Complementary and Integrative Medicine in Cancer Care and Prevention

Foundations & Evidence-Based Interventions

Marc S. Micozzi, MD, PhD, Editor

Complementary and Integrative Medicine in Cancer Care and Prevention

Marc S. Micozzi, MD, PhD, is a physician-anthropologist who has worked to create science-based tools for the health professions to be better informed and productively engaged in the new fields of complementary and alternative (CAM) and integrative medicine. He was the founding editor-in-chief of the first U.S. journal on CAM (1994) and of the first review journal (2002). He organized and edited the first U.S. textbook, *Fundamentals of Complementary & Integrative Medicine* (1996), now in a third edition (2006). It has been translated into Spanish and Japanese. He serves as series editor for Medical Guides to Complementary and Alternative Medicine with eighteen titles in print on a broad range of therapies and therapeutic systems within the scope of CAM. He organized and chaired continuing education conferences on the theory, science, and practice of CAM in 1991, 1993, 1995, 1996, 1998, and 2001.

Dr. Micozzi has conducted and published original research on diet, nutrition, and cancer. He worked as a Senior Investigator in the Cancer Prevention Studies Branch of the National Cancer Institute from 1984–86. He continued this line of research in collaboration with NIH colleagues when he was appointed Associate Director of the Armed Forces Institute of Pathology in 1986.

His early work on carotenoids (including lycopene), iron and cancer (with Nobel laureate Baruch Blumberg), anthropometric methods for age-related assessment of nutritional status, and other research made important contributions to this field. He received the young investigator award at Walter Reed Army Medical Center in 1992, at which time he was jointly appointed as a Distinguished Scientist in the American Registry of Pathology. During this time he coedited two comprehensive technical volumes on application of clinical trials methods to new investigations of the role of micronutrients and macronutrients in cancer. He has published 275 articles in the medical, scientific, and technical literature.

In 1995, he returned to Philadelphia (where he had completed his medical and graduate training at the University of Pennsylvania from 1974–83) to serve as Executive Director of the College of Physicians of Philadelphia, including creation of the C. Everett Koop Community Health Information Center. The White House Commission recognized this work in 2001. He has been a frequent speaker, as well as an effective spokesperson with the print and broadcast media.

In 2002, he became Founding Director of the Policy Institute for Integrative Medicine in Washington, DC. From 2003–2005, he accepted an interim appointment as Director of the Center for Integrative Medicine at Thomas Jefferson University Hospital in Philadelphia. He is presently a Senior Fellow of the Health Studies Collegium and maintains a part-time consulting practice in forensic medicine. He lectures at major universities in Philadelphia, San Diego, and Washington, DC. He can be contacted at marcmicozzi@aol.com.

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In Memory of David Larson

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Preface

This volume on complementary and integrative therapies (CIM) and cancer addresses a difficult but important subject. The largest, most comprehensive survey on utilization of CIM in the United States has shown that 80% of patients with cancer use complementary, alternative, and integrative treatments (Barnes, Powell-Griner, McFann, & Nahin, 2004). Virtually all these patients are also under treatment by oncologists, radiation therapists, and many other medical specialists. These patients come to their regular physicians seeking answers and guidance about what CIM may have to offer them. They prefer not to be told there is nothing they can do. However, what advice can be responsibly provided? Evidence indicates that a blanket rejection of CIM is no longer appropriate.

On the one hand, it is widely acknowledged in medicine that it is very important to develop new ideas and approaches to the prevention, treatment, and control of cancer. On the other hand, complementary and integrative medicine in cancer is fraught with unproven remedies, marketing claims, and unusual and idiosyncratic approaches that have generally shed more heat than light on the subject. The basic approach to cancer therapy in the 20th century had been to kill cancer cells in a manner that would be less toxic to noncancerous cells in the human body. At the end of the 19th century, the understanding and acceptance of the germ theory of disease led to the control of bacterial agents through the development of "magic bullets" to kill bacteria (bactericidal compounds) or to interfere with their reproduction (bacteriostatic drugs). Antibiotics have proven to be extremely successful in helping to cure bacterial infections, usually without unduly harming the human host. Until the development of antibiotic drug resistance, which turned "magic bullets" into "friendly fire," such approaches were seen as an unalloyed achievement in medicine and public health.

In cancer treatment, we have likewise harbored the hope that magic bullets can be developed but in the meantime rely on surgery, radiation therapy, and chemotherapy. In this manner, the medical historian may be reminded of the preantibiotic approach to infectious diseases—when bleeding, blistering, puking, and purging were the four modalities of choice to rebalance the bodily humours. Can complementary and integrative medical modalities, with their promise of gentler, less invasive, "more natural" approaches, hold promise for cancer treatment, prevention, or control?

Cancer is clearly a challenging area of medicine for the application of CIM. The amount of misinformation often seems to exceed the amount of real clinical scientific

information available. Irresponsible marketing claims and appeals to desperate patients with "incurable" disease create a climate of reluctance for physicians to engage themselves or their patients in this troubling arena (Part 5).

As a medical examiner in 1983, I had the opportunity to investigate a cancer death in a woman with breast cancer under treatment with alternative (but not conventional) therapies. I investigated this category of remedy (that was employed subsequently in research at the National Institutes of Health) and have done "field investigations" in the office of the alternative practitioner in question. Keeping an open mind, I cannot determine whether the death was consistent with essentially untreated breast cancer or whether the alternative treatment ultimately had a negative or positive effect on the course of the disease. Scientific investigation is the only answer to questions such as these. Unfortunately, the lack of access of alternative practitioners to the mainstream medical system, especially for treatment of cancer, the devotion of practitioners and their patients to these alternative therapeutic modalities, the desire for "freedom" in "health choices," and the resulting lack of scientific attention, funding, and studies all contribute to a potentially confusing picture for the medical practitioner.

In addition to these practical concerns, there is a theoretical concern. One of the basic tenets of much of complementary and integrative medicine is that human societies over time are able to develop useful therapies and application of *materia medica* to the alleviation of human suffering and treatment of illness. Much of what we have called "complementary/alternative" medicine today actually represents the "traditional" medicine of other human societies (what anthropologists call ethnomedicine). Certainly the use of many medicinal plants by traditional cultures has been repeatedly validated by scientific study. Diseases that have been part of human heritage since earliest documented times, as proven by paleopathologic studies, yield opportunity and motivation for cultures to develop remedies as has clearly been the case in Ancient Egypt, China, India, Greece, and Rome, as well as indigenous societies in Asia, Africa, and the Americas (Part 4). Although many common diseases have been documented in ancient and prehistoric populations, there is very sparse evidence for cancer, which may be considered to be a "disease of modernization" or a "disease of modern civilization" (Chapter 3). If cancer was not there to be treated, on what basis could effective alternative treatments have been developed in the context of traditional cultures?

However, there is developing clear evidence that many CIM therapies may be effectively used in an adjunctive and supportive role in the cancer patient for the management of both complications of the disease and complications of medical treatment. There is evidence that CIM modalities may help improve quality of life and even help prolong survival in cancer patients (Part 2). Evidence that CIM may prevent or "cure" cancer has been more problematic, although some traditional (ethnomedical) herbal remedies from China (Chapter 15) and India (Chapter 16) appear to have the ability, in laboratory studies, to transform cancer cells through redifferentiation (as has been postulated for the role of vitamin A and its derivatives; for example, see Part 3). These properties are in contrast to the approach of seeking cures for cancer in nature by assessing only cytotoxicity against cancer cells (as with chemotherapy).

Aside from these considerations, CIM clearly may help patients reduce proven risk factors for cancer and other chronic diseases related to diet, smoking, and other behaviors, as has been the subject of serious epidemiologic study for over 25 years (Part 3).

Finally, the dictum that cancer is "not one disease, but many diseases" has proven useful for research and public health efforts. However, this book addresses various cancer sites taken together (with the exception of Chapter 9), partially in light of the limitations of evidence for most site-specific cancers and partially because the probable biological basis of carcinogenesis often does not hold significance when distinguished by site with regard to the possible applications of supportive CAM modalities.

The active participation of the medical and scientific community is essential to appropriately analyze and apply the possible benefits of CIM modalities for cancer prevention, treatment, and control. This volume is intended to provide a useful tool toward that goal.

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Barnes, P. M., Powell-Griner, E., McFann, K., & Nahin, R. L. (2004). Complementary and alternative medicine use among adults: United States, 2002. *Seminars in Integrative Medicine, 2:* 54–71.

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Natural Products in Cancer Care and Treatment

13

Marc S. Micozzi

Introduction

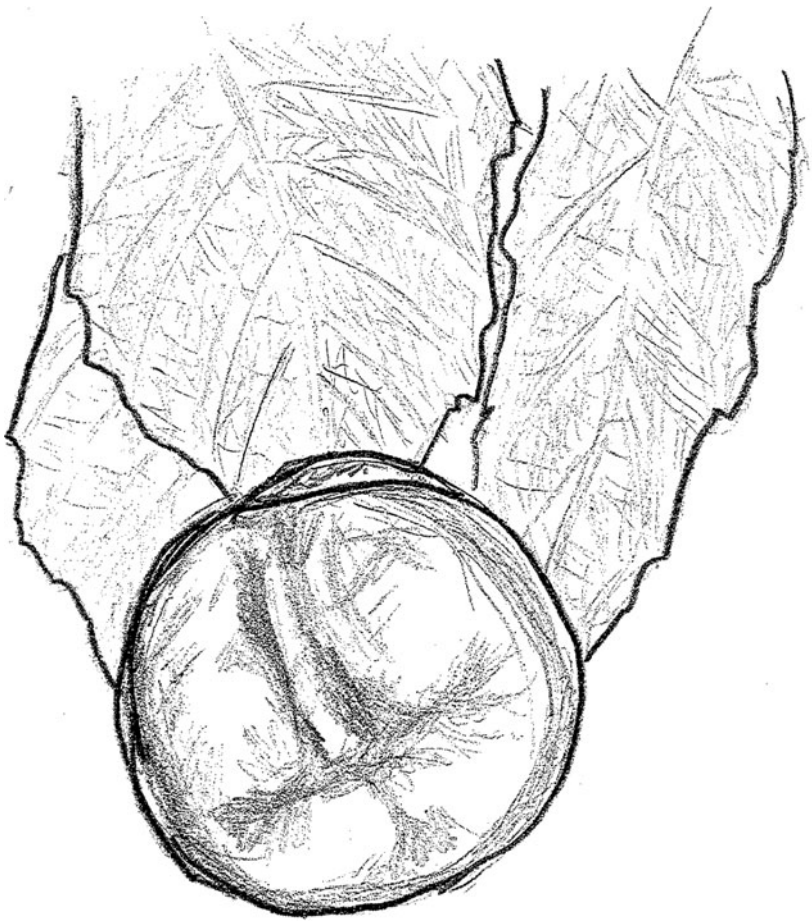
As with nutrients, plants have figured prominently in complementary care of cancer. Some medicinal plants are used in isolation (e.g., Iscador and green tea) or in combinations (e.g., Essiac and Hoxsey). Some plants that we consider as foods (e.g., garlic) are here used medicinally.

A long list of herbs and other natural products has been considered with various mechanisms of action ascribed. In alphabetic order, they are aloe vera, arsenic, berberine, bromelain, *Bufo bufo* (toad), cartilage (bovine and shark), Chinese herbs (see Chapter 15), coenzyme Q10, cysteine, dimethyl sulfoxide, echinacea, feverfew, flax, garlic, genistein, ginseng, glutathione, horse chestnut (see Figure 13.1), limonene, melatonin, quercetin, and soy (see Chapter 9). They are thought to have anticancer properties variously through effects on anticarcinogenesis (e.g., horse chestnut and cartilage), cytotoxicity, cell differentiation, hormonal balance (soy), immune stimulation (echinacea), and various combinations. A selective review of the most clinically observed herbs and herbal combinations is provided.

Iscador (Mistletoe)

Iscador is the trade name of the most commonly available brand and extract of *Viscum album*, a European species of mistletoe—a variety of mistletoe that differs from the North American species. Mistletoe was considered to be sacred in ancient times by certain Germanic tribes as well as by the Celts and Druids in Britain. It has been used in Europe as a treatment for a variety of both acute and chronic health conditions for centuries.

Figure 13.1



Horse Chestnut (*Aesculus hippocastannum*).

The use of mistletoe as a cancer therapy was popularized in the early 20th century by Rudolf Steiner, PhD (1861–1925). Dr. Steiner founded anthroposophy—a blend of spiritual and scientific concepts—and applied these principles to the practice of medicine with a particular focus on the treatment of cancer. Dr. Steiner theorized that the human body was subject to certain forces, some of which result in cell growth and multiplication ("lower organizing forces") and some of which control and organize cell growth to form tissues and organs in an orderly fashion ("higher organizing forces"). He believed that the balance between these forces determined an individual's susceptibility to cancer and that serious imbalance in these forces resulted in cancer.

Dr. Steiner studied the folk remedy mistletoe, a semiparasitic plant that lives symbiotically (in a mutually beneficial relationship) with several tree species. His observations of the biologic properties of mistletoe led him to propose the use of mistletoe extracts as a key component of cancer therapy. He observed that the overall shape of mistletoe is spherical when most other plants are vertical; its growth is not influenced by gravity,

it has no direct contact with the Earth because, unlike most other plants, it has no roots. It produces berries all year long and flowers in the winter (thereby explaining its popularity in support of amorous pursuits in winter). Steiner considered these features to indicate that mistletoe exhibits more independence from natural, gravitational, and magnetic forces; shows "strong antagonism towards regular organization" and that it would stimulate the "higher organizing forces" that he believed were needed by cancer patients.

Iscador is prepared by fermenting an aqueous (water-based) extract of the whole mistletoe plant with the bacterium *Lactobacillus plantarum*. Following fermentation the product is mixed and filtered to remove bacteria before being packaged in ampoules for injection. The ampoules contain the active ingredient in specified concentrations ranging from 0.0001 mg mistletoe extract/ampoule to 50.0 mg mistletoe extract/ampoule.

Iscador and other mistletoe preparations are subclassified according to the host tree on which the mistletoe was growing and from which it was harvested. Some of these preparations are recommended for both men and women [e.g., Iscador P (from pine trees) and Iscador U (from elm trees)], whereas others are recommended for women only [e.g., Iscador M (from apple trees)] or men only [e.g., Iscador Qu (from oak trees) or Quercus].

Today, mistletoe preparations are principally advocated and used by physicians practicing in special anthroposophic medical clinics in Switzerland and Germany that have been operating since the 1920s and where in excess of 80,000 patients have been treated with Iscador. In several European countries and in South Africa Iscador is registered for commercial purposes and can be legally prescribed. It is not commonly used in North America but can be obtained from the manufacturer (Waleda AG) in Germany or Switzerland. Some North American patients travel to European clinics for this treatment, and there are several practitioners of anthroposophic medicine who prescribe mistletoe preparations in the United States and Canada.

As is the case with many alternative therapies, proponents of Iscador recommend it be administered as one component of several "holistic" therapies. Thus, at anthroposophic clinics Iscador is given in conjunction with selected artistic, movement, and dietary therapies all intended to strengthen "higher organizing forces" and enhance natural cancer-fighting abilities. These clinics recommend concurrent administration of required conventional therapies. Iscador is most commonly administered as complementary therapy prior to surgery or following completion of chemotherapy and/or radiation.

Some Iscador preparations may be modified by the addition of very dilute concentrations of various metals. These are claimed to enhance the action of Iscador on particular body organs and systems. For example, proponents recommend the addition of silver for the treatment of diseases of the breast and urogenital system; copper for diseases of the liver, gallbladder, stomach and kidneys; and mercury for diseases of the intestine and lymphatic systems. For cancers of the tongue, oral cavity, esophagus, nasopharynx, thyroid, larynx and extremities, Iscador without added metals is utilized.

Iscador is usually administered by subcutaneous injection. It may be injected into the abdominal wall or near the tumor site, if possible. In the case of cancer of the bladder, prostate, or esophagus, anthroposophic practitioners may inject these preparations directly into the tumor. Proponents state that in some cases (for example, in patients

with tumors of the brain and spinal cord), Iscador may be administered orally, although a rationale for this difference in treatment protocol is apparently not established.

Proponents recommend that Iscador be used early in the course of the disease. Although Iscador may be administered to patients whose tumors are advanced and/or inoperable, the dosage and treatment regimen should be adjusted to take into consideration the general condition of the patient. Considering the possibility that Iscador is a cytotoxic agent and an immunomodulatory agent, close observation with appropriate lab work, including a complete blood count and standard chemistry panels, are appropriate for patients on this treatment.

A typical course of treatment requires that Iscador be administered daily early in the morning when the body temperature normally rises. However, some proponents recommend only three injections per week. Iscador is administered at gradually increasing concentrations in accordance with Steiner's protocol. In some cases it is recommended that a maintenance dose (which may often be quite high) be continued for many years depending on the individual's health and tumor status.

In the case of patients whose cancer is to be treated surgically, proponents recommend a course of injections 10 to 14 days prior to surgery followed by a maintenance dose of Iscador for a period of several years. Again, the dose and frequency of injection are determined by the general health and tumor status of the patient.

It should be noted that proponents of Iscador also recommend its use in patients who have certain conditions that may place them at increased risk of cancer such as ulcerative colitis, cervical dysplasia, leukopenia, Crohn's disease, papilloma of the bladder or colon, and senile keratoses.

Proponents claim that Iscador stimulates the immune system, causes cancerous cells to revert to more normal forms, improves general well-being and may improve survival especially in patients with cancers of the cervix, ovary, breast, stomach, colon, and lung. It is rarely claimed to reduce the size of solid tumors and is said to be less effective for nonsolid tumors, such as leukemia.

Following injections of Iscador, there is usually local inflammation (redness and swelling) at the injection site and an increase in body temperature that may be accompanied by headache and/or chills. No other evidence of toxicity has been reported. However, proponents note that the recommended dosages must be carefully followed as high concentrations may be dangerous. Several investigators have advocated the use of purified preparations of mistletoe lectins as a way of reducing the frequency of toxic effects.

Evidence

Review of the literature to assess the effectiveness of Iscador includes review of the information available on all mistletoe preparations because many do not focus specifically on the preparation marketed specifically as Iscador.

Mistletoe preparations contain a number of biologically active constituents but these vary widely depending on whether the extract is crude or fermented, on the host species (variety of tree) from which the mistletoe has been obtained, and on the season in which it was harvested. These variations make it difficult to predict the likely effects of nonstandardized mistletoe preparations, including Iscador. Despite these difficulties, research over several decades studying biologic activity of mistletoe preparations in cell cultures,

a variety of animals and among patients with cancer has identified two key components of mistletoe preparations as viscumin (also known as mistletoe lectin I) and viscotoxin.

Viscumin is a lectin (a complex protein/sugar compound that binds to cell surfaces) that can interfere with intracellular protein synthesis. Viscumin also stimulates the production of substances known as interleukins that in turn increase the number of white blood cells, which may help combat cancer.

Viscotoxin is similar to viscumin but has a different molecular structure and is cytotoxic and can cause cellular death. In addition to viscumin and viscotoxin, extracts of mistletoe contain a variety of other polysaccharides and alkaloids, some of which have been shown to have biologic activity.

Laboratory Experiments

Several in vitro experiments have confirmed the biologic activity of Iscador and of other mistletoe extracts (which may not be bacterially fermented). Iscador appears to enhance the resistance of cells to damage caused by cancer causing substances. Its use is also associated with increases in immune function. The extent to which these effects are of clinical significance in humans is unknown. The use of mistletoe lectins as a component of cancer immunotherapy is currently under evaluation. At higher concentrations mistletoe lectins appear to have the ability to kill cancer cells. Mistletoe viscotoxins have been shown to increase natural killer-cell-mediated cytotoxicity (Tabiasco et al., 2002).

Clinical Studies

In studies of patients taking Iscador there are several anecdotal reports of beneficial responses, including improvement in quality of life, pain relief, improved appetite, and higher white blood cell counts in patients exposed to chemotherapy or radiotherapy. Stabilization or reduction of tumor size, as well as increased survival, has also been reported anecdotally.

There are reports of some small case series and a few clinical trials. Results from the clinical trials have been mixed—some have suggested a beneficial effect (such as increased survival or improved quality of life) and some have shown no effect. However, all of the trials had significant design limitations, which make them difficult to interpret and seriously limit the value of their findings. Multicentered, controlled clinical studies evaluating the potential anticancer activity of Iscador have been underway in Germany. A cohort study recently evaluated the effects of Iscador mistletoe extract in cancer treatment (Grossarth-Maticek et al., 2001).

Iscador has been used in many thousands of cancer patients since the early 1930s. Although there is some evidence of biologic activity that might be expected to be beneficial to cancer patients, the evidence from human studies remains inconclusive. There is, therefore, no current scientific basis for the widespread use of mistletoe preparations. The absence of serious side effects combined with limited evidence that this agent may offer some therapeutic advantage, particularly in the area of quality of life, suggests further research is warranted (American Cancer Society, 1983; Becker, 1986; Berger & Schmahl, 1983; Beuth, et al., 1992; Bradley & Clover, 1989; Dixon et al., 1994; Gabius et al., 1992; Gawlik et al., 1992; Grossarth-Maticek et al., 2001; Hall et al., 1986; Harvey

& Colin-Jones, 1981; Holtskog et al., 1988; Jung et al., 1990; Kjaer, 1989; Kleijnen & Knipschild, 1994; Kovacs et al., 1991; Stipe et al., 1982; Wagner et al., 1986).

Green Tea

Tea is a familiar drink that we may not consider as an herb, let alone as an herbal remedy. In many parts of Asia it has been used medicinally as a "tonic" (stimulant and digestive remedy) for 5,000 years.

Tea remains popular throughout the world and is still the most frequently consumed beverage after water. The term *tea*, although commonly used to describe the infusion that results when the dried leaves and leaf buds of the shrub *Camellia sinensis* are steeped in boiling water for 5–15 min, can also be used as a generic term for any infusion made from other plants, such as herbal teas, red tea, and so on. Green tea is one of the three main types of tea prepared from *Camellia sinensis*.

Throughout the world, approximately 2.5 million tons of tea are manufactured annually. Black tea accounts for nearly 80% of production and is prepared by drying and fermenting the leaves. This is the type of tea most widely consumed in Europe, India, and North America. Oolong tea is a specialty tea and comprises only 2% of production. It is only partly fermented and is consumed mostly in southeastern China and Japan.

Green tea accounts for nearly 20% of production and is consumed mostly in China and Japan. The leaves are steamed or pan-fried and dried without fermentation. Approximately 36%, by dry weight of green tea leaves is composed of polyphenols, principally flavonols (mostly catechins), flavonoids, and flavondiols. About 4% is composed of plant alkaloids, including caffeine, theobromine, and theophylline. Other constituents include proteins, carbohydrates, phenolic acids, minerals (including fluoride and aluminum), and fibers. The precise composition of green tea (and all teas) varies with the geographic origin of the leaf, the time of harvest and the manufacturing process. It should be noted that the constituents of black tea are different from those of green tea because of the oxidation process that is part of fermentation. In black tea there are fewer polyphenols and catechins are altered.

When green tea is taken for medicinal purposes, 1–2 teaspoons of the dried herb are steeped in a cup of boiling water for about 15 minutes. Up to 3 cups a day are consumed without the addition of milk or sugar, although recent research shows that the addition of milk to the tea apparently does not alter its medicinal properties.

The medicinal use of green tea has not been reported to have adverse side effects. A cup of black or green tea contains between 10 and 80 mg of caffeine depending on the type of tea and method of preparation. Excess caffeine may cause nervousness, insomnia, and irregularities in heart rate. Herbal handbooks advise that pregnant women, nursing mothers, and patients with cardiac problems should limit their intake to no more than 2 cups daily.

A possible relation between tea consumption and cancer risk has been explored by several researchers and reports of both increased and decreased risk of cancer associated with tea drinking among populations of tea drinkers have been published. There has also been a suggestion that the consumption of very hot or highly salted beverages,

including tea, may increase the risk of cancer of the esophagus. However, when the International Agency for Research on Cancer reviewed the available information in 1989 it concluded that there was inadequate evidence to conclude that tea drinking itself presented a carcinogenic risk.

There have been a number of epidemiological studies suggesting that the regular consumption of tea, particularly green tea, decreases the risk of cancer, especially cancers of the upper digestive system. A chemopreventive effect for other cancers in humans remains controversial.

In lab studies, the effects of green tea have been contradictory and inconclusive showing both pro- and anticancer effects. However, a large number of animal studies, mostly using mice and rats, have demonstrated an anticancer effect of green tea given by mouth, by injection, or applied topically. Specifically, the application of extracts of green tea to mouse skin have been shown to inhibit the development of skin cancer in response to known skin carcinogens. Oral and intraperitoneal administration of green tea and green tea extracts have also been shown to reduce the incidence of tumors in animals exposed to carcinogenic agents.

Studies using extracts of green tea have suggested that the polyphenols present are responsible for this chemopreventive effect. Specifically the polyphenols have been shown to decrease the frequency of genetic damage in response to exposure to known carcinogens. Polyphenols are also seen to inhibit cellular proteins that may permit development of cancer (Leone et al., 2003). A particular polyphenol of interest is a flavonoid known as epigallocatechin gallate. This constituent is undergoing further research testing to determine the nature and the extent of its anticarcinogenic activity in humans.

The possible mechanism of action of the tea polyphenols against cancer is uncertain but there is some data to suggest that they function in several ways: as antioxidants decreasing the carcinogenicity of known carcinogens (e.g., UVB light and nitrosamines), by inhibiting enzymes involved in cell multiplication and DNA synthesis, and by interfering with cell to cell adhesion and by inhibiting some of the intracellular communication pathways required for cell division.

There is little research investigating the possible role of green tea in treatment of cancer. Some animal studies have shown that extracts of tea catechins injected intraperitoneally cause previously implanted breast and prostatic tumors to decrease. Several other studies have reported that green tea and green tea extracts reduce the metastatic potential of cancer cells. The capacity of cancer cells to spread to other parts of the body (i.e., their metastatic potential) results in most of the disability and death caused by cancer. The evidence that green tea extracts interfere with both the processes of cancer initiation and cancer promotion, and that they suppress chromosomal abnormalities induced by carcinogens, suggests that green tea could play a role in delaying the cumulative damage necessary for a cell to evolve from normal to cancer.

In summary, moderate consumption of green tea appears safe. There is some evidence that green tea may prevent the occurrence of some forms of cancer. There is preliminary evidence of the potential effectiveness of green tea as a supportive treatment for cancer and early studies suggest that further research would be warranted (Gao et al., 1994; Graham, 1992; He & Kies, 1994; Imanishi et al., 1991; Ito et al., 1989; Junshi, 1992; Kapadia et al., 1976; Kinlen et al., 1988; Komori et al., 1993; Lee et al., 1995; Leone et al., 2003; Oguni et al., 1988; Tewes et al., 1990; Weisberger, 1992; Yang & Wang, 1993).

Red Tea

The consumption of teas (infusions) made from the African red bush (*Aspalathus linearis*) has long been a popular pastime in South Africa. The Afrikaans name for red bush is *rooibos*. This is the name that is becoming increasingly familiar to consumers in the United States. It is a replacement for regular teas and for green tea because it is caffeine free and lower in tannins, yet has an antioxidant profile similar to that of green tea.

The science on rooibos is increasing. Studies are demonstrating that rooibos is high in many of the ingredients that are proving of interest to cancer prevention, among them the natural constituents of plants that protect the body against oxidants. Many scientists increasingly feel it is important that antioxidants come from rich mixtures of biologically active compounds in plants rather than from isolated synthetic antioxidants. For example, studies on the isolated synthetic antioxidant beta-carotene did not show it to be protective against cancer (Chapter 10). Studies of mixtures of herbal constituents, as found in teas, appear promising.

Red tea specifically contains significant levels of antioxidants that are a possible explanation for its apparent health-promoting properties. Red tea has comparable amounts of the polyphenol antioxidants, such as flavonoids, that are present in green tea. It is thought that the antioxidant effect of green tea is partially because of these phenolic components.

Studies comparing rooibos with other teas found rooibos to have similar levels of the known antioxidants associated with green tea, for example. However, rooibos appears to contain additional active antioxidant components that are not present in green and other teas. Unlike green and black tea, for example, rooibos tea also contains additional polyphenols, such as certain flavonols, flavones, and other antioxidants. These antioxidants may account for the association of teas with anticancer and other beneficial effects. These effects persist over long periods of tea consumption. In addition, rooibos is reported to act immediately, most likely because of the presence of other active plant compounds in this tea. Botanically, as a legume, rooibos contains other plant chemicals that may account for its observed short-term effects in calming the nervous system and the gastrointestinal system and other widely reported effects.

The methods of preparation of rooibos can influence its activity, and the water-soluble component of rooibos also appears active therapeutically. As rooibos has no caffeine, unlike green tea and other teas, higher consumption of rooibos can be comfortably taken without known unwanted side effects. Red tea is more appropriate for children and others who should limit caffeine intake. Studies on red tea indicate this source is an effective way to get the benefits of many of the plant chemicals that appear to help protect against cancer (Marnewick et al., 2000).

Pacific Yew and Hazelnut

In the late 1950s the National Cancer Institute (NCI) organized a nationwide search and screening program aimed at finding botanical sources with anticancer properties. To help accomplish this goal, the NCI turned to the U.S. Department of Agriculture (USDA),

who agreed to send botanical experts into the fields and forests of North America to collect a large variety of plant samples for medical research. In 1962, during the search for medicinal plant samples, members of the USDA botanical team came upon the Pacific yew tree (*Taxus brevifolia*) in the state of Washington, where the small, bushy, needle-bearing trees grow in the wild among dense canopies of old growth forests (U.S. Office of Technology Assessment 1990).

USDA botanists collected and dried samples of the Pacific yew tree bark and needles and sent them to the National Cancer Institute, where research into yew's anticancer properties began. The cancer research on the Pacific yew tree spanned 30 years, leading to a specific anticancer ingredient extracted from the yew tree bark called *paclitaxel*. In 1992, Bristol-Myers Squibb introduced paclitaxel in drug form to the market under the trademark name Taxol, with significant success. Taxol is now semisynthesized and paclitaxel from the Pacific yew tree bark is no longer used as a source or constituent of the drug.

The Pacific yew tree contains many different types of natural anticancer plant chemicals called taxanes. Paclitaxel itself is a taxane, but it is only one of many taxanes that Pacific yew contains. The primary reason that the paclitaxel taxane was selected for cancer research was that it was molecularly less complex and could be isolated and studied. Taxol stabilizes microtubular formation, which inhibits depolymerization of tubulin subunits, resulting in the cessation of cell replication during metaphase. Pacific yew (*Taxus brevefolia*) has been analyzed for its anticancer activity and has also historically been used in its natural form as tea for treating kidney problems, tuberculosis, liver dysfunction, ulcers, and digestion problems.

Historically, Native Americans crushed Pacific yew tree needles to make salves for skin cancer, skin disease, and chest poultices for bronchitis. Needles and bark were brewed as tea to relieve headaches, dizziness, colds, fever, arthritis, rheumatism, wounds, internal injuries, and scurvy, as well as for stomach, kidney, and lung problems. People in the Pacific Northwest have been brewing tea from Pacific yew tree needles for many years as a natural remedy for health problems such as colds, flu, bronchitis, arthritis, rheumatism, and fungal infections, as well as skin problems, and various types of tumors, skin lesions, or cancer.

Recently, Pacific yew has been used as a dietary supplement for thousands of patients at the Bio-Medical Cancer Clinic (Mexico). Over 2,000 cancer patients have included Pacific yew tea capsules and salves in their treatments. Patients are advised to continue the yew in their diets for 1 year. Improvement has been reported with lung cancer patients who mist their lungs with the Pacific yew tea in nebulizers. The use of Pacific yew tree salve on a 63-year-old man with basal cell carcinoma was said to eliminate irritation and produce a 70% decrease in the size of his skin lesions that had not responded to allopathic treatment.

Obvious notes of caution exist for such remedies. Given the crude delivery of such substances, practitioners have limited information about the pharmacokinetics, serum levels, dosing, and toxicity as well as long-term consequences of use of the Pacific yew tree.

Other Sources of "Taxol"

While trying to find ways to combat eastern filbert blight that was attacking hazelnut trees, researchers in Oregon "found something that looked like Taxol." The Pacific yew (*Taxus*

brevifolia) and the needles of other *Taxus* species were the main sources of paclitaxel, and it was not generally known that the substance could be found outside the Taxaceae.

In her presentation to the American Chemical Society in San Francisco on March 29, 2000, Sister Angela Hoffman announced that she had found quantities of paclitaxel in at least 12 species of hazelnut trees and at least 8 species of fungus associated with hazelnut trees. Botanically interesting is the fact that the hazelnut is a flowering tree while the yew is a conifer, which are far apart in the plant world (Meserole, 2006).

This is potentially good news for cancer patients, because hazelnut trees are now known to provide another source for the drug, and it could become less expensive and more available. The research team found paclitaxel in the nuts, shells, leaves, limbs, and bark of the hazelnut tree. The hazelnuts themselves contain very low levels of paclitaxel. There is no evidence that eating hazelnuts regularly would be clinically relevant.

Garlic

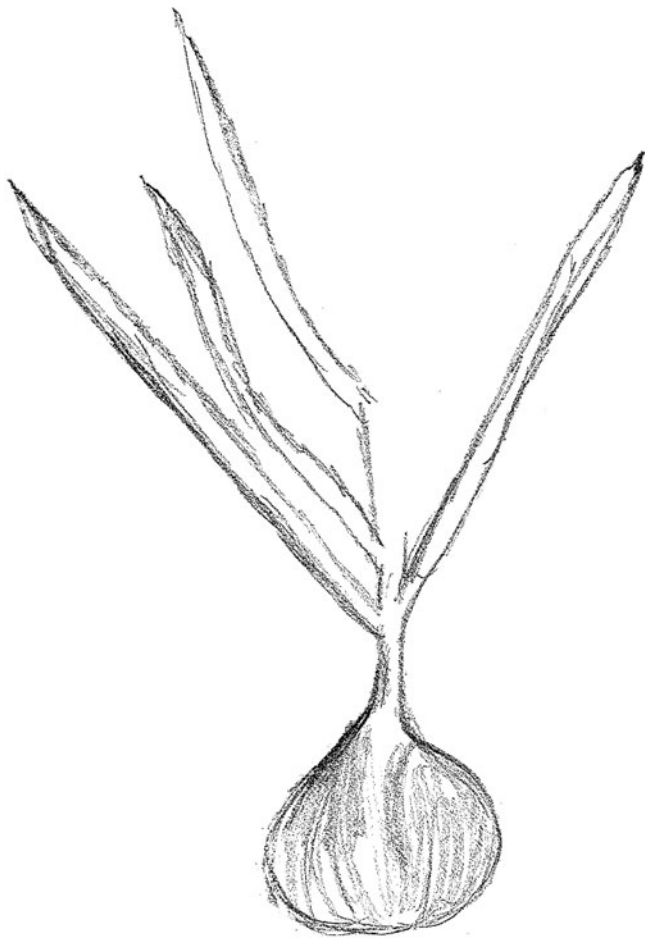
Garlic is a biologically active food with presumed medicinal properties, including possible anticancer effect (Figure 13.2). It is used as a whole food and as an herbal remedy or a natural product. In this context, garlic is covered in this chapter on natural products. Clinical studies of garlic as an herbal remedy or natural supplement in humans address three areas: (1) effect on cardiovascular-related disease and risk factors such as lipids, blood pressure, glucose, atherosclerosis, and thrombosis; (2) protective associations with cancer; and (3) clinical adverse effects. There are multiple clinical studies with promising but conflicting results. High consumer usage of garlic as a health supplement has persisted.

Scant data, primarily from case-control studies, suggest dietary garlic consumption is associated with decreased risk of laryngeal, gastric, colorectal, and endometrial cancer and adenomatous colorectal polyps. Single case-control studies suggest that dietary garlic consumption is not associated with breast or prostate cancer. No epidemiological study has assessed whether using particular types of garlic supplements is associated with reduction in cancer incidence. Preliminary evidence from a large cohort study suggest consumption of any garlic supplement does not reduce risk of breast, lung, colon, or

Table 13.1 Research Questions on Garlic

- Whether oral ingestion of garlic (fresh, cooked, or supplements) compared with no garlic, other oral supplements, or drugs lowers lipids, blood pressure, glucose, and cardiovascular morbidity and mortality
- Whether garlic increases insulin sensitivity and antithrombotic activity
- Associations between garlic and precancerous lesions, cancer, or cancer-related morbidity and mortality
- Types and frequency of adverse effects of oral, topical, and inhaled garlic dust
- Interactions between garlic and commonly used medications

Figure 13.2



Garlic (*Allium sp.*).

gastric cancer. This study had not reported associations relevant to consumption of fresh or raw garlic, and its data about supplements are limited because information is not available about different types and brands of garlic supplementations.

Cholesterol levels have been related to risk of cancer as well as heart disease. Thirty-seven randomized trials, all but one in adults, consistently showed that compared with placebo, various garlic preparations led to small, statistically significant reductions in total cholesterol at 1 month (range of average pooled reductions 1.2 to 17.3 mg per deciliter [mg/dL]). Garlic preparations studied included standardized dehydrated tablets, "aged garlic extract," oil macerates, distillates, raw garlic, and combination tablets. Statistically significant reductions in low-density lipoprotein levels (0–13.5 mg/dl) and in triglycerides (7.6–34.0 mg/dL) also were found. One multicenter trial involving 100 adults with hyperlipidemia found no difference in lipid outcomes at 3 months between persons who were given an antilipidemic agent and persons who were given a standardized dehydrated garlic preparation.

Garlic has a range of biologic activities. Twenty-seven small, randomized, placebo-controlled trials, all but one in adults and of short duration, reported mixed but never large effects of various garlic preparations on blood pressure outcomes. Most studies did not find significant differences between persons randomized to garlic compared with those randomized to placebo.

Twelve small, randomized trials, all in adults, suggested that various garlic preparations had no clinically significant effect on glucose in persons with or without diabetes. Two small short trials, both in adults, reported no statistically significant effects of garlic compared with placebo on serum insulin or C peptide levels. There are insufficient data to confirm or refute effects of garlic on clinical outcomes such as heart attack.

Adverse effects of oral ingestion of garlic are "smelly" breath and body odor. Other possible, but not proven, adverse effects include flatulence, esophageal and abdominal pain, small intestinal obstruction, contact dermatitis, rhinitis, asthma, bleeding, and heart attack. The frequency of adverse effects with oral ingestion of garlic and whether they vary by particular preparations are not established. Adverse effects of inhaled garlic dust include allergic reactions such as asthma, rhinitis, urticaria, angioedema, and anaphylaxis. Adverse effects of topical exposure to raw garlic include contact dermatitis, skin blisters, and ulcerative lesions. The frequency of reactions to inhaled garlic dust or topical exposures of garlic is not established.

Long-Term Use

Using any garlic supplement for less than 3 to 5 years was not associated with decreased risks of breast, lung, gastric, colon, or rectal cancer. Some case-control studies suggest that high dietary garlic consumption may be associated with deceased risks of laryngeal, gastric, colorectal, and endometrial cancers, and adenomatous colorectal polyps.

Notable limitations in findings from garlic research include the substantial variability in types of garlic and garlic preparations that have been studied and an inadequate definition of the active, biologically available constituents in the various preparations. In addition, many trials that evaluated the effects of garlic are limited by short durations, inadequate procedures, and lack of clear specification of contents of garlic preparations.

For the studies on associations between garlic consumption and cancer, some pertinent observations may be missed because they address associations with multiple foods and either did not report or analyze findings specific to garlic. Studies sometimes failed to distinguish the type of garlic exposure (raw, cooked, or specific supplement). Adverse effects in general are frequently underreported or reported in ways that do not allow causality and frequency to be determined.

Future studies to evaluate the effect of garlic on cancer and the main constituents of various garlic preparations must be established. Placebos designed to stimulate garlic odor should be assessed in trials. Trials that are longer than 6 months in duration and can assess cancer morbidity and mortality outcomes, as well as lipid outcomes, are needed.

Additional cohort and case-control studies that assess associations between garlic and precancerous and cancerous lesions are likely to be helpful if the frequency, types, and formulations of garlic that are consumed are specified clearly. Such studies should use sampling techniques that allow multiple levels of garlic consumption to be represented.

Consideration should be given to mounting more studies as in China, that evaluate the protective effects of different garlic preparations in persons with very high risk of

cancer or precancerous lesions. Reviews in this area should search more broadly for diet-related population studies and aim to place findings specific to garlic in a broader context that takes into account findings regarding other allium-containing vegetables, as well as other foods.

The frequency and severity of adverse effects related to garlic should be quantified. Whether adverse effects are specific to particular preparations, constituents, or doses should be elucidated. In particular, adverse effects related to bleeding and interactions with other drugs such as aspirin and anticoagulants warrant study. Garlic is a common and widely consumed herb for which the evidence regarding its anticancer activities merit serious consideration (Junshi, 1992)

Camphor

A camphor preparation called 714-X is an unconventional cancer therapy developed in Canada by Gaston Naessens, a French-born scientist and researcher, who worked out of a privately financed laboratory in Quebec for more than 30 years. Early in his career he developed a specialized microscope, which he called a *somatoscope*, that was said to enable one to examine fresh, unstained human blood and study the structure of blood cells at a significantly higher magnification than was possible at the time with ordinary light microscopes. When cells or tissues are examined under the microscope, they are usually preheated with various dyes or stains that help the observer to see the various components of the cells or tissues more clearly. However, this pretreatment process may distort cell structures. The later development of the electron microscope, which allows even higher magnification (although it does not allow the examination of fresh, unstained tissues), displaced interest in the somatoscope and other similar microscopes that used a technique known as dark-field microscopy. Using his somatoscope to examine fresh blood from healthy individuals and those with various diseases, Naessens reported that he could identify entities that he called *somatids* in the blood of individuals with serious disease, including cancer. He believed somatids to be live organisms distinct from bacteria and viruses and he described a life cycle for these organisms—the *somatidian cycle*. Specifically, he identified two distinct life cycles for the somatids—a *microcycle* consisting of three forms, which he observed in healthy individuals, and a more complex *macrocycle* consisting of 16 forms, in which somatids occur in a wide variety of shapes, some resembling bacteria, yeasts, and fungi. He stated that he usually observed this more complex life cycle in individuals with degenerative diseases, including cancer, and claimed to be able to diagnose and monitor disease processes by observing the number and forms of somatids in the blood.

Based on his own research studies, he developed the theory that the complex life cycle of the somatid only occurred when disease processes had damaged the immune system and altered the nature of the intercellular fluids. He considered that when stress or some other environmental factor initiated the somatid macrocycle the somatids secrete "toxic" substances and growth hormones (that he called *trephones*) that disrupt normal cell metabolism and cell division. He stated that under these circumstances cells become more primitive, derive their energy anaerobically, and may become cancerous. Rapidly growing cells also deplete the body of nitrogen and could be thought of as acting as

"nitrogen traps." He also believed that the metabolic disruption of immune cells caused by the somatidian macrocycle incapacitates them from effectively fighting disease and thus allows the disease to progress more rapidly.

This theory of disease in which somatids play a central role is not consistent with current thinking about the causes of diseases in general or cancer in particular. However, a number of researchers have long believed that certain bacteria, viruses, and other organisms, such as cell wall-deficient bacteria, play a more important role in the development of cancer than is generally accepted (see Chapters 1 and 2). These are bacteria that assume a variety of shapes or forms because their cell walls or boundaries are deficient in their structure. Cell wall-deficient bacteria are also sometimes known as pleomorphic organisms. Although Naessens did not hold that somatids cause cancer (or other degenerative disease), he considered their presence to be associated with degenerative diseases and regarded them as indicators of disease progression.

Although Naessens, over the years, developed a number of substances (ISO 142, Pacikom, Anablast, and 714-X) for use in the management of cancer and other conditions, this chapter focuses on so-called 714-X, the agent that is made available to cancer patients. He considered that the agent 714-X interferes with the somatidian cycle, permits recovery of the immune system and allows diseases, such as cancer, to regress. He also claimed that 714-X administered to cancer patients can decrease tumor size and the discomfort sometimes associated with cancer while improving appetite and the individual's overall sense of well-being.

The name of this agent (714-X) reflects a proprietor's ample pride in its creation. The numbers 7 and 14 stand for G and N (Naessens's initials), which are the 7th and 14th letters of the alphabet, respectively. The X stands for 1924, the year of Naessens's birth, X being the 24th letter in the alphabet.

The base of 714-X is a camphor compound that has been chemically combined with nitrogen as well as ammonium salts, sodium chloride, and ethanol. Camphor is a natural product derived from the shrub *Cinnamomum camphora*. Naessens selected camphor as the base of 714-X because he believed it has a special affinity for cancer cells. He added nitrogen because of his observation that cancer cells were "nitrogen traps" and considered that, if their needs for nitrogen were met by 714-X, the immune cells would avoid nitrogen depletion and recover to fight disease again. He also considered that nitrogen-enriched camphor decreases the cancer cells' secretion of "cocancerogenic K factor" (CKF), a substance that he believed inhibits the immune functions that would normally control cancer. Proponents state that they have isolated "CKF" but they have not provided information on its biochemical structure, and thus, other researchers have not been able to evaluate its presence and activity. Naessens also believed that the lymphatic fluid of patients with cancer becomes thickened and creates blockages in the lymphatic system. He included ammonium sulfate salts in 714-X because he believed these serve to liquefy the lymph and allow it to flow through the lymphatic system more easily. He also considered that the ammonium salts in 714-X activate certain substances released by the immune system that inhibit abnormal cell growth and enhance the healthy functioning of the immune system. 714-X is prepared as a sterile solution with the same pH as the blood.

The principle proponent of 714-X has been Gaston Naessens, assisted by his stepsons, Stephan and Daniel Sdicu, and his research associate, Jacinthe Levesque. 714-X is available by prescription under the Emergency Drug Release Program of Health Canada

when prescribed for a specific patient on compassionate grounds. The Canadian Health Protection Branch has not received the documentation of safety and efficacy required to approve 714-X for general therapeutic use. 714-X is also available in Mexico and Western Europe (distributed by the Centre D'Orthobiologie Somatidienne de l'Estrie, Inc., a Naessens enterprise) but not in the United States, where it has been under investigation by the Food and Drug Administration (FDA).

714-X is administered by injection, usually into the lymph nodes in the groin. This is a very unusual route of administration for a drug and most health care providers require special instruction to enable them to do it safely and effectively. The proponents have developed training materials (videos and printed matter) to allow caregivers to administer the agent or to allow a patient to self-administer. The area surrounding the injection site is cooled with ice packs prior to and following the injection to minimize discomfort. More recently, proponents have suggested that 714-X can be administered by nasal inhalation. In this case, 714-X is administered using a "nebulizer" similar to that used by patients with asthma. The solution consists of 0.6cc 714-X and 1.9cc saline and is recommended for patients with lung or oral cancer. Naessens does not recommend that 714-X be administered intravenously or by mouth.

Naessens and his colleagues advise that 714-X be administered each morning by injection for a least three cycles of 21 days each. A rest period of 3 days should follow each 21-day treatment cycle. Seven to 12 treatment cycles are recommended for patients with advanced cancer.

Naessens and his colleagues recommend that 714-X be used by patients with several diseases, including cancer and AIDS. They state that it can be given in conjunction with conventional therapies. Although they recommend that it be given as early as possible in the course of disease, they consider that 714-X is more likely to be beneficial in patients who have not received chemotherapy or radiation therapy. They further advise that 714-X not be administered to patients receiving vitamin B or vitamin E supplements and that no alcohol be consumed during treatment.

714-X appears to cause few side effects, although local redness, tenderness, and swelling are common at the injection site, particularly when the injection process has been difficult. There have been no published reports of infection, local or systemic, associated with the use of 714-X. An animal study found that 714-X was well tolerated and there were no noticeable side effects.

Many individuals have provided anecdotal reports of success with the use of 714-X for cancer and other disease, including AIDS. Although these testimonials are of interest, they are not reliable evidence of the effectiveness of 714-X. It is very difficult, when evaluating testimonials, to confirm the diagnosis and the stage of disease at the outset and end of treatment; assess the impact of other therapies (conventional and unconventional) that might have been used; formally evaluate outcomes such as survival, tumor growth, tumor spread or quality of life; or to compare the reported results with those of similar patients who did not use 714-X. Nonetheless, many individuals remain convinced that 714-X has helped them survive longer or better. Many of these individuals have felt so strongly about the benefits of 714-X that they have incurred significant cost and inconvenience to support Naessens in court and elsewhere when his practices have been challenged.

Naessens and his colleagues have tried to maintain appropriate follow-up of individuals who have received 714-X but they have found the data difficult to obtain from

patients and their caregivers. Accordingly, their information is incomplete. There have been very few published animal studies of the safety and/or effectiveness of 714-X and those that have been conducted have shown no beneficial effect. However, it should be noted that in these studies 714-X was administered intraperitoneally or intratumorally (directly into the tumor) rather than intralymphatically (into the lymphatic system), which is the route recommended by Naessens. At the recommended dosage, toxic effects have been minor.

A few animal studies using camphor have demonstrated some anticancer activity, specifically a positive effect on some measures of immune function, on enzymes that breakdown carcinogens, and on increasing the susceptibility of cells to radiation. This latter effect may offer some advantage if radiotherapy is employed. However, research into the effects of camphor remains at an early stage.

There is one unpublished study involving administration of 714-X to dogs and cows that developed spontaneous lymphoma. The investigators encountered several difficulties in the course of the study but were not able to demonstrate any benefit associated with the administration of 714-X in animals with this type of cancer. Clinical studies, case series, or clinical trials of the safety and effectiveness of 714-X have not been done. A "best case series," the complete data collection and follow-up on a limited number of cases considered by proponents to be their most convincing examples of success has been considered but not completed.

In summary, 714-X is a Canadian alternative cancer therapy whose use has been increasing over the past 30 years, particularly among patients with breast and prostate cancer. Its formulation and administration are based on unconventional views about the causes of cancer that are not substantiated by mainstream researchers. There are many anecdotal reports of successful outcomes among patients who have used 714-X, although there are no formal clinical studies, animal studies, or in vitro studies documenting its effectiveness.

To further evaluate 714-X, additional laboratory research in parallel with a best case series may be helpful. New information yielded by such studies would likely help in designing a future clinical trial. Proponents of 714-X have expressed an interest in a willingness to participate in research designed to assess its safety and effectiveness. Theories of cancer etiology that incorporate a role for organisms such as bacteria, viruses, and cell wall-deficient organisms may also merit further investigation.

Finally, further exploration of the potential of Naessens's somatoscope (and/or the adaptor he developed in 1991 for standard light microscopes) as a tool to assist in the diagnosis, treatment monitoring, and understanding of cancer may be justified. It is possible that the effects of 714-X are primarily related to the natural product camphor (Banerjee, 1995; Bird, 1991; Gibson et al., 1989; Goel & Rao, 1998).

Essiac

Essiac, a mixture of a least four different herbs, has been used widely since the 1920s. The original recipe is said to have been formulated in northern Ontario by an Ojibwa healer "to purify the body and place it back in balance with the great spirit." The four main

herbs in Essiac, burdock root (*Arctium lappa*), Indian rhubarb (*Rheum palmatum*), also known as turkey rhubarb, sheep sorrel (*Rumex acetosella*), and the inner bark of slippery elm (*Ulmus fulva* or *Ulmus rubra*), have also been used individually in North America among immigrants from Britain and Europe since the early 18th century. Burdock root is also a component of another unconventional therapy—the Hoxsey dietary regimen (see Hoxsey Method in this chapter)

Proponents of Essiac claim that it strengthens the immune system, improves appetite, relieves pain, and improves overall "quality of life" of cancer patients. They also claim that it may reduce tumor size and may prolong the lives of people with many types of cancer.

In the 1920s, the recipe was given to Rene Caisse, a nurse working in Bracebridge, Ontario, by a woman who believed to have been cured of breast cancer many years earlier. She had received the recipe for the herbal tea from an Ojibwa healer. Mrs. Caisse named the herbal mixture *Essiac* (her surname spelled backwards), and she prepared and administered it to several hundred cancer patients over a 40-year period. She modified the formula and reportedly administered one herb by injection, in or near the tumor site when this was possible, and the other three herbs as a tea. The recipe was further modified in the 1950s through 1970s by Rene Caisse working in partnership with an American physician, Dr. Charles Brusch. Four additional herbs (watercress, blessed thistle, red clover, and kelp) were included on the basis of a number of experiments to enhance the action of Essiac, improve its taste, and allow all herbs to be administered orally.

In Canada, Essiac was manufactured by Resperin Corporation, who obtained a formula for Essiac from Mrs. Caisse shortly before her death in 1978. It is now manufactured by Essiac Products in Brunswick and is available directly from the manufacturer or through the Emergency Drug Release program of Health Canada. Another product, Flor-Essence, manufactured in British Columbia, is said to be based on recipes provided by Rene Caisse and Dr. Charles Brusch to Mrs. Elaine Alexander and is widely available through health food stores. The proponents and manufacturers of Flor-Essence are careful not to make claims that it is useful as a cancer therapy. Rather, they promote it as a health enhancing herbal tea.

Different information sources recommend different methods of preparation and dosage. For example, some formulations require spring or nonfluoridated water, and most require refrigeration after brewing. Manufacturers usually recommend that the tea be taken one to three times a day. Because Essiac may cause nausea, vomiting, and diarrhea if taken with food or soon after meals, proponents recommend that it be taken 2 or 3 hours after meals or a least 1 hour before meals.

Most individuals trying Essiac today use it as an addition to conventional treatments or as a component of care for terminal disease after the completion of conventional chemotherapy and radiotherapy. Proponents advise the Essiac is compatible with all other cancer treatment modalities, including chemotherapy and radiation.

There are many anecdotal or testimonial reports describing positive outcomes associated with the use of Essiac in individual patients, some of which have been corroborated by physicians. However, the fact that these reports rarely classify patients by diagnosis or by the stage of their disease as a measure of extent to which the cancer is advanced makes comparison with the results of conventional treatment difficult. In addition, most

reports do not provide information on a complete series of patients treated with Essiac, including those who did and those who did not experience benefits in terms of survival. For this reason, the clinical value of Essiac as compared to conventional treatments has not been clearly established.

There is some evidence from laboratory research that each of the main herbs found in the Essiac formula have some biologic activity. However, herbalists believe that the synergistic interaction of herbal ingredients (i.e., the combined effect of the constituent herbs) is critical to their beneficial treatment effects and to the control of side effects. The proponents of Essiac also claim that its effect is dependent on the herbs being present in the correct proportions, in accordance with approved recipes. They caution that laboratory tests of single compounds, isolated from a complex formula, fail to detect possible synergistic effects resulting from the interaction of the components in a living organism. Laboratory evidence of effectiveness is established by applying an agent directly to cancer cells; it will not necessarily have the same effect when the agent is injected or ingested and metabolized in the body. Laboratory studies, using cells or animals, provide a useful indication, but not a guarantee, of the effectiveness of an agent when administered to people.

Some plant constituents found in Essiac herbs, specifically polyphenols, flavones, and polysaccharides, present in all four of the constituent herbs of Essiac, have been shown to have some antitumor and immunomodulatory activity in preliminary studies.

Studies of the four major herbs in Essiac have shown preliminary evidence of biologic activity:

Burdock root (*Arctium lappa*)

A purified extract of burdock injected into mice with transplanted solid tumors has been reported to result in tumor inhibition, slowing the growth or spread of tumor. In another study burdock was shown to reduce the ability of an agent to cause changes in the DNA of chromosomes in cell systems. Other laboratory studies have been negative.

There have been some unconfirmed reports of possible burdock toxicity. The most common side effects are those characteristic of the plant alkaloid atropine—disorientation, flushing of the skin, and the enlargement of the pupils. However, it is not clear whether these symptoms were because of burdock root toxicity or contaminants in the preparation of the specific mixtures administered to the patients.

Indian or turkey rhubarb (*Rheum palmatum*)

Extracts of rheum palmatum have been shown to cause significant tumor necrosis in a mouse study.

Another constituent of plants in the rhubarb family—aloe emodin, a naturally occurring anthraquione (a class of chemicals already used as drugs)—has been tested in mice lymphocytic leukemia and shown to have tumor inhibition properties. The activity of aloe emodin in this study varied with the extraction method used to remove and concentrate aloe emodin for testing purposes. This emphasizes the need to consider the extraction methods used, as well as the strength and potency of herbal extracts when evaluating and interpreting experiments on these agents. Some studies have suggested that emodin itself, at high doses, is a carcinogen; however, other studies have shown that it has anticancer properties when taken orally. The role of aloe emodin

and indeed most other anthraquinones as anticancer agents remains uncertain and controversial.

Slippery Elm (*Ulmus fulva or Ulmus rubra*)

This plant is known to contain a number of fatty acids and fatty acid esters.

Although the specific fatty acids and fatty acid esters in slippery elm have not been tested, similar fatty acids and fatty acid esters have been shown to have toxic activity in cell systems and in mouse studies.

Sheep Sorrel (*Rumex acetosella*)

Caisse considered this herb to be the most potent herb in the Essiac mixture. It has been used for centuries by healers in many countries and is known to contain a number of biologically active constituents. However, no cancer-related laboratory studies investigating this herb were found.

Essiac as an Herbal Mixture

There are a number of unpublished papers and letters reporting on laboratory tests using Essiac. Rene Caisse and Charles Brusch claim to have conducted studies in their efforts to refine the formula for Essiac. Unfortunately, the results of these studies have not been published. However, in a letter Dr. Brusch reported that the herbs had to be used together rather than separately to achieve an effect. Some of the other reports have yielded positive results but none of the available studies can be considered definitive Laboratory studies of Essiac conducted by Memorial Sloan-Kettering (MSK) laboratories were carried out in 1959 and from 1973 to 1976. However, the researchers encountered difficulties with their test systems, as well as with the necessary collaboration and information-sharing between Rene Caisse and MSK. Therefore they were unable to ensure that the tests of the herbal mixtures or individual herbs were appropriate or to reach any definite conclusions. Other reports are incorporated into unpublished personal correspondence and provide preliminary evidence of effectiveness. For instance, in one study mice injected with human carcinoma cells and then treated with intravenous Essiac showed more tumor necrosis and degradation than control mice. Unfortunately, these studies were never completed or published.

An unpublished Canadian study, in the late 1970s, using an oral Essiac preparation found no evidence of an effect on the cancer process but some subjective improvements in quality of life. No formal clinical studies demonstrating any observed positive outcomes in cancer patients can be attributed to the use of Essiac rather than to other therapies or to the natural history of the disease. Health Canada gave permission for Essiac to be tested for its safety and effectiveness in 1978 but withdrew this permission in 1982 when it became clear that the research was not proceeding according to plan. At the time they reviewed available, but incomplete, data derived from patients who had received Essiac during 1978–1982, they were unable to find clear evidence of improved survival. They did not evaluate other outcomes such as pain control and quality of life. However, because there was no evidence of harm, Health Canada continues to permit the release of this agent on compassionate grounds and it continues to be available in Canada as it has since the 1920s. There is weak evidence of effectiveness and little evidence of harm, and. although Essiac is a widely used agent, it remains incompletely studied (Bryson 1978, Bryson et al 1978, Caisse 1938, Rhoads et al 1985).

Hoxsey Method

A similar herbal mixture to Essiac is the Hoxsey treatment. Harry Hoxsey (1901–1974) popularized his great-grandfather's herbal formula, which had reputedly cured horses of cancer. His formula included bloodroot, burdock, buckthorn, cascara, barberry, licorice, red clover, pokeroot, zinc chloride, and antimony trisulfide. Hoxsey's controversial style led to many encounters with federal officials and the American Medical Association. At one time, Hoxsey had thousands of cancer patients going to 17 clinics across the country. With continued pressure from officials, Hoxsey was forced to close his Dallas clinic in the late 1950s and moved to Mexico to continue practicing. Hoxsey's general formula has appeared in topical ointments used to "burn away" surface skin cancers. The use of red clover in the Hoxsey mixture is of particular interest in light of recent research.

Red Clover (*Trifolium pratense*)

Red clover has been used since antiquity as a treatment for skin disorders and minor respiratory ailments. The National Formulary listed red clover as a skin remedy until the mid-1900s. In the 1940s, the flower heads found their way into Harry Hoxey's controversial anticancer formula, together with numerous other plants. Red clover contains formononetin, biochanin A, daidzein, genistein, and coumestrol, substances that act as weak estrogens in the body (see Chapter 10). Constituents within red clover have been shown to alter vaginal cytology, increase follicle stimulating hormone, and reduce luteinizing hormone in animal models. Sheep in Australia grazing on a related clover (*T. subterraneum*) developed "clover disease," a condition associated with abnormal lactation, infertility, and prolapsed uterus. These adverse effects were thought to be the result of estrogenic substances in the clover. Consumption of large amounts of red clover is associated with infertility in livestock. It is because of these "estrogenic" activities in animals that some researchers and herbal manufacturers began to explore and promote the use of red clover for relief of menopausal symptoms.

Human trials have been small and conflict with the data generated by animal studies. The largest and most recent randomized, double-blind, placebo-controlled trial of 252 menopausal women failed to find any significant benefit for two different strengths of red clover. Women who were recently postmenopausal (mean = 3.3 years since menopause) experiencing 8 hot flashes per day were included in the trial. Exclusion criteria included vegetarianism, consumption of soy products more than once per week, or ingestion of medications that would affect isoflavone absorption. After a 2-week placebo run-in, participants were randomly assigned to Promensil (82 mg of total isoflavones per day), Rimostil (57 mg of total isoflavones per day), or an identical placebo and followed-up for 12 weeks. Two hundred forty-six women (98%) completed the 12-week protocol. The reductions in mean daily hot flash count at 12 weeks were similar for the Promensil (5.1), Rimostil (5.4), and placebo (5.0) groups. However, women in the Promensil group, but not in the Rimostil group, had faster relief of hot flashes than women in the placebo

group. Quality-of-life improvements and adverse events were comparable in the three groups.

A 1999 double-blind, placebo-controlled, cross-over trial was conducted with 51 menopausal women who had been at least 6 months without menses and were experiencing at least three hot flashes per day. They received placebo or red clover extract Promensil (40 mg of total isoflavones; genistein 4 mg, daidzein 3.5 mg, biochanin 24.5 mg, formononetin 8 mg). The first phase lasted 3 months followed by a 4-week wash-out period. The second phase lasted 14 weeks. The Greene Menopause Score was used to evaluate symptoms in a diary kept by participants. At the beginning and conclusion of each phase of the trial, participants were evaluated by blood work that included a complete blood cell count, liver function tests, follicle stimulating hormone, estradiol, and sex hormone binding globulin; a 24-hour urine to test for isoflavone levels; vaginal cytology; and transvaginal ultrasound to evaluate endometrial thickness. Forty-three women completed the study. There were no significant differences between groups in Green Scores, blood work, vaginal cytology, endometrial thickness, or body weight. Hot flashes were reduced by 18% in the placebo group and by 20% in the treatment group.

Another randomized, placebo-controlled study enrolled 37 postmenopausal women who were having at least three hot flashes per day. Participants received placebo, Promesil (40 mg total isoflavones), or Promensil (160 mg total isoflavones) per day for 12 weeks. Evaluation was similar to the trial mentioned above. There were no significant differences between the three groups in blood work or vaginal cytology. Urinary isoflavone levels rose in both of the groups taking Promensil. A small but insignificant rise in urinary isoflavones was noted in the placebo group. Though not adequately confirmed, this small rise was thought to be because of the consumption of alfalfa (a phytoestrogen also included in herbal mixtures) by one participant.

These three studies are in contrast to a small randomized, double-blind, placebo-controlled trial of 30 women with more than 12 months amenorrhea and experiencing more than five hot flashes per day that showed a beneficial effect with 80 mg/d isoflavones (Promensil). After a single-blind placebo run-in for 4 weeks, the women were randomized to either 80 mg isoflavones or placebo for 12 weeks. Efficacy was measured by the decrease in number of hot flashes per day and changes in Greene Climacteric Scale Score. During the first 4 weeks of placebo the frequency of hot flashes decreased by 16%. During the subsequent double-blind phase, a further, statistically significant decrease of 44% was seen in isoflavones group, whereas no further reduction occurred within the placebo group. The Greene Score decreased in the active group by 13% and remained unchanged in the placebo group. The small sample size and low placebo response challenge the results of this study.

Safety for women who have had an estrogen receptor positive cancer is unclear. Although red clover is a prominent ingredient in the Hoxsey cancer formula, an in vitro study found that the herb was equipotent to estradiol in its ability to stimulate cell proliferation in estrogen receptor positive breast cancer cell. Other researchers found that methanol extracts of red clover showed significant competitive binding to estrogen receptors alpha (ER alpha) and beta (ER beta) and exhibited estrogenic activity in cultured endometrial cells. Until further research is available, it would seem wise to avoid prolonged use of red clover in women with a history of breast cancer. This is especially true given the fact that three of four trials, including the largest and best done study, fail to show any clinically significant benefit for relieving menopausal symptoms.

Figure 13.3

Ginseng (*Panax sp.*).

Chinese Herbal Mixtures

PC-SPES Chinese Herbal Mixture

PC-SPES is a traditional Chinese herbal preparation used for the treatment of prostate cancer. Commercially available since November 1996, PC-SPES consists of extracts from the following eight distinct herbs: *Dendrantherma morifolium, Tzvel; Ganoderma lucidium, Karst; Glycyrrhiza glabra* L.*; Isatis indigotica, Fort; Panax pseudo-ginseng, Wall; Robdosia rubescens; Scutellaria baicalensis, Georgi;* and *Serenoa repens* (Figure 13.3; Table 13.2). Three studies evaluating PC-SPES have been published in peer-reviewed journals.

A joint study conducted by the UCSF Comprehensive Cancer Center and Memorial Sloan-Kettering Cancer Center used PC-SPES to treat 32 patients with

androgen-dependent or -independent prostate cancer. After treatment with PC-SPES, all those in the androgen-dependent group had a PSA decline of more than 80%. In the androgen-independent group, 54% of patients had a PSA decline of more than 50%.

Two other studies indicated PC-SPES is effective in alleviating symptoms of advanced prostate cancer in patients, including those who have failed conventional therapy. Researchers at the Brander Cancer Institute propose that this complex composition of herbal material could "target many signal transduction and metabolic pathways simultaneously thereby eliminating the back-up and redundant mechanisms that otherwise promote cell survival when single-target agents are used."

Workers at Columbia University, in collaboration with French researchers, demonstrated that PC-SPES can induce apoptosis of cancer cells in vitro. PC-SPES was also effective in suppressing the growth rate of hormone insensitive prostate cancer cells in human volunteers.

All three studies agreed that PC-SPES appeared to stabilize the disease and improve quality of life in patients suffering from advanced prostate cancer. With the exception of a low incidence of deep venous thrombosis or thromboembolic events, side effects of PC-SPES are relatively mild and comparable to those associated with estrogen treatment.

The Brander study suggests that because of its complex make-up, PC-SPES is potentially able to eliminate back-up mechanisms that otherwise promote cell survival. Among major concerns associated with both single herb commodities and multiherb patents are herb/herb and herb/drug interactions. Complex preparations, such as PC-SPES, represent a challenge from the standpoint of authentication, quality control, and standardization. Recently, an National Institutes of Health-sponsored study of PC-SPES ran into difficulty when it was discovered that the PC-SPES source was adulterated (as may often be the case with herbs from China). Controversy ensued about halting the study because many of the enrolled subjects nonetheless experienced benefits and wanted to continue the treatments.

Safety and Herb/Drug Interactions

Herb safety and herb/drug interactions are complex and controversial issues. With the increasing use of herbs by Westerners has come legitimate concern for potential abuse and toxicity. The safety of a drug, herb, or food is always relative and contextual. Safety

Table 13.2

PC-SPES Formula Composed of Eight Herbs

- Chrysanthemum flowers (*Chrysanthemum morifolium*)
- Reishi mushroom (*Ganoderma lucidum*) (see Mushrooms in this chapter)
- Licorice root (*Glycyrrhiza glabra*)
- Dyer's woad (*Isatis indigotica*)
- Sanchi ginseng (*Panax pseudoginseng*)
- *Huang qui* or Baikal skullcap root (*Scutellaria baicalensis*)
- *Radhosia rubescens*, Lamiaceae [D1]
- Saw Palmetto fruit (*Serenoa repens*)

is determined by defining the conditions under which a substance is considered to be safe or dangerous and weighing potential benefits against possible short and long-term adverse effects. Herb/drug interaction is a similar puzzle: All substances that enter the body interact with each other, ultimately affecting all body processes. The issue, again, is determining the benefit or detriment of such interactions.

Compared to the record of approved pharmaceutical drugs, with a few well-known exceptions such as *Aconitum carmichaelii* (*fu zi*), Cinnabaris (*zhu sha*), *Aristolochia fangchi* (*guang fang ji*), and *Ephedra sinica* (*ma huang*), Chinese medicinal herbs are safer. Aconite contains aconitine, a recognized poison that is traditionally detoxified by boiling and then combined with other herbs such as *Zingiberis officinale* (*jiang*) (Figure 13.3), *Ziziphus jujuba* (*da zao*), and *Glycyrrhiza uralensis* (*gan cao*) that further mitigate its toxicity, yielding important therapeutic benefits. For example, treated Aconite is combined with *Panax ginseng* in the treatment of acute cardiac failure. Cinnabaris, a crude ore, contains mercuric oxide and although considered unsafe by American standards, it is still utilized in small doses in China for the short-term treatment of acute mental agitation without negative consequences. Many *Aristolochia* species have recently been shown to exert carcinogenic effects when used continuously for longer than 6 months, yet these species continue to be used in China with good results in the treatment of cancer and nephropathy, the very conditions for which they have been considered causative agents in the West. *Ephedra sinica* (*ma huang*) has appropriately been used as an antiasthmatic, antitussive diaphoretic, and vasodilating component of numerous pulmonary and antiarthritic formulas for centuries. In the United States since the late 1970s, *Ephedra* has been inappropriately marketed over the counter as a natural energy and weight loss stimulant, resulting in incidences of high blood pressure, palpitations, agitation, and insomnia. It is unfortunate that abuse and misuse have caused herbs such as these to become less available to professional health care providers and have cast a dark shadow over the credibility and safety of Chinese medicinal herbs in general.

The hundreds of herbs that are in common use in China and the West are rarely associated with adverse effects that are not easily reversible. These effects are seldom serious and include such transient reactions as nausea, indigestion, diarrhea, headache, dizziness, hot flashes, chills, and rashes that are rapidly abated by discontinued use or dose reduction. The preponderance of evidence shows that when used as an adjunct to conventional medicine, Chinese herbs both enhance the desired effects and mitigate the harmful ones.

Sophisticated monitoring with biologic testing, sterilization, and spectrographic analyses by manufacturers in the United States is ensuring that herbal products are free of chemical contaminants, adulterants, pathogens, and substitutions. This heightened awareness along with stringent standards is encouraging Chinese manufacturers to adopt the good manufacturing practices required by the Food and Drug Administration and the Federal Trade Commission.

There is a paucity of data that describe the interactions between pharmaceutical agents and even less between herbs and drugs. A few herbs and foods have well-understood interactions with drugs. Tetracycline absorption can be impeded by milk-based foods, whereas grapefruit juice increases the blood volume of certain drugs (e.g., antidepressants, antihistamines, and antihypertensives) by inhibiting a drug-metabolizing enzyme (cytochrome P-450). *Hypericum perforatum* (St. John's Wort; *tian ji huang*) reduces blood

Figure 13.4

Ginger (*Zingiber officinale*).

levels of protease inhibitors by increasing their metabolism while potentiating the effects of monoamine oxidase and selective serotonin reuptake inhibitor antidepressants by elevating seratonin levels. Green vegetables high in vitamin K can oppose the blood-thinning action of drugs such as heparin, Coumadin or warfarin. Because *Gingko biloba* (*yin guo ye*), *Salvia miltiorrhiza* (*dan shen*), and *Angelica sinensis* (*dang gui*) promote microcirculation and inhibit platelet aggregation, they can potentiate the effects of anticoagulants, as can *Allium sativum* (garlic; *da suan*) (Figure 13.2) and *Zingiberis officinale* (ginger; *jiang*) (Figure 13.4). *Astragalus membranaceus* (*huang qi*), because of its immunostimulating properties, may counter the immunosuppressive action of antirejection drugs such as cyclosporin. In high doses, *Glycyrrhiza uralensis* (licorice; *gan cao*) can mimic the action of cortisol, elevating blood pressure and increasing fluid retention. These findings are based on the use of these herbs as single agents.

When *Angelica sinensis* is incorporated into a formula such as *Shi Quan Da Bu Tang*, which supplements *qi* and *blood* and activates circulation, its hematopoietic properties are enhanced and its anticoagulant properties are reduced by the inclusion of herbs such as *Rehmannia glutinosa* (*di huang*) and *Peonia lactiiflora* (*bai shao*), making it an effective

treatment for the anemia, bruising, and bleeding caused by radiation and chemotherapy. One of the side effects of standard anticoagulant therapy is anemia. To solve this problem with Chinese medicine, the herbs *Panax pseudoginseng* (*tian qi*) and *Millettia reticulata* (*ji xue teng*) are used because of their triple hematopoietic, circulation-activating, and antihemorrhagic properties. *Glycyrrhiza uralensis* is ubiquitous, appearing in countless formulas in part because of its ability to modulate adrenal function. For example, the decoction of *Bupleurum chinense* (*chai hu*) and *Poria cocos* (*fu ling*) (*Chai Ling Tang*) contains many herbs, including *Glycyrrhiza uralensis*, and is used to aid in the withdrawal from corticosteroid dependence.

Rather than suggesting that people stop eating grapefruit or green vegetables, new information is broadening our understanding of the complexity of drug/food and drug/herb combinations, enhancing our ability to make prudent choices. Biologist Subhuti Dharmananda, PhD, suggests,

> Herb-drug interactions may be minimized by having patients take the herbs and drugs at different times (one hour apart to avoid direct interaction in the digestive tract; 1.5 hours to avoid maximum blood levels of drug and herb at the same time). The dosage of herbs that are aimed therapeutically at the same function as the drugs (e.g. both are sedatives; both are hypoglycemics; both are anti-coagulants) should be reduced to alleviate concerns about additive or synergistic effects that are too great. A certain level of additive effects might be desired in cases where the drug therapy is not producing the desired response.

Anecdotal Report

From 1984 to 1997 William Fair was the Chairman of the Department of Urology at Memorial Sloan-Kettering Cancer Center in Manhattan, directing surgical oncology research projects. Oncologist Jerome Groopman recorded his story in a *New Yorker* article appearing in 1998. In 1994 Dr. Fair was diagnosed with colon cancer, and during surgery he was found to have two lymph nodes adjacent to the tumor site with signs of metastatic disease. His statistical chances of 5-year survival were 40%, and his cancer type was particularly resistant to both radiation and chemotherapy. He underwent adjuvant chemotherapy initially for 3 months and then for another 12-month period. In 1997 a mass was found in a lymph node near his liver. Suddenly his 5-year survival chances had reduced to 1 in 10, with no viable conventional treatment options. Research associates of Dr. Fair harvested cells from his tumor and proceeded to grow his cell line in mice. Because Fair's tumor was found to have a p53 mutation, he was determined to be a good candidate for the Chinese herbal preparation SPES, the parent formula for PC SPES developed for prostate cancer by Dr. Xu-Hui Wang at Shanghai Medical University in conjunction with Sophie Chen at New York Medical College. First the herbal preparation was tested on Fair's tumor-bearing mice. Within several weeks, the tumors in the SPES-fed mice regressed by 50%, whereas the masses in the control group grew. Then Dr. Fair began ingesting large doses of the formula for more than a year, and his tumors shrunk, with no evidence of new tumor growth. By 2002, Dr. Fair continued to enjoy the benefits of his personal experiment with Chinese herbal medicine before eventually succumbing to the disease.

Mushrooms and Mushroom Extracts

Although there has been relatively little clinical research and few clinical observations in the United States, interest has developed over the years in the potential anticancer effects of certain mushrooms and their constituents. Since the early 1970s, reports of possible anticancer activities have been coming to light, primarily from Asia. Historically, herbalists and other healers have ascribed various healing properties to mushrooms. There have been many attempts to market various mushrooms by elements of the natural products industry without any research to substantiate the claimed attributes. Patients should be cautioned against the common claims for mushrooms made in marketing materials.

There has been strong interest and experience in medical practice with various toxic mushrooms and the effects of and treatments for mushroom poisoning. These biologic properties may point to the potential for other potent activities of mushrooms against cancer. Many of the most effective chemotherapeutic drugs have cytotoxic activities against cancer cells that are also quite toxic to the patient (see Chapter 1).

Sun soup is a traditional Chinese herbal mixture that contains Chinese mushrooms (see Chapter 15). Some studies have been conducted in China on traditional Chinese medicine combined with radiation and chemotherapy for cancer. In Japan, interest has centered on the shiitake and maitake mushrooms. In addition, extracts of the *Coriolus versicolor* (Turkey tail) mushroom have been studied in the laboratory.

As part of their metabolic activity, mushrooms produce a variety of polysaccharides. Polysaccharides form components of cellular walls in plants and cellular membranes in animals and appear to play a role in cellular communication. As a result of these properties, specific polysaccharides are known to stimulate the immune system. The immune system may recognize certain polysaccharides on cells as foreign. This characteristic is one mechanism by which the immune system may recognize and attack a cancer cell.

The immune system cells involved in recognizing and killing cancer cells are known as natural killer (NK) cells. Some of the mushrooms used for cancer in traditional Asian medicine appear to contain polysaccharides that activate these immune system NK cells. In addition, some mushroom extracts are able to directly kill cancer cells in vitro but are not harmful to normal cells.

These observations have been made with mushrooms that are edible, such as shiitake, maitake, and gandoderma. Other polysaccharides have been extracted from mushrooms that are not edible, or poisonous. Some polysaccharides from mushrooms may also help protect the bone marrow from the harmful effects of chemotherapy and may ultimately find clinical application in complementary cancer care.

Phase I, II, and III clinical trials are under way in Japan to evaluate the use of mushrooms as adjunctive therapy to chemotherapy. The National Cancer Center Research Institute of Japan demonstrated in a 15-year epidemiological study from 1972 to 1986 whereby among close to 175,000 individuals, farmers of the edible mushroom *Flammulina velutipes* had overall lower cancer death rates when compared to those of nonfarmer populations (160.1 per 100,000 compared to 97.1 per 100,000).

A case-control study from Korea evaluating 272 patients adjusted for sex, age, socioeconomic status, family history of gastric cancer, and duration of refrigerator use found

an odds ratio of 0.38 for medium intake and high intake of mushrooms and prevalence of gastric cancer.

The only randomized, placebo-controlled, double-blind study known by these authors was conducted using a polysaccharide peptide isolate of *Coriolus versicolor* in a total of 68 patients with advanced nonsmall cell lung cancer. Leukocyte and immunoglobulin levels were found to be increased in the intervention group, but no complete or partial responders were noted. More patients withdrew from the study in the placebo group, possibly indicating a reduced rate of deterioration from the intervention.

Essential Oils Therapy

Essential oils therapy (often called aromatherapy) is the therapeutic use of essential oils extracted from plants and is often applied to supportive care of the cancer patient. Food and perfume industries are the largest users of essential oils. Some confusion about the therapeutic potential of aromatherapy may be because of this link with the cosmetic industry. Essential oils are described as oils forming the odiferous part of plants and are ethereal, suggesting not only a chemical constituent but also a spiritlike or airy quality. Aromatherapy treatment uses a range of organic compounds of which the odor or fragrance play an important part.

Essential oils are extracted from different parts of plants such as the roots, bark, stalks, flowers, or leaves. These extracts are mostly distilled, although other methods might be used. Essential oils might be applied to the body via massage with a vegetable oil, inhaled, used as a compress, mixed into an ointment, or inserted internally through the rectum, vagina, or mouth. The latter method is used chiefly by the medical profession in France.

Modern-day aromatherapy is one of the fastest growing complementary therapies. This growth includes not only training and practice of aromatherapy but also production of essential oils. Aromatherapy gradually is becoming more accepted in the orthodox medical field as a treatment to enhance both physical and psychologic aspects of cancer patient care.

Essential Oils

Essential oils are volatile, fragrant, organic constituents that are obtained from plants either by distillation, which is most common, or by cold pressing, which is used for the extraction of citrus oils. Oils may be extracted from leaves (e.g., eucalyptus and peppermint), flowers (e.g., lavender and rose), blossoms (e.g., orange blossom or neroli), fruits (e.g., lemon and mandarin), grasses (e.g., lemongrass), wood (e.g., camphor and sandalwood), barks (e.g., cinnamon), gum (e.g., frankincense), bulbs (e.g., garlic and onion), roots (e.g., calamus), or dried flower buds (e.g., clove). Varying amounts of essential oil can be extracted from a particular plant; 220 pounds of rose petals will yield less than 2 ounces of the essential oil, whereas other plants, such as lavender, lemon, or eucalyptus, yield a much greater proportion. This accounts for the variation in price among essential oils. Essential oils come from sources worldwide, such as lavender from France, eucalyptus from Australia, and sandalwood from India.