

## Cancer Radiation Therapy

Along with surgery and chemotherapy, radiation therapy (radiotherapy) is one of the most important methods of cancer treatment. At least 50 percent of all cancer patients will receive radiotherapy at some stage during the course of their illness. It is currently used to treat localized solid tumors, such as cancers of the skin, brain, breast, or cervix, and can also be used to treat leukemia and lymphoma (Tobias JS 1992).

Most types of radiation do not attack cancer cells specifically, and therefore cause injury to normal tissues surrounding the tumor. The adverse effects are a major factor limiting the success of radiation treatment. However, proton therapy and CyberKnife® therapy are technologically advanced forms of radiotherapy that cause little damage to normal tissue because they focus intensely on the tumor.

The effectiveness of radiation therapy can be enhanced by both radiosensitizers, such as genistein, curcumin, green tea, and hyperthermia, and radioprotectors, such as ginseng, glutathione, whey protein, and shark liver oil. Overall, the use of specific nutritional supplements, drugs, and other strategies may prevent and help to alleviate and treat the side effects caused by radiation, and thereby improve the effectiveness of radiotherapy.

### PRINCIPLES OF RADIATION THERAPY (RADIOTHERAPY)

Radiation therapy is the treatment of cancer with ionizing radiation. Radiation works by damaging the DNA (genetic material) within the tumor cells, making them unable to divide and grow. Radiation is often given with the intent of destroying the tumor and curing the disease (curative treatment). However, although radiation is directed at the tumor, it is inevitable that the normal, non-cancerous tissues surrounding the tumor will also be affected by the radiation and therefore damaged (Burnet NG et al. 1996). The goal of radiation therapy is to maximize the dose to tumor cells while minimizing exposure to normal, healthy cells (Emami B et al. 1991).

Because no single therapy can provide complete treatment for a patient with a solid tumor, radiotherapy is often used in combination with surgery or chemotherapy to improve the chances of a successful treatment outcome. Sometimes radiation is used to relieve symptoms, such as pain or seizures; this is called palliative treatment (Hoskin PJ et al. 1992).

### WHAT IS IONIZING RADIATION?

Radiation used for cancer treatment is called ionizing radiation because it forms ions as it passes through a tissue. Ions are atoms that have acquired an electric charge through the gain or loss of an electron (Dunne-Daly CF 1999). Ions can cause cell death or genetic change either directly or indirectly. The direct effect causes a change in the molecular structure of biologically important molecules, most likely DNA. The indirect action of radiation occurs when it interacts with water molecules in the cells, resulting in the production of highly reactive and unstable free radicals or reactive oxygen species, which immediately react with any biomolecules in the surrounding area, producing cellular damage (Fang YZ et al. 2002).

This damage can lead to cell death by two mechanisms (Ross GM 1999). The first process, known as apoptosis, results in cell death within a few hours of radiation (Kerr JF et al. 1994). The second mechanism is radiation-induced failure of cell division and the inhibition of cellular proliferation, which in turn leads to cell death. Several enzymatic and nonenzymatic antioxidant defense mechanisms exist in cells and prevent excessive damage through the scavenging and inactivation of these reactive oxygen species (Mates JM et al. 2000).

### TYPES OF RADIATION THERAPY

**External beam radiation therapy (EBRT).** EBRT creates a radiation beam and aims it at the tumor. The radiation adequately covers the tumor but minimizes the dose to the non-tumor normal tissues. Radiation is given in fractions rather than as a single dose, and the use of this fractionated radiotherapy allows normal cells time to repair between each radiation session, protecting them from injury.

Conventional fractionation in the United States is 1.8 to 2 Gray (Gy) per day, administered five days a week for five to seven weeks, depending on the particular clinical situation. (Gray is a unit of measure of absorbed radiation dose.) While this schedule is strictly for the convenience of physicians trying to maintain a normal workweek, the relatively long intervals between doses of radiation may allow cancer cells (as well as normal cells) to recover and regrow.

A number of different radiotherapy schedules have been suggested to overcome this problem (Shah N et al. 2000). These include hyperfractionation, in which the time between fractions is reduced from 24 hours to 6 to 8 hours to enhance the toxic effects on tumor cells (Fu KK et al. 2000) while still preserving an adequate time interval for the recovery of normal cells. Continuous hyperfractionated accelerated radiation therapy (CHART) is an intense schedule of treatment, in which multiple daily fractions are administered within a short period of time. Clinical studies have shown benefits of altered fractionation over conventional treatment for several cancers, including head and neck cancer (Goodchild K et al. 1999) and non-operable lung cancer (Ghosh S et al. 2003).

**Proton beam radiation therapy.** This is one of the most precise and sophisticated forms of external beam radiation therapy available. The advantage of proton radiation therapy over x-rays is its ability to deliver higher doses of shaped beams of radiation directly into the tumor while minimizing the dose to normal tissues. This leads to reduced side effects and improved survival rates (Suit HD 2003). As of 2002, more than 32,000 patients around the world had received part or all of their radiation treatment by proton beams.

There are approximately 19 proton treatment centers worldwide. Two major hospital-based facilities in the United States that regularly treat patients with proton beams (often fractionated) are Loma Linda University Medical Center in southern California (LLUMC Proton Treatment Center) and the Northeast Proton Treatment Center at Massachusetts General Hospital in Boston. The Midwest Proton Radiotherapy Institute in Bloomington, Indiana (<http://www.mpri.org/>) treats children and adults with certain brain tumors, as well as those with tumors that are close to vital organs and therefore cannot be treated successfully using traditional methods.

The efficacy of proton beam radiation therapy has been clinically proven (Shipley WU et al. 1995) in prostate (Slater JD et al. 1999; Zietman AL et al. 2005), lung (Bush DA et al. 1999), hepatocellular (Matsuzaki Y et al. 1995), and uveal melanoma (Courdi A et al. 1999; Munzenrider JE 1999; Spatola C et al. 2003), sarcomas of the skull base and cervical spine (Munzenrider JE et al. 1999), optic pathway gliomas (Fuss M et al. 1999), astrocytomas (Habrand JL et al. 1999), benign meningioma (Gudjonsson O et al. 1999), non-resectable rectal, esophageal (Koyama S et al. 2003), and liver cancers (Ask A et al. 2005b), head and neck cancers, including thyroid cancer (Ask A et al. 2005a; Sugahara S et al. 2005), and more.

**Intensity modulated radiation therapy (IMRT).** IMRT creates a shaped radiation beam, delivering high doses of radiation to the tumor and significantly smaller doses of radiation to the surrounding normal tissues (Hurkmans CW et al. 2002; Nutting C et al. 2000). This may result in a higher cancer-control rate and a lower rate of side effects (Garden AS et al. 2004; Welsh JS et al. 2005).

IMRT has been used successfully in the treatment of several types of cancer, including prostate (De Meerleer G et al. 2004), cervical (Ahmed RS et al. 2004), nasopharyngeal (Kwong DL et al. 2004), and pediatric cancers (Penagaricano JA et al. 2004).

**Brachytherapy.** Brachytherapy can be used for many types of cancers, but it is most commonly used to treat prostate cancer (Woolsey J et al. 2003) and gynecologic cancers, such as cervical or uterine cancer (Nakano T et al. 2005). Brachytherapy usually involves the insertion of devices around or within the tumor to hold radioactive sources or seeds. Radioactive isotopes, such as cesium, are then inserted into the delivery device, either temporarily or permanently, allowing for the slow delivery of a high dose of radiation to the interior of the tumor (Fieler VK 1997).

**Radioimmunotherapy (RIT).** Radioimmunotherapy, one of the newest developments in the treatment of non-Hodgkin's lymphoma (Harris M 2004), has achieved a high tumor response rate (up to 80 percent) in several clinical trials (Witzig TE et al. 2002). Radioimmunotherapy uses drugs called monoclonal antibodies, which have a radioactive isotope attached to them. This is targeted to the surface of a cancer cell, destroying it. Radioimmunotherapy can be used (in a targeted fashion) to treat single cells that have spread around the body (Riley MB et al. 2004). Because the radiation does not concentrate in any one area of the body, radioimmunotherapy does not cause side effects commonly seen with external beam radiation therapy. The most significant side effect associated with radioimmunotherapy may be a temporary drop in white blood cell or platelet count (Witzig TE et al. 2003).

**Stereotactic body radiation therapy (SBRT).** SBRT is a standard form of treatment for primary and metastatic brain cancer (Phillips MH et al. 1994). It is delivered using a machine called a gamma knife, which uses converging beams of gamma radiation that meet at a central point within the tumor, where they add up to a very high, precisely focused dose of radiation in a single fraction. Due to this precision, the cancer can be located in an area of the brain or spinal cord that might normally be considered inoperable (Song DY et al. 2004).

**CyberKnife®.** CyberKnife® is a non-invasive, precise radiation technique that can deliver concentrated and accurate beams of radiation to any site in the body. This system combines robotics and advanced image guidance cameras to locate the tumor's position in the body and deliver highly focused beams of radiation that converge at the tumor, avoiding normal tissue. It is a successful method used to treat spinal tumors (Gerszten PC et al. 2004b) or tumors at other critical locations that are not amenable to open surgery or radiation, as well as to treat medically inoperable patients (Gerszten PC et al. 2004a). It can also be used to treat benign tumors and lesions in a previously irradiated site, or to boost standard radiotherapy (Bhatnagar AK et al. 2005; Degen JW et al. 2005).

**Three-dimensional conformal radiation therapy (3D-CRT).** 3D-CRT is a technique that uses imaging computers to precisely map the location of a tumor (Symonds RP 2001). The patient is fitted with a plastic mold or cast to keep the body part still so that the radiation can be aimed more accurately from several directions. By aiming the radiation more precisely at the tumor, it is possible to reduce radiation damage to normal tissues surrounding the tumor by up to 50 percent (Perez CA et al. 2002).

### **Radiation Therapy versus Medical X-rays (Diagnostic Imaging)**

Although diagnostic x-rays provide great benefits, including the earlier detection of cancers and the possibility of early treatment, their use is associated with small increases in cancer risk (Ron E 2003). One study estimated that cancer risk due to diagnostic x-rays varied from 0.6 percent to 3 percent in the 15 developed countries studied (Berrington de Gonzalez A et al. 2004).

Therefore, it is prudent to avoid unnecessary x-ray procedures. Up to 30 percent of chest x-rays may not be necessary (McCreath GT et al. 1999). Unnecessary computed tomography (CT) examinations may result in increased radiation exposure (Fleszler F et al. 2003; Frush DP 2004). The cumulative risk of cancer mortality from CT examinations in the United States is about 800 radiation-induced cancer deaths per 1 million examinations in children under the age of 15 (Brenner D et al. 2001).

Mammography (chest x-ray) uses low-dose x-rays to create a detailed image of the breasts. Although there is some controversy regarding mammography's effectiveness in reducing breast cancer mortality, successful treatment is linked to early diagnosis, as mammography can often show changes in the breast before they can be detected by manual examination (Olsen O et al. 2001).

The effective radiation dose from a mammogram is about the same as the average person receives from background radiation over a three-month period (Sabel M et al. 2001).

At present, the consensus view is that the benefits of screening women over 50 years of age with yearly or twice-yearly mammograms substantially outweighs the associated risks due to radiation exposure (Beckett JR et al. 2003). However, there appears to be no significant benefit for women under the age of 40, and there may be harm for women under 30 due to the danger of cancer developing after exposure to radiation (Brenner DJ et al. 2002). Therefore, the main area of controversy concerns women between the ages of 40 and 49.

### **Typical effective doses from diagnostic medical exposures in the 1990s**

<b>Diagnostic procedure</b>	<b>Typical effective dose in millisieverts (mSv)</b>	<b>Equivalent number of chest x-rays</b>	<b>Approximate equivalent period of natural background radiation(1)</b>
<i>X-ray examinations:</i>			
Limbs and joints (except hip)	<0.01	<0.5	<1.5 days
Chest (single PA film)	0.02	1	3 days
Skull	0.07	3.5	11 days
Thoracic spine	0.7	35	4 months
Lumbar spine	1.3	65	7 months
Hip	0.3	15	7 weeks
Pelvis	0.7	35	4 months
Abdomen	1.0	50	6 months
Intravenous urogram (IVU)	2.5	125	14 months
Barium swallow	1.5	75	8 months
Barium meal	3	150	16 months
Barium follow-through	3	150	16 months
Barium enema	7	350	3.2 years
CT head	2.3	115	1 year
CT chest	8	400	3.6 years
CT abdomen or pelvis	10	500	4.5 years
<i>Radionuclide studies:</i>			
Lung ventilation (Xe-133)	0.3	15	7 weeks
Lung perfusion (Tc-99m)	1	50	6 months
Kidney (Tc-99m)	1	50	6 months
Thyroid (Tc-99m)	1	50	6 months
Bone (Tc-99m)	4	200	1.8 years
Dynamic cardiac (Tc-99m)	6	300	2.7 years
PET head (F-18 FDG)	5	250	2.3 years

(1) UK average background radiation = 2.2 mSv per year: regional averages range from 1.5 to 7.5 mSv per year.

*With advice from Wall, B. National Radiological Protection Board.*

## RADIATION: A CAUSE OF CANCER?

The link between radiation and cancer was first recognized by studying atomic bomb survivors in Japan (Wakeford R 2004). Some cases of leukemia are related to radiation exposure and usually develop within a few years of exposure, peaking at five to nine years after exposure, then slowly declining (Ron E 2003; Wakeford R 2004). The development of other types of cancer after radiation exposure can take much longer to occur. Most cancers do not occur until 10 years after radiation exposure and some are diagnosed 15 or more years later (Hall EJ et al. 2003).

### ***What You Have Learned So Far***

- Radiation therapy is one of the primary methods currently used to treat cancer.
- It involves targeting the tumor with a beam of ionizing radiation, leading to the death of tumor cells through either the production of reactive oxygen species or from direct DNA damage.
- Radiation cannot selectively target the tumor; therefore, normal cells within the radiation field suffer damage, leading to potentially serious side effects (Porock D 2002).
- Ionizing radiation is used in many diagnostic techniques, such as mammography and computed tomography (CT) scans.
- Radiation is a potent carcinogen that can give rise to a second radiation-induced cancer.
- Exposure to diagnostic x-rays should be kept to a minimum, and women under the age of 49 should not undergo yearly mammograms.

## STRATEGIES TO OPTIMIZE RADIOTHERAPY RESPONSE

**Tumor gene analysis.** An examination of the genetic material of tumor cells often reveals differences between the cells that can be manipulated therapeutically. For example, the tumor suppressor gene p53 is the most frequently mutated gene in human tumors (Cuddihy AR et al. 2004), and tumors containing wild type p53 (p53 that is not mutated) are associated with a significantly better prognosis when treated with radiation (Alsner J et al. 2001; Ma L et al. 1998). However, this is not a universal finding (Saunders M et al. 1999).

Results of the largest known biomarker study of prostate cancer patients treated with radiation therapy indicate that the presence of a protein biomarker called Ki-67 is a significant predictor of outcome in men treated with both radiation and hormones (Li R et al. 2004). When a tumor cell tests positive for Ki-67, the tumor is actively growing, and the greater the proportion of prostate tumor cells with Ki-67, the more aggressive the cancer (Wilson GD et al. 1996). Ki-67 can be measured by a test offered by Genzyme Genetics ([www.GenzymeGenetics.com](http://www.GenzymeGenetics.com)).

**Guarding against anemia.** Anemia is one of the most common blood abnormalities of cancer. In patients with solid tumors, the incidence of anemia has been reported to vary between 45 percent in those with colon cancer up to 90 percent in patients with small-cell lung cancer (Knight K et al. 2004). An association between hemoglobin level and controlling tumor growth and survival has been identified for a large number of cancers, including breast (Henke M et al. 2004), cervical (Winter WE3 et al. 2004), and head and neck cancers (Daly T et al. 2003).

Cancer patients with low hemoglobin levels do not respond as well to radiotherapy as non-anemic patients (Ludwig H et al. 2001), due to impairment of oxygen transport to tumor cells (Dunst J 2004). Hemoglobin values measured during treatment are believed to be predictive of outcome (Tarnawski R et al. 1997).

Treatment outcome might be improved by correcting anemia (low hemoglobin levels) (Grogan M et al. 1999). Nutritional supplements that may help correct anemia include melatonin, folic acid, and vitamin B12; for more information, refer to the Blood Disorders chapter. The use of erythropoietin (sold under the drug brand name Procrit®) with minimal iron supplementation (Olijhoek G et al. 2001) or blood transfusions (Bokemeyer C et al. 2004) may be required in some cases. Erythropoietin is a growth factor that produces a steady, sustained increase in hemoglobin levels (Cheer SM et al. 2004; Stuben G et al. 2003).

**Measurement of tumor oxygen levels.** Low tumor oxygen levels (hypoxia) and anemia in the patient are associated with increased risk of spread (metastasis) and recurrence (Harrison L et al. 2004; Vaupel P 2004), especially for cervical cancers, head and neck cancers, and soft tissue sarcomas (Brizel DM et al. 1996; Nordmark M et al. 2004). Hypoxia presents a problem for radiotherapy because radiation's ability to kill cancer cells (i.e., radiosensitivity) rapidly decreases in areas of oxygen depletion, as free radicals cannot be produced due to limited oxygen supply (Fridovich I 1999).

Tumor oxygen levels are usually measured by the use of electrodes inserted directly into the tumor (Coleman CN 2003; Vaupel P et al. 2001). If a tumor is found to be hypoxic, strategies to improve oxygen levels could be employed to improve radiotherapy (Overgaard J et al. 2005) or, alternatively, radiotherapy may be reconsidered.

Tumor hypoxia has been exploited in cancer treatment (Brown JM 2000). A number of chemical agents, such as misonidazole, that preferentially sensitize hypoxic cells to radiation have been developed and tested in the clinic, particularly for the treatment of head and neck cancers (Brown JM et al. 2004). However, some have poor clinical effectiveness (Brown JM 1995). A number of approaches (e.g., carbogen and nicotinamide (ARCON)) have been introduced and are now in clinical trials (Kaanders JH et al. 2004).

Hypoxia is also implicated in the activation of angiogenic cytokines—especially vascular endothelial growth factor (VEGF)—that are necessary for the growth of new tumor blood vessels (Shweiki D et al. 1992; Vaupel P 2004) and thus tumor growth. Angiogenic inhibitors seek to interrupt the process of angiogenesis (the creation of new blood vessels) to prevent new tumor blood vessel formation, whereas vascular (blood vessel)-disrupting agents aim to cause direct damage to the existing tumor blood supply (Tozer GM et al. 2004). Lead agents of both categories (e.g., Combretastatin A-4) have now advanced into clinical trials (Thorpe PE 2004).

Silymarin/silibinin inhibits VEGF secretion in a range of human cancer cell lines, in concentrations that should be clinically feasible (Yang SH et al. 2003). Other naturally derived agents that impede cancer-induced angiogenesis include green tea polyphenols, fish oil, selenium, copper restriction, and curcumin (Gururaj AE et al. 2002).

**Hyperbaric oxygen treatment (HBOT).** Following the identification of hypoxia as a possible source of radiation resistance, a major effort was made to solve the problem through the use of hyperbaric oxygen. Hyperbaric oxygen is a mode of therapy in which the patient breathes pure, 100-percent oxygen at pressures two to three times greater than normal atmospheric pressure (Feldmeier JJ 2004). The concentration of oxygen normally dissolved in the bloodstream is thus raised many times above normal (up to 2000 percent).

This hyperoxygenation provides immediate support to poorly perfused tumor tissue in areas of compromised blood flow (Plafki C et al. 1998). These include radiation-damaged tissue that has lost blood supply and is oxygen deprived due to scarring and narrowing of the blood vessels within the area treated (Anderson DW 2003). Healing is dependent on oxygen delivery to the injured tissues, and hyperbaric oxygen therapy provides a better healing environment, leads to the growth of new blood vessels, and also helps to eradicate anaerobic bacteria that may cause infection via toxin inhibition and inactivation (Anderson DW 2003; Marx RE et al. 1990).

Hyperbaric oxygen has been used to treat normal tissue injury caused by radiation therapy in several sites, including the head and neck (Feldmeier JJ et al. 2002), pelvis (Corman JM et al. 2003), breast (Carl UM et al. 2001), prostate (Mayer R et al. 2001), and brain (Kohshi K et al. 2003), with few serious side effects.

In a study of 45 patients with radiation-induced late side effects, the majority showed improvement in their condition after either hyperbaric oxygen therapy alone or hyperbaric oxygen therapy followed by other surgical or medical procedures (Bui QC et al. 2004). In particular, osteoradionecrosis (necrosis, or death of the bone following radiotherapy) appeared to be highly responsive to hyperbaric oxygen therapy (Mounsey RA et al. 1993). This condition usually involves the lower jaw in a minority (8 percent) of head and neck cancer patients treated with radiation therapy, is difficult to treat, leads to intense pain and fracture, and makes oral feeding impossible (Reuther T et al. 2003).

However, the use of hyperbaric oxygen therapy is not widespread, partly because it is cumbersome and difficult in practice and partly because many of the studies to date have involved small numbers of patients (Gothard L et al. 2004; Haffty BG et al. 1999). Larger trials are needed to investigate the true efficacy of hyperbaric oxygen therapy.

**Breathing oxygen during radiotherapy.** The inhalation of oxygen during radiotherapy may increase the radiation kill effect on the tumor by counteracting areas of hypoxia-based radioresistance, and thus improve overall survival. Stage II cervical cancer patients, with squamous cell carcinoma, who received oxygen (normobaric) during all radiotherapy sessions had significantly improved loco-regional cancer control (Sundfor K et al. 1999).

Patients with Stage III (7 percent) and Stage IV (93 percent) advanced squamous cell carcinomas of the head and neck who breathed pure, normobaric oxygen for 15 to 20 minutes during irradiation had improved mean survival time (15.8 versus 11.8 months) and three-year survival (19 percent versus 2 percent), respectively ( $p < 0.05$ ). Thus, breathing normobaric oxygen before and during radiation therapy could increase the effectiveness of conventional radiotherapy for advanced squamous cell carcinomas of the head and neck (Zajusz A et al. 1995).

**Radioprotectors/radiosensitizers.** Researchers are investigating two types of drugs that may increase the effectiveness of radiation therapy (Yuhas JM et al. 1977). Radiosensitizers make tumor cells more susceptible to radiation damage, while radioprotectors protect normal tissues from the damaging effects of radiation, allowing a higher dose of radiation to be directed at the tumor.

Radiosensitizers are chemicals that increase the damaging effects of radiation if administered simultaneously. Two types of radiosensitizers have been used in conjunction with radiation therapy:

1. **Halogenated pyrimidines**, such as bromodeoxyuridine, which depend on the amount of drug incorporated in the cell (Jackson D et al. 1987). As tumor cells divide more rapidly than the surrounding normal cells, they take up more of the radiosensitizer.
2. **Hypoxic cell sensitizers**, which increase the radiosensitivity of only those cells located in areas of low oxygen (Brown JM 1989). As many tumors contain large regions of hypoxic cells compared to normal tissues, these drugs are able to produce a differential effect, that is, they are toxic to hypoxic cells only.

**Amifostine** (Ethyol®) has been approved by the FDA specifically for use as a radioprotector. It is approved for the prevention of xerostomia (dry mouth) in head and neck cancer patients treated with radiation therapy (Hensley ML et al. 1999). Adequate hydration is critical before amifostine administration (given intravenously once daily as a 3-minute infusion starting 15 to 30 minutes before standard fraction radiation therapy).

The two major side effects of amifostine that cause treatment discontinuation are vomiting and transient low blood pressure

(hypotension) (Capizzi RL et al. 2000), and these adverse effects limit its wide acceptance.

**Ginseng.** Ginseng has several beneficial effects on blood vessels (Yun TK 2001). In experimental studies, ginseng was shown to be a promising radioprotector (Kim SR et al. 2003), that is, it may protect normal healthy tissue from damage during radiation therapy (Kim TH et al. 1996; Lee TK et al. 2004). In a clinical study, ginseng polysaccharide injection improved immune function in nasopharyngeal carcinoma patients during radiotherapy (Xie FY et al. 2001).

**Glutathione** is a natural antioxidant synthesized from the amino acids glutamine, cysteine, and glycine (Walzem RL et al. 2002). A severe reduction in glutathione content can predispose cells to oxidative damage. When tumor cells are irradiated, either lethal damage can occur and the cells die, or the damage can be modified via DNA repair and not lead to permanent cell death.

Cancer cells have higher glutathione levels than the surrounding normal healthy cells. Therefore, selective tumor depletion of glutathione presents a promising strategy in cancer management. Dietary glutamine supplementation lowers glutathione levels in tumor cells (Kennedy RS et al. 1995; Todorova VK et al. 2004), but increases production in normal tissues. Furthermore, glutamine supplementation decreases the toxicity of radiation therapy (Klimberg VS et al. 1992; Rouse K et al. 1995).

**Whey protein** is an effective and safe cysteine donor for glutathione replenishment (Kennedy RS et al. 1995; See D et al. 2002). Radiation therapy is known to cause immunosuppression (Wara WM et al. 1979). Cysteine is the critical limiting amino acid for intracellular glutathione synthesis (Bounous G 2000). The amino acid precursors to glutathione present in whey might increase glutathione concentration in relevant tissues, stimulate immunity, and detoxify potential carcinogens (Bounous G 2000). Glutathione stimulation is thought to be whey's primary immune-modulating mechanism (Marshall K 2004).

**Alkylglycerols** are active ingredients of shark liver oil. They have been widely used for the treatment of cancer in Scandinavian countries (Krotkiewski M et al. 2003), and research suggests their use may result in a lower incidence of normal tissue radiation damage (Hasle H et al. 1991). Although their protective mechanism is not fully understood (Hichami A et al. 1997), they cause increased tumor cell death (apoptosis) and have many beneficial effects on the immune system, including the stimulation of neutrophils and macrophages (Tchorzewski H et al. 2002). Doses of shark liver oil up to 100 mg three times a day can be taken with no unfavorable side effects (Pugliese PT et al. 1998).

**Hyperthermia with radiotherapy.** Hyperthermia is the artificial elevation of the temperature of a tissue. Tumor cells can be selectively killed by temperatures between 40° and 44° centigrade (C) as compared with normal cells (van der Zee J 2002) because of improved tissue oxygenation and a consequent temporary increase in radiosensitivity (Song CW et al. 1997).

Numerous studies have shown that the combination of hyperthermia and radiation therapy improves clinical outcomes, particularly in breast cancer, melanoma, head and neck tumors, cervical cancer, and glioblastoma (van der Zee J et al. 2003).

Normal tissue toxicity with hyperthermia only results if the tissue temperature exceeds 44° C for more than one hour (Fajardo LF 1984). The toxicity from superficial hyperthermia is usually a skin burn; for deep-seated tumors, a subcutaneous fat or muscle burn may occur, which heals spontaneously (van der Zee J 2002).

**Phytochemicals.** Phytochemicals such as epigallocatechin-3 gallate (EGCG) found in green tea, curcumin, and genistein have been shown to enhance the radiation-induced death of cancer cells in addition to restraining tumor growth in animal models (Dorai T et al. 2004; Sarkar FH et al. 2004). They also have antioxidant properties and can therefore neutralize the detrimental effects of reactive oxygen species on normal cells (Katiyar SK et al. 2001).

**EGCG** (mainly derived from green tea) may increase the efficacy of radiation therapy by decreasing the activity of vascular endothelial growth factor (VEGF) (Lee YK et al. 2004). VEGF acts as a crucial survival factor for tumor cells (Ferrara N 2005).

**Soy isoflavones**, including genistein, daidzein, and glycitin (mainly derived from soybean), have been found to slow cancer growth in experimental animal studies (Sarkar FH et al. 2004). Genistein significantly enhances the radiation effect (that is, acts as a radiosensitizer) for cervical cancer cells (Yashar CM et al. 2005).

**Curcumin**, a natural anti-proliferative compound for many types of tumor, is extracted from the spice turmeric (Sikora E et al. 1997). Curcumin blocks the nuclear factor-kappa beta (NF- $\kappa$ B) activation process (Singh S et al. 1995). The maintenance of appropriate levels of NF- $\kappa$ B activity is crucial for normal cell division, and NF- $\kappa$ B activation is involved in the enhanced growth properties observed in several cancers (Bharti AC et al. 2002). Curcumin can sensitize squamous cell carcinoma cells to the ionizing effects of radiation (Khafif A et al. 2005). In prostate cancer cell lines, curcumin is a potent radiosensitizer and acts by overcoming the effects of radiation-induced prosurvival gene (bcl-2) expression (Chendil D et al. 2004).

## PREVENTING AND COUNTERACTING ADVERSE EFFECTS OF RADIOTHERAPY

## **Antioxidant use and radiation therapy**

A survey of cancer patients found that 63 percent use vitamins and herbs (including antioxidants), and the majority combine them with conventional therapies (Richardson MA et al. 2000). Critics argue that excessive nutrient-derived antioxidant use during radiation therapy could, in theory, protect cancer cells against the damaging effects of reactive oxygen species or oxidants, which are formed by radiation. This could occur by the antioxidants directly scavenging reactive oxygen species or repairing cellular damage in tumor cells (Salganik RI 2001). However, this theory has never been confirmed by clinical studies, and antioxidants can have protective effects that have nothing to do with oxidation (Block KI 2004).

Furthermore, there is no controversy surrounding physician-prescribed antioxidants such as amifostine (Ethyol®), an FDA-approved orphan drug for the prevention of xerostomia (dry mouth) in head and neck cancer patients undergoing radiation treatment. Amifostine has been clearly shown to reduce the incidence of side effects (xerostomia and mucositis) in patients receiving head and neck irradiation (Schuchter LM et al. 2002). It has also been used in combination with radiation therapy in the treatment of lung, prostate, breast, cervical, and esophageal cancer patients, with much success. The problem with amifostine is that it causes intolerable nausea, vomiting, diarrhea, and abdominal cramping, which limits its use.

The use of supplemental antioxidants is further supported in that they may help protect normal cells from the increased damage and side effects caused by radiation therapy (Lamson DW et al. 1999). Moreover, it has been shown that levels of antioxidants are decreased in cancer patients in response to radiation therapy (Sabitha KE et al. 1999). Thus, supplementation with dietary antioxidants (such as vitamins C and E) may improve the efficacy of radiation therapy by increasing tumor response and decreasing some of its toxicity on normal cells (Prasad KN et al. 2002).

Dietary antioxidants (including vitamin E, vitamin C, and selenium) as well as antioxidant enzymes found within cells (e.g., superoxide dismutase and glutathione peroxidase) can help maintain an appropriate balance between the desirable and undesirable effects of reactive oxygen species formed by radiation therapy (Seifried HE et al. 2003).

In several clinical radiotherapy studies, supplementation with the antioxidants vitamin E, selenium, and melatonin during treatment was shown to improve the efficacy of radiation therapy by decreasing radiation toxicity in normal cells and enhancing the immune response (Kiremidjian-Schumacher L et al. 2000; Malmberg KJ et al. 2002; Prasad KN et al. 2002).

Many clinical studies (detailed herein) have shown that antioxidant supplementation (with vitamins C and E, N-acetylcysteine, glutamine, and glutathione) both before and during radiotherapy prevents normal tissue complications (De Maria D et al. 1992; Ersin S et al. 2000; Huang EY et al. 2000; Kaya E et al. 1999; Kim JA et al. 1983; Klimberg VS et al. 1990; Mills EE 1988; Wagdi P et al. 1996), thus improving radiotherapy outcomes.

Overall, the data suggest that careful, sensible use of the antioxidants outlined herein may be helpful in improving the outcome of radiation therapy. Natural antioxidants (such as tocopherols, ascorbic acid, squalene, and lecithin) are present in most plant-based foods (Foley DJ et al. 2002) and in fruit, fish, herbs, and cereals (Shahidi F 2000).

**Vitamin A.** Radiation therapy effectiveness is increased when combined with vitamin A, which is thought to be due to an increased immune response against the tumor (Tannock IF et al. 1972). Vitamin A (8000 IU taken orally twice daily for seven weeks) appeared to be very effective in the treatment of radiation-induced anorectal damage in a patient with human immunodeficiency virus (HIV) infection (Levitsky J et al. 2003).

In a randomized, double-blind trial comparing retinol palmitate (vitamin A, 10,000 IU taken orally for 90 days) to placebo, oral retinol palmitate significantly reduced the rectal symptoms of radiation proctopathy in 19 patients six months after pelvic radiotherapy (Ehrenpreis ED et al. 2005).

**Vitamin C.** Experimental studies show that radiation treatment reduces the level of vitamin C in the body (Beliaev IK 1991). Conversely, studies of mice have shown that supplementing vitamin C at high doses preferentially radiosensitizes tumors while offering some protection to normal tissues (Tewfik FA et al. 1982).

**Vitamin E.** Vitamin E has been recognized as one of the most important antioxidants. Tocopheryl succinate (dry powder vitamin E) enhanced radiation damage to ovarian and cervical cancer cells in culture, while protecting healthy cells (Kumar B et al. 2002).

Vitamin E and selenium have been reported to have an increased beneficial effect when used in combination (Weiss JF et al. 2000). A study of rats showed that pre-treatment with both selenium and vitamin E for four weeks before radiation gave some protection against radiation-induced intestinal injury.

**Selenium.** A large number of selenium derivatives have been studied for their radioprotective effects (Weiss JF et al. 2003). Selenium is a very efficient scavenger of reactive oxygen species and a radiosensitizer, with a very low toxicity profile (Schueller P

Supplementation with 200 mcg daily of sodium selenite for eight weeks, beginning on the first day of standard treatment (surgery and/or radiation) for squamous cell carcinoma of the head and neck, resulted in a significantly enhanced immune response during and after therapy (Kiremidjian-Schumacher L et al. 2000).

**Coenzyme Q10.** Coenzyme Q10 (CoQ10), a mitochondrial enzyme, has been shown to have a therapeutic benefit in cancer patients at doses of 90 to 390 mg daily. A decrease in distant metastasis (Lockwood K et al. 1994) and increase in long-term survival (Lockwood K et al. 1995) have been noted in breast cancer patients. However, a study of mice indicated that CoQ10 reduced the effect of radiation therapy when used at a dose equivalent to 700 mg in humans; therefore, as a precaution, a dose of 100 to 400 mg a day should not be exceeded (Lund EL et al. 1998).

**Melatonin.** Melatonin is the chief secretory hormone of the pineal gland. Melatonin reduces oxidative damage from the production of free radicals (Reiter RJ 2004). Several studies indicate that melatonin functions as a radioprotector (Karbownik M et al. 2000), reducing the toxic effects of radiation on mammalian cells (Vijayalaxmi et al. 2004). In experiments and animal models, administration of melatonin has inhibited the growth and division of several types of cancer cells, particularly breast cancer and melanoma cells (Blask DE et al. 1986; Subramanian A et al. 1991).

Several reports indicate that melatonin administration improves quality of life for many cancer patients (Conti A et al. 1995). Patients with glioblastoma generally experience a poor survival rate, which is typically less than six months. A radio-neuroendocrine approach utilizing radiotherapy with melatonin supplementation (20 mg daily) in patients with untreatable glioblastoma showed that the likelihood of survival at one year was significantly higher in those who received melatonin with radiotherapy (6 of 14 patients alive) versus radiotherapy alone (1 of 16 patients alive) (Lissoni P et al. 1996a). A reduction in radiation-induced toxicity was also observed in the melatonin-treated group.

Melatonin reduces gamma radiation-induced primary DNA damage in human white blood cells (lymphocytes) (Vijayalaxmi 1998). It has been suggested that supplementing with an adjuvant therapy of melatonin may benefit cancer patients who are suffering from toxic therapeutic regimens such as radiotherapy and/or chemotherapy, and may alleviate symptoms caused by radiation-induced organ injuries (Karslioglu I et al. 2005).

### ***Preventing Normal Tissue Complications***

The goal of radiation therapy is to deliver a precisely measured dose of ionizing radiation to a defined tumor area, with as little damage as possible to surrounding healthy, non-cancerous tissue (Burnet NG et al. 1996). However, a number of patients undergoing radiation therapy will experience a range of side effects, which may lead to an interruption of treatment or limiting the dose of radiation (Fowler JF et al. 1992).

Radiation's effects on normal tissues are commonly divided into two categories: "early" and "late" reactions. Early, or acute, effects occur within a few days or weeks of irradiation (Herskind C et al. 1998). Late effects appear after a period of months or years and occur predominantly in slowly growing tissues such as the lungs, kidneys, heart, liver, and central nervous system.

The size of the radiation treatment field, the dose per fraction, and the total dose of radiation received are important factors associated with these effects (Emami B et al. 1991).

**Heart damage.** The use of 3D-CRT reduces the dose and volume of radiation exposure to the heart (Hurkmans CW et al. 2002). However, significant risks remain, and cardiovascular abnormalities may result following radiation therapy (Lipshultz SE et al. 1993). Hodgkin's disease survivors treated with chest radiation therapy are at increased risk of death as a result of cardiovascular disease (Lee CK et al. 2000). Women treated with radiation therapy following mastectomy for left-sided breast cancer, which involves exposure of the heart, have been shown to have an increased frequency of cardiovascular disease (Gyenes G et al. 1998).

In a small trial of a mixture of antioxidants—including vitamin E (600 mg), vitamin C (1 gram), and N-acetylcysteine (200 mg)—taken during treatment, researchers sought to determine the mixture's ability to prevent heart damage during chemotherapy and radiation therapy. No patient taking the antioxidant mixture had a decrease in ejection fraction (the amount of blood pumped out of the heart during each heartbeat) of greater than 10 percent. By contrast, in the control group, in which four of six patients were treated with radiation therapy and two of seven patients underwent chemotherapy, the ejection fraction reduction was greater than 10 percent, indicative of a weakened heart (Wagdi P et al. 1996).

**Gastrointestinal mucositis (inflammation of the gut lining).** More than 70 percent of patients treated for cancer of the prostate, bladder, and other malignancies in the pelvic region develop acute inflammatory small intestinal changes (Resbeut M et al. 1997). Acute enteritis or proctitis (inflammation of the intestine or rectum, respectively) is characterized by diarrhea, abdominal pain, and tenesmus (fecal urgency with cramp-like rectal pain) that usually starts during the second week of radiation therapy and resolves within two weeks of completing treatment (Ajlouni M 1999). In 5 percent to 10 percent of patients, serious gastrointestinal problems

may occur, including bowel obstructions and bleeding (Denton AS et al. 2000).

Both glutamine (Hall JC et al. 1996) and arginine (Gurbuz AT et al. 1998) are amino acids that have an important role in maintaining mucosal growth and function. Supplementation with these amino acids before or after abdominal irradiation appears to decrease the likelihood of both acute and chronic effects on the lower intestine (Ersin S et al. 2000; Kaya E et al. 1999; Klimberg VS et al. 1990), but not all studies have shown benefits (Hwang JM et al. 2003; Kozelsky TF et al. 2003). Oral glutamine supplementation may enhance radiation therapy by protecting normal tissues from (and sensitizing tumor cells to) radiation damage (Savarese DM et al. 2003). In one study, oral glutamine supplementation (30 grams per day) reduced gut permeability and protected lymphocytes in patients with esophageal cancer during radiochemotherapy (Yoshida S et al. 1998).

Patients receiving 1200 mg of intravenous glutathione (diluted in normal saline solution) 15 minutes before pelvic irradiation suffered less post-therapy diarrhea (28 percent, compared to 52 percent for controls) and were more likely to complete their treatment without interruption than a control group (71 percent, compared to 52 percent) (De Maria D et al. 1992).

Several studies have reported a positive effect of hyperbaric oxygen therapy in patients with chronic radiation cystitis or proctitis (inflammation of the bladder or rectum, respectively) (Ennis RD 2002). Radiation-induced hemorrhagic cystitis can be treated successfully with hyperbaric oxygen therapy; it is well tolerated even in patients debilitated by advanced cancer and blood loss. Long-term remission is possible in most patients, and re-treatment effectively manages recurrent bleeding (Chong KT et al. 2005; Neheman A et al. 2005).

Short-chain fatty acids and butyrate are derived from the bacterial fermentation of unabsorbed carbohydrates within the colon (Cook SI et al. 1998). They are readily absorbed in the large bowel and are beneficial in treating colitis (inflammation of the bowel) (Kim YI 1998). A small study of seven patients who had received previous radiation therapy (for an average of 23 months before the study) examined the use of short-chain fatty acid enemas (administered twice daily for four weeks) for the treatment of proctitis (inflammation of the rectum) and found a significant decrease in rectal bleeding (al-Sabbagh R et al. 1996). This was confirmed in another study of 20 patients who presented with proctitis within three weeks of completing radiation therapy. Half were treated daily with one 80-ml sodium butyrate enema (80 mmol/L) and half with a sodium chloride placebo over a three-week period (Vernia P et al. 2000). All patients treated with butyrate reported a significant improvement in their symptoms compared to only three patients in the placebo group who reported a slight improvement.

**Hair loss.** Radiation therapy can cause hair loss (alopecia), but only in the area being treated (Irvine L et al. 1999). Hair loss is usually temporary and re-growth is evident within a few weeks after completion of therapy.

Melatonin has been reported to have a beneficial effect on hair growth in animals (Oxenkrug G et al. 2001). Furthermore, a study of 40 women suffering from alopecia sought to determine whether topically applied melatonin influences hair growth. A melatonin solution (0.1 percent) or placebo was applied to the scalp daily for six months. Positive results were obtained in the melatonin-treated group (Fischer TW et al. 2004).

**Liver damage.** Hepatocellular carcinoma is a common malignancy, and 3D-conformal radiation therapy is increasingly used in treatment as part of multimodal therapy (Cheng JC et al. 2000). However, one of the most frequently encountered complications following such treatment is radiation-induced liver disease, occurring in approximately 18 percent of patients (Cheng JC et al. 2002b). Patients present with fatigue, rapid weight gain, and, in rare cases, jaundice, approximately four to eight weeks after treatment (Lawrence TS et al. 1995). Radiation-induced liver disease leads to the deterioration of liver function, and up to half of radiation-induced liver disease patients may die from this complication (Cheng JC et al. 2002a).

Silymarin, a flavonoid complex found in the herb milk thistle, is frequently used in the treatment of liver disease (Levy C et al. 2004; Saller R et al. 2001). It functions as an antioxidant (Feher J et al. 1987), maintains cellular glutathione content (Soto C et al. 2003), and has a low toxicity profile (Ladas EJ et al. 2003). A study of rats found that an intravenous injection of silymarin (50 mg/kg) 30 minutes before a single dose of radiation protected against radiation-induced liver disease (Ramadan LA et al. 2002). Silymarin is well tolerated and produces a small increase in glutathione and a decrease in lipid peroxidation in peripheral blood cells in certain patients (Lucena MI et al. 2002). Treatment with silymarin (600 mg/day) was found to reduce the lipoperoxidation of cell membranes and insulin resistance (Velussi M et al. 1997).

**Hypersensitivity reactions: skin/fibrosis.** Acute radiation dermatitis (inflammation of the skin) is a common side effect of radiotherapy. Dermatitis includes redness (erythema) and dry or moist peeling skin (desquamation). It has been estimated that 87 percent of all women undergoing radiation therapy for breast cancer will develop some degree of radiation dermatitis (Fisher J et al. 2000). Severe radiation dermatitis can be painful, may lead to infections, and can cause permanent scarring.

No standard treatment has been recommended for the prevention of radiation-induced dermatitis, though several therapies have been suggested (Westbury C et al. 2000; Wickline MM 2004). Several dressing types used to treat radiation dermatitis can provide a moist healing environment that is optimal for cell migration across the wound, thereby shortening healing time (Margolin SG et al. 1990).

Topical agents such as corticosteroid creams and other products, including aloe vera gel or trolamine (Biafine®), are commonly prescribed at the onset of radiation dermatitis or at the beginning of radiotherapy (Bostrom A et al. 2001; Schmuth M et al. 2002). Biafine® is a water-based emulsion that has been used in France since 1973 to alleviate symptoms of radiation dermatitis (Fenig E et al. 2001; Fisher J et al. 2000).

Calendula, derived from the marigold flower, has purported anti-inflammatory properties and is often used for wound healing. A recent trial found that calendula was significantly better than Biafine® in preventing mild-to-severe acute radiation dermatitis in breast cancer patients, as well as in providing pain relief (Pommier P et al. 2004). Patients applied the preparation to the irradiated skin at least twice a day at the onset of radiation therapy and continued this until completion of treatment.

In clinical trials, the application of aloe vera gel was no better than placebo or aqueous cream in reducing radiation-induced dermatitis (Heggie S et al. 2002; Williams MS et al. 1996). However, aloe vera gel added to soap has a protective effect for patients who received higher cumulative radiation doses, prolonging the time to detectable skin damage from three to five weeks (Olsen DL et al. 2001).

Dexpanthenol (vitamin B5) creams have been shown to improve acute radiotherapy skin reactions in some (Roper B et al. 2004) but not all studies (Lokkevik E et al. 1996).

N-acetylcysteine is capable of stimulating radio-protective cytokines (Baier JE et al. 1996). The application of gauze soaked in 10 percent N-acetylcysteine for 15 minutes before radiation therapy was associated with more rapid healing of skin reactions and less use of pain relievers compared to an untreated control group (Kim JA et al. 1983).

Unsaturated essential fatty acids (EFAs) are necessary for the production of prostaglandins (PGEs) (inflammatory modulators) and play an important role in maintaining cell membrane structure by regulating membrane fluidity (Horrobin DF 1992). The ability of EFAs containing both gamma-linolenic acid (GLA) and eicosapentaenoic acid (EPA) to modify radiation-induced skin reactions was studied in pigs (Hopewell JW et al. 1994). Oral administration of 3 ml of oil daily for four weeks before and up to 16 weeks after irradiation significantly reduced both acute and late radiation skin damage. Prospective studies suggest that prostaglandins have

great potential in minimizing the adverse effects of radiotherapy on normal tissue. The potential use of misoprostol, a PGE(1) analogue, before irradiation may be considered in the prevention of radiation-induced side effects (Lee TK et al. 2002).

**Radiation-induced fibrosis**, a serious late effect of radiotherapy, is mainly characterized by changes in the connective tissue involving excessive extracellular matrix deposition and hyperactive fibroblasts (Burger A et al. 1998). A combination of pentoxifylline (Trental®), a methylxanthine derivative structurally related to theophylline and caffeine, and vitamin E (alpha tocopherol) may be effective in treating radiation-induced fibrosis (Delanian S et al. 1999). Pentoxifylline promotes healing and relieves pain following radiation damage (Futran ND et al. 1997), and vitamin E was used for its ability to scavenge reactive oxygen species (Rudolph R et al. 1988). Twenty-two patients who developed radiation-induced fibrosis following radiotherapy for breast cancer were treated with 800 mg/day of pentoxifylline and 1000 IU/day of vitamin E. The area of radiation-induced fibrosis was significantly reduced when these patients were examined after six months, with no adverse effects reported (Delanian S et al. 2003). For more information, see the later section of this chapter on Pulmonary Toxicity.

**Lymphedema.** Lymphedema is an accumulation of protein-rich fluid that results in swelling of the underlying skin. It may occur in the arm following radiotherapy for breast cancer, due to interruption of axillary (armpit) lymphatic drainage or because of axillary lymph node dissection or axillary radiation, or both. It results in pain, decreased stretching ability of tissue around the joints, and increased weight of the extremity (Allegra C et al. 2002). The reported incidence of lymphedema varies, with rates of 2 percent to 24 percent reported in a review of breast cancer patients (Petrek JA et al. 1998), and of 22 percent to 56 percent for the head and neck region (Dietz A et al. 1998).

Several non-pharmacological options are available for managing lymphedema (Harris SR et al. 2001), including the use of graded compression garments (Collins CD et al. 1995) and pneumatic compression pumps (Dini D et al. 1998).

Arm exercises may also help to control the symptoms caused by lymphedema, by strengthening the muscle-pumping action and consequently increasing lymph flow. Many clinicians encourage patients to continue exercising two or three times a day for six months, then daily for life (Granda C 1994). Scrupulous skin care should be followed and maintenance of an ideal body weight should be encouraged, as obesity is a contributing factor for the development of lymphedema (Johansson K et al. 2002).

Clinical studies have shown a beneficial effect of selenium in treating lymphedema at different locations (Bruns F et al. 2004; Kasseroller RG et al. 2000). Forty-eight patients were evaluated either 10 months (upper-limb) or 4 months (head and neck) after the end of radiotherapy. Patients received 500 mcg of sodium selenite per day over four to six weeks. Approximately 80 percent of patients showed a significant improvement in their lymphedema and quality of life (Micke O et al. 2003).

Other investigators concluded that sodium selenite represents a suitable adjuvant treatment of secondary lymphedema. Treatment with sodium selenite (1000 mcg daily for three weeks) can be instituted immediately after treatment and before wound healing when manual lymphatic decongestion therapy cannot be applied (Zimmermann T et al. 2005).

### ***The Importance of Exercise***

Fatigue is a major determinant of quality of life and is present in as many as 50 percent to 70 percent of patients with cancer at diagnosis (Irvine D et al. 1994). Several studies have investigated fatigue during radiation therapy for both breast (Geinitz H et al. 2001) and prostate cancer (Janda M et al. 2000). The initiation of radiation therapy is accompanied by significant increases in fatigue (Kurzrock R 2001). However, levels of fatigue tend to return to pre-treatment levels within several weeks of completing treatment (Jacobsen PB et al. 2003).

A number of studies have examined the therapeutic value of exercise during cancer treatment (Brown JK et al. 2003; Courneya KS 2003). A trial was performed to determine whether aerobic exercise would reduce the incidence of fatigue and prevent deteriorating physical function during radiotherapy for localized prostate carcinoma (Windsor PM et al. 2004). Those men who followed advice to rest if they became fatigued demonstrated a slight deterioration in physical function and a significant increase in fatigue at the time of radiotherapy. By contrast, a home-based, moderate-intensity walking program produced a significant improvement in physical function, with no significant increase in fatigue.

An exercise program of walking (self-paced walks of 20 to 30 minutes, 4 to 5 days per week) was evaluated in participants who were to receive radiation therapy after surgery for breast cancer (Mock V et al. 1997). Before radiation therapy, patients were assigned to either the exercise intervention group or a control group. Those who underwent the walking program experienced significantly less fatigue on the completion of radiation therapy than those in the control group.

**Kidney toxicity (nephrotoxicity).** The kidney is one of the most radiosensitive organs at risk of developing damage after abdominal irradiation. Radiation nephropathy takes various forms, the most common of which, acute radiation nephritis, presents as azotemia (dangerously high levels of nitrogen waste products in the bloodstream), hypertension, and anemia, starting at 6 to 12 months following treatment (Cohen EP et al. 2003). If left untreated, this can lead to renal failure, and survival on chronic dialysis is poor (Cohen EP et al. 1998).

Dietary protein restriction is effective in treating various chronic kidney diseases (Levey AS et al. 1999) though care must be taken to maintain adequate nutrition (Youngman LD 1993).

All-trans retinoic acid (a vitamin A-like drug) exacerbates radiation nephropathy, possibly by inhibiting renal nitric oxide production, and its use should be restricted during renal irradiation (Moulder JE et al. 2002).

**Nerve toxicity (neurotoxicity).** The nervous system is particularly sensitive to radiation therapy, and radiation-induced neurotoxicity can involve the central nervous system and peripheral nervous system (Liang BC 1999).

Radiation therapy for skull-base, orbital, and sinus tumors invariably involves the irradiation of brain tissue (Chong VF et al. 2002). Following brain irradiation, acute toxicity may cause headaches, dizziness, fatigue, and problems with speech (Young DF et al. 1974). Corticosteroids are useful in relieving a number of these acute complications, but should be used only as long as medically necessary, as they may have side effects. Early physical therapy can prevent lymphedema, frozen shoulder, and atrophy (muscle wasting). For more information, see the Peripheral Neuropathy chapter.

**Radiation necrosis.** Radiation necrosis (tissue ulceration) and cognitive dysfunction are the main late complications of brain irradiation. Radiation necrosis may occur from six months to two years following treatment (Keime-Guibert F et al. 1998), and is caused primarily by blood vessel damage (Lyubimova N et al. 2004). Up to 20 percent of patients receiving stereotactic radiosurgery and 80 percent undergoing interstitial brachytherapy will develop symptoms of radiation necrosis (Wen PY et al. 1994).

This is a serious condition with symptoms that vary from fatigue to dementia, and may require surgical intervention (Strohl RA 1998). Non-surgical treatments that have been clinically investigated include steroids, heparin, low-iron diets with iron chelators, pentoxifylline, and hyperbaric oxygen therapy (Chuba PJ et al. 1997; Hornsey S et al. 1990). Hyperbaric oxygen therapy is important in the treatment and healing of soft tissue radiation necrosis, particularly of the brain (Dion MW et al. 1990; Hart GB et al. 1976; Kohshi K et al. 2003).

The use of pentoxifylline is deemed safe and effective in preventing radiation necrosis, particularly in the prevention of radiation-induced lung toxicity (Ozturk B et al. 2004). At an oral dose of 400 mg three times daily, pentoxifylline has a protective effect against radiation necrosis complications, possibly by reducing platelet aggregation and preventing tumor necrosis factor-mediated inflammation (Aygenç E et al. 2004; Hong JH et al. 1995).

Osteoradionecrosis (see the earlier section of this chapter on Hyperbaric Oxygen Treatment) is a late adverse effect of radiation therapy that does not resolve spontaneously. In a preliminary study, a combination of pentoxifylline (800 mg daily), tocopherol (vitamin E, 1000 IU daily), and clodronate (1600 mg daily, Bonefos®) was of clinical benefit, with more than 50 percent regression of progressive osteoradionecrosis observed at six months in 12 patients (Delanian S et al. 2002b; Futran ND et al. 1997). In another study, this same regimen completely reversed severe progressive osteoradionecrosis when administered daily for three years (Delanian S et al. 2002a).

**Oral complications.** Between 60 percent and 90 percent of head and neck cancer patients receiving standard radiation therapy will develop inflammation of the lining of the mouth (mucositis) (Sutherland SE et al. 2001), which usually improves within a few weeks after completing treatment (Sonis ST et al. 2001).

One of the most important factors that predisposes someone to oral mucositis is preexisting oral or dental disease (Dodd MJ et al. 1996). Oral mucositis can lead to secondary complications, including infection, poor nutritional intake, and xerostomia (dry mouth). Several treatment interventions have been suggested for preventing and treating oral mucositis, though no effective treatment currently exists (Clarkson JE et al. 2003; Worthington HV et al. 2004).

Maintaining good oral hygiene is important in preventing mucositis, and it is particularly important to instigate this at least a week before starting radiation therapy (Shieh SH et al. 1997). Patients should brush twice daily with a soft-bristled tooth brush, floss daily, and rinse the mouth once daily with normal saline (1/2 teaspoon of salt in eight ounces of water) or sodium bicarbonate (baking soda or Alka-Seltzer®) (Dodd MJ et al. 2000).

A trial of head and neck cancer patients indicated that oral glutamine (16 grams in 240 ml of normal saline, four times daily during radiation) may significantly reduce the duration and severity of oral mucositis during radiotherapy (Huang EY et al. 2000).

Honey reduces the symptoms of mucositis. Forty patients diagnosed with head and neck cancer were divided into two groups. One group was advised to take 20 ml of pure honey 15 minutes before, 15 minutes after, and 6 hours after radiotherapy. In the honey-treated group, symptomatic mucositis was reduced significantly, and there was either no change in weight or positive weight gain compared to the control group (Biswal BM et al. 2003).

Antibiotics supplied either as a topical pastille or paste may be beneficial in preventing mucositis (Donnelly JP et al. 2003; Okuno SH et al. 1997). The overgrowth of certain yeast and bacteria, which occurs following radiation therapy, may be important in the progression of this condition (Spijkervet FK et al. 1991). Head and neck cancer patients who were given a pastille containing amphotericin, polymixin, and tobramycin to suck four times daily were significantly less likely to develop the most serious form of mucositis than those who received a placebo (Symonds RP et al. 1996). However, this beneficial finding has not been seen in all studies using antibiotics (Stokman MA et al. 2003; Wijers OB et al. 2001).

Alternatively, the flower *Matricaria camomile* may be beneficial in reducing mucositis during radiotherapy (Henriksson R et al. 1999), due to its antibacterial properties (Carl W et al. 1991). In a study in which Kamillosan® (a camomile preparation) oral rinse was given to patients receiving radiation therapy and chemotherapy, mucositis was less severe than expected (Carl W et al. 1991).

Hydrolytic enzymes have anti-inflammatory properties and are effective in reducing normal tissue reactions such as oral (Kaul R et al. 1999) and gastrointestinal mucositis (Dale PS et al. 2001). They function by reducing cytokine levels (Lehmann PV 1996). In one clinical study, 53 patients were given three tablets, three times a day, containing papain (100 mg), trypsin (40 mg), and chymotrypsin (40 mg). The treatment was started three days before radiation therapy and continued until five days after completion of treatment (Gujral MS et al. 2001). Both mucositis and skin reactions were significantly reduced in the enzyme-treated group compared to controls.

Beta-carotene (75 mg daily) during radiation therapy for advanced squamous cell carcinoma of the mouth markedly reduced the incidence of severe mucositis without causing noticeable side effects (Mills EE 1988).

Damage to the salivary glands is another common adverse effect of radiotherapy. Reduced saliva production can cause chronic dry mouth. This is a significant problem for cancer patients, with a reported prevalence of between 29 percent and 77 percent (Maltoni M et al. 1995). Xerostomia can greatly impair a patient's ability to speak, chew, swallow, and taste, and therefore is often accompanied by a loss of appetite and weight, leading to adverse effects on quality of life (Brown CG et al. 2004).

To manage this condition, some patients use artificial saliva substitutes, but most patients find them inadequate (van der Reijden WA et al. 1996). Salivary gland dysfunction after therapeutic radiation is a difficult, if not impossible, condition to reverse, though some evidence suggests that patients with this condition should be considered for hyperbaric oxygen therapy (Bui QC et al. 2004). The use of non-cinnamon or mint-based sugar-free drops, chewing gum, fresh pineapple chunks, or frequent sips of water to maintain adequate hydration has been suggested to stimulate salivary flow (Krishnasamy M 1995).

**Poor appetite and cachexia.** Patients undergoing radiotherapy for cancer of the head and neck or gastrointestinal tract are at higher risk of developing malnutrition (van Bokhorst-de van der S et al. 1999). Malnutrition increases the risk of infections and treatment toxicities, and decreases the response to treatment (Nitenberg G et al. 2000).

Cachexia is treated by attempting to increase nutritional intake and inhibit muscle and fat wasting. This is done by manipulating the metabolism with various pharmacological agents and by treating the causes of reduced food intake, such as nausea and vomiting (Davis MP et al. 2004) (for more information, see the chapter on Catabolic Wasting). Diets that include the omega-3 fatty acids EPA and DHA (Wigmore SJ et al. 2000), melatonin (Lissoni P et al. 1996b), and vitamin supplements (alpha-lipoic acid, 300 mg/day; carbocysteine lysine salt, 2.7 grams/day; vitamin E, 400 mg/day; vitamin A, 30,000 IU/day; vitamin C, 500 mg/day) (Mantovani G et al. 2004) have shown promise in some, but not all (Bruera E et al. 2003), studies undertaken.

**Pulmonary toxicity.** The lung is among the most radiosensitive organs, and therefore the risk of severe side effects seriously compromises treatment outcome. Radiation pneumonitis (inflammation of the lung) is a common acute side effect occurring in 5 percent to 30 percent of patients treated for lung cancer between one month and six months after radiotherapy (Tsujino K et al. 2003). Radiation therapy-induced fibrosis is associated with scarring of the lung and typically occurs months to years after radiotherapy.

The amino acids taurine and L-arginine may protect against radiation-induced lung fibrosis by reducing production of collagen, a protein implicated in the fibrotic process (Song L et al. 1998).

The drug pentoxifylline down-regulates the production of proinflammatory cytokines, particularly tumor necrosis factor-alpha (TNF-alpha), and may therefore protect against radiation-induced, cytokine-mediated damage (Rube CE et al. 2002). In a clinical trial, 64 patients with non-small cell lung cancer were randomly divided into a pentoxifylline (400 mg, three times a day) plus radiotherapy group or a radiotherapy-only group (Kwon HC et al. 2000). Following treatment, patients in the pentoxifylline plus radiotherapy group had significantly longer survival and time to relapse.

A potentially important determinant of lung toxicity risk may be vitamin A nutritional status. Human studies have linked low vitamin A intake and/or reduced serum retinol levels with an increased risk of lung dysfunction (Chytil F 1992). Low levels of vitamin A have been found in human lung tissues obtained from patients undergoing lung resection (Redlich CA et al. 1996). Retinoids may exert their effects by modulating inflammatory cytokines and growth factors (Zitnik RJ et al. 1994). Experimental animal studies suggest

that supplemental vitamin A may reduce lung inflammation after thoracic radiation and may be an important radioprotective agent in the lung (Redlich CA et al. 1998).

**Radiation-induced nausea and vomiting** typically occur within 24 hours of treatment, and over 80 percent of patients undergoing radiation of the upper body will develop symptoms of nausea and vomiting (Anonymous 1999; Goldsmith B 2004). If untreated, nausea and vomiting can cause physiological changes, including dehydration, electrolyte imbalance, malnutrition, and cachexia (Henriksson R et al. 1992).

The use of 5-hydroxytryptamine (5-HT<sub>3</sub>)-receptor antagonists, such as granisetron (Kytril®), is the current “gold standard” in treating nausea and vomiting resulting from radiation therapy (Goldsmith B 2004).

Hypnosis effectively treated anticipatory nausea in pediatric (Zeltzer LK et al. 1991) and adult cancer patients (Morrow GR et al. 1982). Clinical research found acupuncture to be effective for nausea in cancer patients, whether it be postoperative nausea or chemotherapy-induced nausea (Dundee JW et al. 1989a; Dundee JW et al. 1989b; Mayer DJ 2000). Acupuncture may also reduce radiation-induced symptoms (Johnstone PA et al. 2002; Lu W 2005; Samuels N 2003).

**Second cancers.** Although long-term survival following treatment for primary cancer has increased significantly in recent years, one of the most serious side effects of cancer treatment is the induction of a new tumor (Fossa SD 2004). Second cancers account for up to 10 percent of all cancer diagnoses (Bhatia N et al. 2001). A study of patients with primary cancer in adulthood showed a 1.3-fold increased risk of developing a second cancer from radiation therapy (Curtis RE et al. 1985).

The increased risk of second malignancy usually, though not exclusively, occurs in the radiation field. The risk is dose dependent and appears to be higher when radiation exposure occurs at a younger age. The latency period is long; for example, secondary leukemia usually develops 1 to 10 years after radiotherapy, whereas an interval of more than 6 years and often decades is usual for solid tumors (Somerville HM 2003).

A large number of studies have evaluated the risk of solid tumors following radiotherapy for Hodgkin's disease (Bhatia S et al. 2002; Ng AK et al. 2002). Survivors of Hodgkin's disease appear to face a 2 percent to 4 percent greater risk of second malignancy per person per year (Somerville HM 2003).

Overall, it should be noted that the risk of second cancers is generally low, and the benefit of radiation therapy for patient survival outweighs the risk of developing a second tumor (Travis LB 2002).

**Sexual dysfunction.** Erectile dysfunction occurs in 7 percent to 84 percent of prostate cancer patients treated with radiation, even with the development of advanced radiation techniques such as proton beam therapy and 3D-CRT, which spare more normal tissue (Incrocci L et al. 2002).

Sixty patients presenting with erectile dysfunction 39 months after radiation treatment for prostate cancer were enrolled in a 12-week study to determine the efficacy of sildenafil citrate (Viagra®). Patients reported a significant increase in erectile function, with only mild side effects, at a dose of 100 mg taken one hour before sexual activity (Incrocci L et al. 2003).

Vaginal stenosis (narrowing) occurs in up to 88 percent of women undergoing brachytherapy for gynecological cancers (Hartman P et al. 1972). The time of onset of stenosis varies widely, from six weeks to several years after treatment (Lancaster L 2004). Stenosis leads to thinning of the vaginal mucosa, scarring, and eventually scar tissue (Abitbol MM et al. 1974). This results in shortening and narrowing of the vagina, leading to dyspareunia (pain during intercourse) and sexual dysfunction (Bergmark K et al. 1999).

Several treatment options have been suggested to manage radiation injuries of the vulva and vagina (Fraunholz IB et al. 1998). Proper personal hygiene is crucially important in managing acute vulva skin reactions (Grigsby PW et al. 1995). Dilatation of the vagina either through the use of vaginal dilators or regular sexual intercourse should be performed to help prevent stenosis. Use of dilators should start before or immediately on completion of treatment and continue indefinitely (Lancaster L 2004).

### ***A Cancer "cure" that may be lethal: Radiation Therapy Increases stroke risk***

Although head and neck cancer is the fifth most common cancer, most people are not familiar with this type of cancer (Vermorken JB 2005). The mortality rate for those diagnosed with head and neck cancer (which does not include brain tumors) is high (Fortin A et al. 2001).

Radiation therapy is an important part of treating many different head and neck tumors, and is often used after surgery (Hunter SE et al. 2003). Lethal radiation necrosis to the brain is one potential side effect (Eisbruch A et al. 1999).

Another danger of radiation therapy to the head is increased risk of stroke (Abayomi OK 2004). A study of head and neck cancer patients who received radiation therapy found that stroke rates were five times greater than expected (Dorresteijn LD et al. 2002). This elevated stroke risk was found many years after administration of radiation. The average time between radiation treatment and stroke was 10.9 years, but the increased risk of stroke persisted for 15 years after radiation therapy.

For cancer patients treated with radiation therapy who later die from a stroke, the official cause of death is stroke, even though the cancer radiation therapy probably caused the stroke. This is an example of how cancer cure statistics are misleading. The government contends that radiation therapy is curing cancer patients, yet long-term radiation side effects cause many deaths that are not attributed to cancer.

The government claims that more cancer victims are living beyond five years, but ignores the fact that the toxic therapies often used to eradicate cancer can themselves cause premature death (Lassen UN et al. 1999).

(The authors of this study do not recommend that head and neck cancer patients refuse radiation therapy, as it often adds years to their lives. Patients who have received radiation therapy to the head or neck should take extra precautions to reduce their risk of stroke.)

### ***Importance of Diet During Treatment***

Radiation therapy can change nutritional needs and alter the body's absorption and use of food (Brown JK et al. 2003). Common cancer symptoms and toxic effects of radiation treatment include fatigue, anorexia, weight change, nausea, vomiting, pain, and changes in taste and bowel habits (Brown JK et al. 2003).

Some researchers have suggested a low-fat (10 percent of calories from fat) and high-fiber (25 to 30 grams from vegetables and fruits) diet be consumed during and after cancer treatment (Boyd NF et al. 1997). Such a diet can interfere with tumor growth by reducing tumor-stimulating signals (Rao CV et al. 1993). Lifestyle changes that should be encouraged include quitting smoking, reducing consumption of caffeine and alcoholic beverages, exercising daily, and reducing stress levels (Prasad KN et al. 1999).

### ***Nutritional Intervention During Radiotherapy***

Dietary changes such as the use of low-residue and elemental diets are suggested for those patients undergoing pelvic radiotherapy, as they place less strain on the digestive system than do conventional diets (McGough C et al. 2004). Several studies have investigated dietary interventions in those undergoing pelvic radiotherapy (McGough C et al. 2004):

**Dietary fat regimens**, using 20 to 40 grams of fat per day, significantly reduced diarrhea and the frequency of bowel motions (Bye A et al. 1992). There was no difference in stool frequency or use of anti-diarrhea medication through dietary lactose restriction (Stryker JA et al. 1986).

**Probiotics**. The use of probiotics has a positive effect on gastrointestinal toxicity (Delia P et al. 2002). Probiotics refer to "friendly" bacteria that contribute to the health of the gastrointestinal tract. Twenty-four female patients suffering from gynecological malignancies all received dietary counseling recommending a low-fat, low-residue diet during their radiotherapy. Half the patients also received 150 ml of a fermented milk product supplying at least  $2 \times 10^9$  Lactobacillus acidophilus bacteria daily and 6.5 percent lactulose as substrate for the bacteria. The results indicated significantly reduced diarrhea in the group receiving probiotics, though with increased flatulence (Salminen E et al. 1988).

**Elemental diets** are liquid diets consisting of essential amino acids, glucose, vitamins, and necessary minerals (Bounous G 1983). Nutrients are usually in digested form so they do not stress the digestive system. The use of an elemental diet during radiotherapy (Brown MS et al. 1980) resulted in a statistically significant decrease in the incidence and severity of acute diarrhea (Craighead PS et al. 1998; McArdle AH et al. 1986). In one favorable study, the elemental diet began three days before radiation therapy and was continued until completion. Patients were also placed on a modified diet that recommended low fiber, moderate fat intake, and adequate proteins and carbohydrates (Craighead PS et al. 1998).

**Micronutrient supplementation** in patients with proctitis (inflammation of the rectum) has been previously outlined (Levitsky J et al. 2003). A study of 19 patients treated with pelvic radiotherapy for more than six months examined whether vitamin A could reduce the resulting radiation-induced proctitis (Ehrenpreis ED et al. 2005). Ten patients received 10,000 IU of oral vitamin A for 90 days, after which seven reported a significant improvement in symptoms, compared to only two of nine placebo-treated patients who reported improvement.

In a pilot study, 20 patients with chronic radiation proctitis due to previous pelvic irradiation took vitamin E (400 IU, three times daily) and vitamin C (500 mg, three times daily) supplements for up to one year. Significant improvements were reported in the side effects of bleeding and diarrhea, but not pain (Kennedy M et al. 2001). However, in another study in which the same doses were administered, all symptoms subsided following 6 to 12 weeks of treatment (El Younis C et al. 2003).

### ***For More Information***

The complications related to radiation can be acute (such as low blood cell counts) and chronic (gastrointestinal, pulmonary, neuropathic, and cardiac). For more information on some of the topics outlined in this chapter, please consult the following chapters:

- Blood Disorders
- Catabolic Wasting
- Complementary Adjuvant Cancer Therapies
- Erectile Dysfunction
- Neuropathy.

For general information on all aspects of radiation therapy, please visit: <http://www.cancerlinksusa.com/radiation.htm>.

### **Proton Therapy Centers in North America**

The Loma Linda University Medical Center (LLUMC), California. LLUMC sponsors Prolit, a proton therapy literature database.

Northeast Proton Therapy Center at Massachusetts General Hospital in Boston.

Particle Therapy Co-operative Group (PTCOG) and the PTCOG publication Particles.

Midwest Proton Radiotherapy Institute, Bloomington, Indiana.

Proton Radiation Therapy at TRIUMF Vancouver, Canada. Pion Therapy is also available.

UC-Davis, California. The Berkeley Eye Program.

### **LIFE EXTENSION FOUNDATION RECOMMENDATIONS**

For optimal results, the majority of these supplements or dietary changes should be introduced before starting radiation treatment. Refer to the text for a more detailed explanation of the dose and duration of the specific supplements.

- **R-lipoic acid**—300 milligrams (mg) daily
- **Beta-carotene**—25,000 international units (IU) or 75 mg daily
- **Coenzyme Q10**—100 to 400 mg daily
- **Curcumin**—up to 3.2 grams daily
- **Panax ginseng (Siberian)**—200 to 1000 mg daily
- **Green tea extract**—725 mg three times daily
- **Hydrolytic enzymes**— papain (100 mg), trypsin (40 mg), and chymotrypsin (40 mg): three days before radiation therapy and continuing until five days after completion of treatment
- **Kamillosan**—10 drops in 1 ounce of water, three times daily (<http://www.smallflower.com/>).
- **L-arginine**—900 mg daily
- **L-glutamine**—20 to 40 grams administered before starting radiation therapy
- **Melatonin**—up to 20 mg daily
- **Multivitamin/multimineral supplement** (without copper)
- **N-acetylcysteine**—200 to 600 mg daily
- **Omega-3 fatty acids**—1 to 2 grams (g) daily
- **Probiotics**—2x10<sup>9</sup> Lactobacillus acidophilus daily
- **Pure honey**—20 milliliters (ml), 15 minutes before, 15 minutes after, and 6 hours after radiotherapy
- **Selenium**—200 to 1000 micrograms (mcg) daily
- **Silymarin**—150 to 600 mg daily
- **Soy extract** containing 50 mg of isoflavones—twice daily
- **Taurine**—1000 mg daily
- **Vitamin A**— 8000 to 30,000 IU daily
- **Vitamin C**— 500 mg three times daily
- **Vitamin E**—400 to 1200 IU daily
- **Whey protein isolate**—20 grams daily.

### **CANCER RADIATION THERAPY 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:

#### **All-trans retinoic acid (ATRA)**

- All-trans retinoic acid (ATRA) has been shown to exacerbate radiation nephropathy.

## **Beta-Carotene**

- Do not take beta-carotene if you smoke. Daily intake of 20 milligrams or more has been associated with a higher incidence of lung cancer in smokers.
- Taking 30 milligrams or more daily for prolonged periods can cause carotenoderma, a yellowish skin discoloration (carotenoderma can be distinguished from jaundice because the whites of the eyes are not discolored in carotenoderma).

## **Coenzyme Q10**

- See your doctor and monitor your blood glucose level frequently if you take CoQ10 and have diabetes. Several clinical reports suggest that taking CoQ10 may improve glycemic control and the function of beta cells in people who have type 2 diabetes.
- Statin drugs (such as lovastatin, simvastatin, and pravastatin) are known to decrease CoQ10 levels.

## **Curcumin**

- Do not take curcumin if you have a bile duct obstruction or a history of gallstones. Taking curcumin can stimulate bile production.
- Consult your doctor before taking curcumin if you have gastroesophageal reflux disease (GERD) or a history of peptic ulcer disease.
- Consult your doctor before taking curcumin if you take warfarin or antiplatelet drugs. Curcumin can have antithrombotic activity.
- Always take curcumin with food. Curcumin may cause gastric irritation, ulceration, gastritis, and peptic ulcer disease if taken on an empty stomach.
- Curcumin can cause gastrointestinal symptoms such as nausea and diarrhea.

## **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.

## **Ginseng**

- Consult your doctor before taking ginseng if you have high blood pressure. Overuse of ginseng can increase blood pressure.
- Consult your doctor before taking ginseng if you take nonsteroidal anti-inflammatory drugs (NSAIDs) and/or warfarin (Coumadin). Taking NSAIDs or warfarin with ginseng can increase the risk of bleeding.
- Consult your doctor before taking ginseng if you have diabetes. Taking ginseng can cause an extreme drop in your blood glucose level.
- Ginseng can cause breast pain, vaginal bleeding after menopause, insomnia, headaches, and nosebleeds.

## **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.

## **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.

## **L-Glutamine**

- Consult your doctor before taking L-glutamine if you have kidney failure or liver failure.
- L-glutamine can cause gastrointestinal symptoms such as nausea and diarrhea.

NOTE: Glutamine and Arginine

Many clinical trials utilizing glutamine and arginine resulted in beneficial outcomes for cancer patients, and four clinical trials are ongoing. However, some doctors are concerned that supplemental arginine and glutamine may promote tumor cell proliferation in patients, though this has not been clinically observed and is based solely on laboratory studies.

### **Lipoic Acid**

- Consult your doctor before taking lipoic acid if you have diabetes and glucose intolerance. Monitor your blood glucose level frequently. Lipoic acid may lower blood glucose levels.

### **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.

### **Milk Thistle**

- Consult your doctor before taking milk thistle with tranquilizers such as Haldol, Serentil, Stelazine, and Thorazine. Milk thistle combats the effect of tranquilizers.
- Do not combine milk thistle with the blood pressure medication Regitine. Milk thistle combats the effect of Regitine.

### **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.

### **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.

### **Soy**

- Do not take soy if you have an estrogen receptor-positive tumor.
- Soy has been associated with hypothyroidism.

### **Vitamin A**

- Do not take vitamin A if you have hypervitaminosis A.
- Do not take vitamin A if you take retinoids or retinoid analogues (such as acitretin, all-trans-retinoic acid, bexarotene, etretinate, and isotretinoin). Vitamin A can add to the toxicity of these drugs.
- Do not take large amounts of vitamin A. Taking large amounts of vitamin A may cause acute or chronic toxicity. Early signs and symptoms of chronic toxicity include dry, rough skin; cracked lips; sparse, coarse hair; and loss of hair from the eyebrows. Later signs and symptoms of toxicity include irritability, headache, pseudotumor cerebri (benign intracranial

hypertension), elevated serum liver enzymes, reversible noncirrhotic portal high blood pressure, fibrosis and cirrhosis of the liver, and death from liver failure.

## 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

### BLOOD TEST AVAILABILITY

Cancer cell markers (tumor antigen profile) can be determined via Genzyme Genetics ([http://www.genzymeimpath.com/lymphoma\\_leukemia.html](http://www.genzymeimpath.com/lymphoma_leukemia.html)) and may be ordered by a physician by telephoning 1-800-966-4440.

Tests for angiogenesis markers (e.g., VEGF) are available at UCLA's Jonsson Comprehensive Cancer Center (<http://www.cancer.mednet.ucla.edu/>).

Hemoglobin levels (part of a Chemistry Panel/Complete Blood Count) may be tested via Life Extension/National Diagnostics, Inc. and may be ordered by telephoning 1-800-544-4440 or by ordering online at <http://www.lef.org/bloodtest/>.

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