlic capsule daily while the unfortunate other half received a placebo. The placebo group had 63 percent more infections than the group that took the garlic capsule. Even more significant, those who took garlic capsules who did catch a cold experienced symptoms for an average of only 1.52 days, compared to 5.01 days for the placebo group (Josling P 2001). Aged garlic has also been shown to have antiviral properties, particularly against influenza B (Tsai Y 1985), and to have immunomodulatory effects (Kyo E et al 2001).

Cimetidine: Antiviral Potential

Cimetidine (Tagamet) is an over-the-counter drug used to treat heartburn. It also has potent immune system–boosting effects that can drastically reduce the duration of certain viral infections. Cimetidine has been shown to stimulate natural killer cell activity, increase IL-2 production, and inhibit suppressor T-cell activity (Zeng P et al 1995).

Because cimetidine is safe for most people to take, taking 800 to 1000 mg at night (or 200 mg three times a day and 400 mg at night) can help boost the immune system in the event of exposure to influenza. Cimetidine in 200-mg tablets can be purchased over the counter. The directions in over-the-counter package inserts indicate that it is safe to take up to 800 mg of cimetidine a day. Some published studies state that cimetidine is safe to take in dosages up to 1000 mg a day (Choi YS et al 1993).

HORMONES THAT ENHANCE IMMUNE RESPONSE

DHEA is an adrenal hormone with immune system–boosting effects that seems to protect against a variety of infections, including influenza, in animal models. It works by enhancing cytokine secretion. DHEA enhances the immune response and helps combat bacterial and viral infections, including influenza (Padgett DA et al 1997; Padgett DA et al 2000). The age-associated decline in its concentration correlates with a decline in immunity. DHEA supplementation has been shown to reverse the age-related decline in immunity and protect aged mice against influenza (Danenberg HD et al 1995).

Administering 50 mg of DHEA a day to elderly men resulted in the following immune enhancements compared to placebo (Khorram O et al 1997):

- An increase of 35 percent in the number of monocyte immune cells
- An increase of 29 percent in the number of immune B-cells
- An increase of 62 percent in B-cell activity
- An increase of 40 percent in T-cell activity (total number of T-cells not affected)
- An increase of 50 percent in IL-2
- An increase of 22 to 37 percent in the number of natural killer cells and an increase of 45 percent in natural killer cell activity

One reason that influenza can be so lethal to aging people is that their immune systems are weak. A deficiency in DHEA appears to be partially responsible for the age-related decline in immune function (Fulop T Jr et al 1999; Khorram O et al 1997). One study showed that a metabolite of DHEA augmented activation of T-helper cells and protected mice from a lethal influenza virus infection (Padgett DA et al 1997).

Melatonin is a hormone secreted by the pineal gland that enhances the production of key components of the immune system, such as natural killer cells and several cytokines, including IL-1, IL-6, and IL-12, and interferons (Lissoni P et al 1994c; Lissoni P et al 1994a; Lissoni P et al 1994b; Lissoni P et al 1989; Maestroni GJ 1993; Maestroni GJ 1999). Melatonin is an antioxidant that amplifies IL-2's antiviral and anticancer effects.

The conclusion of one melatonin review article was: "The immunomodulatory, antioxidant, and neuroprotective effects of melatonin suggest that this indole must be considered as an additional therapeutic alternative to fight viral diseases." (Maestroni GJ 1999).

Another study examined the immune function benefits of melatonin and found that melatonin activated IL-2 and gamma interferon, the body's natural hormonelike agents that facilitate T-helper cell production (Bonilla E et al 2004).

Taking higher-than-usual doses (200 to 400 mg) of DHEA in the morning and higher-than-usual doses (10 to 50 mg) of melatonin before bedtime would appear to be logical approaches to battling a viral infection.

The Avian Flu: A Unique Strain

Avian influenza is characterized by a hyper-response of the immune system. People afflicted with avian flu die of pulmonary edema and multiorgan system failure in response to acute inflammation and proinflammatory cytokine response.

While boosting immune function early in the disease process may be beneficial, unleashing the entire nuclear arsenal of immune system–boosting drugs, hormones, and nutrients may be undesirable. In fact, some doctors are prescribing corticosteroid drugs to suppress the body's acute inflammatory response to the avian virus.

As a result of these data, if one were to contract the avian flu, taking high doses of drugs such as cimetidine or hormones such as melatonin would not be advisable (because of their potent immune system–enhancing effects). However, there are nutrients, drugs, and hormones that might suppress the most dangerous proinflammatory cytokines associated with the avian flu. Some of the cytokine-suppressing agents include DHEA, fish oil, green tea, borage oil, curcumin, and flavonoids (such as nobiletin).

A novel cytokine-suppressing strategy might be to take a statin drug such as 40 mg of simvastatin (Zocor) as soon as flu symptoms appear. Some data indicate that statin drugs can block excess production of influenza-induced proinflammatory cytokines. It is not known whether nutritional or drug anticytokine therapy is beneficial in treating avian flu.

Ribavirin

Ribavirin is a broad-spectrum antiviral drug that was first synthesized in 1972 (Snell NJ 2001). It was approved in the United States in the late 1990s to treat the hepatitis C virus, and it is used in other countries to treatment influenza (Cianci C et al 1998). Ribavirin has been proved to be effective at limiting the duration and severity of viral illness. In France, ribavirin, administered by nebulizer, is

successfully used to treat severe cases of influenza (Leophonte P 2005). Ribavirin works by inhibiting the replication of the virus's DNA (Magden J et al 2005).

In a recent study, mice infected with influenza were given ribavirin at a dose between 18 and 37.5 milligrams per kilogram per day (mg/kg/day). The drug was shown to be highly effective in preventing death and reducing the presence of virus in the lungs (Sidwell RW et al 2005). Another study found that ribavirin was 90 to 100 percent effective at preventing death in mice infected with influenza B. The mice were simultaneously given a drug that boosted viral replication to enhance the lethality of the flu strain. Even when treatment with ribavirin was started 4 days after infection, ribavirin still produced a 40-percent survival rate (Smee DF et al 2004).

Other studies have also shown positive results. In one case study, three patients who had severe lower respiratory tract influenza or parainfluenza were treated with a continuous intravenous ribavirin infusion, at 5 mg/kg/hour for the first 8 hours, followed by 1.5 mg/kg/hour for 2 to 6 days. Researchers found the rate of viral shedding (a measure of viral activity) was diminished in one patient and ceased completely in the other two (Hayden FG et al 1996).

Some reports have linked the use of ribavirin to mild anemia. The Life Extension Foundation believes this anemia is linked to drug-related free radical damage that affects red blood cells. Take adequate antioxidants to provide protection against anemia if you take ribavirin for the flu. We recommend taking antioxidants during influenza infection even without ribavirin.

LIFE EXTENSION FOUNDATION RECOMMENDATIONS

The following doses are higher than the usual recommended doses for these supplements. These higher levels should not be taken constantly, or as a general prophylaxis. They should be taken to enhance seasonal support. This program should be followed for only a few days. At the first sign of flu symptoms, consider taking:

- **Cimetidine**—800 to 1000 mg/day
- **Pure Gar brand garlic**—9000 mg once or twice a day
- **Kyolic aged garlic extract**—3600 mg/day
- **DHEA**—200 to 400 mg in the morning
- **Lactoferrin**—1200 mg/day
- **Zinc**—Two 24-mg lozenges every 2 hours while awake. This is a very high dosage of zinc and is toxic if taken for long periods. Only take this much zinc for a few days.
- **Melatonin**—10 to 50 mg at bedtime
- **Vitamin C**—6000 mg/day (1000 mg every hour for the first 6 hours), then 3000 mg/day (1000 mg several hours apart).
- **Vitamin E**—400 international units (IU) daily
- **Green tea**—725 mg/day. A decaffeinated form is available for people who are sensitive to caffeine.
- **Selenium**—200 micrograms (mcg) daily
- **Elderberry extract**—Take lozenges as needed.

INFLUENZA 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:

DHEA

- Do not take DHEA if you could be pregnant, are breastfeeding, or could have prostate, breast, uterine, or ovarian cancer.
- DHEA can cause androgenic effects in woman such as acne, deepening of the voice, facial hair growth and hair loss.

Garlic

- Garlic has blood-thinning, anticlotting properties.
- Discontinue using garlic before any surgical procedure.
- Garlic can cause headache, muscle pain, fatigue, vertigo, watery eyes, asthma, and gastrointestinal symptoms such as nausea and diarrhea.
- Ingesting large amounts of garlic can cause bad breath and body odor.

Green Tea

- Consult your doctor before taking green tea extract if you take aspirin or warfarin (Coumadin). Taking green tea extract and aspirin or warfarin can increase the risk of bleeding.
- Discontinue using green tea extract 2 weeks before any surgical procedure. Green tea extract may decrease platelet aggregation.
- Green tea extract contains caffeine, which may produce a variety of symptoms including restlessness, nausea, headache, muscle tension, sleep disturbances, and rapid heartbeat.

Melatonin

- Do not take melatonin if you are depressed.
- Do not take high doses of melatonin if you are trying to conceive. High doses of melatonin have been shown to inhibit ovulation.
- Melatonin can cause morning grogginess, a feeling of having a hangover or a “heavy head,” or gastrointestinal symptoms such as nausea and diarrhea.

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.

Zinc

- High doses of zinc (above 30 milligrams daily) can cause adverse reactions.
- Zinc can cause a metallic taste, headache, drowsiness, and gastrointestinal symptoms such as nausea and diarrhea.
- High doses of zinc can lead to copper deficiency and hypochromic microcytic anemia secondary to zinc-induced copper deficiency.
- High doses of zinc may suppress the immune system.

For more information see the Safety Appendix

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