Cancer

PHUONG THI KIM PHAM and ARON PRIMACK

Cancer is a major disease category in current health care for people of all ages. Even with beneficial programs, however, such as early detection of breast cancer with improved screening techniques, the overall incidence and mortality attributable to the major cancers (e.g., lung, breast, colon, prostate) have changed little over the past three decades, and conventional medical treatments are inadequate. Considerable progress has been made in genetic research explicating many reasons for susceptibility to cancer.

Radical surgical treatment for cancer has been replaced by more focused surgical approaches in combination with other methods, including radiation therapy, brachytherapy, chemotherapy, and immunotherapy, with some improvement in results. Even with the burgeoning number of new chemotherapeutic agents, however, as well as the general acceptance of severe toxic effects and the many new products to ameliorate these potentially life-threatening toxicities, medical treatment of cancer has resulted in minimal statistical improvement over several decades. Although radiation therapy often can control local areas of disease, local recurrences, and specific complications, it falls short in overall cure rates and longevity.

This chapter delineates some of the cancer treatments in complementary and alternative medicine (CAM) and results of usage of these therapies. Rather than an all-inclusive listing of treatments attempted, used, or rejected, this discussion focuses on directions that have been taken and that need to be taken for CAM to be adjudicated, understood, and incorporated into medical treatment as CAM cancer therapies become scientifically validated.

Survey Results on Usage of CAM Therapies

Patients generally use CAM for chronic diseases such as back pain, headaches, arthritis, musculoskeletal pain, insomnia, depression, and anxiety. However, patients with
cancer are frequent users of CAM therapy as well, often for the accompanying chronic symptoms. Most patients who are using CAM therapy for their diabetes, cancer, and hypertension are also seen by conventional medical practitioners. They have not circumvented the established medical system.

In a survey done in the 1980s and one of the first surveys on CAM usage, Cassileth et al. reported that 54% of patients ($n = 304$) in a major cancer center were also using CAM, 40% of whom ultimately abandoned conventional therapy in favor of CAM. About 60% of the practitioners of CAM were physicians. Patients who used CAM were more likely to be white and well educated. The most common CAM therapies were metabolic treatments, diet treatments, megavitamins, imagery, spiritual treatments, and "immune" treatments. Patients chose CAM to assume personal responsibility for their care and because of an underlying belief that pollution and diet caused the cancer and therefore avoidance of pollution and modification of diet were the best approaches to its cure. Satisfaction with CAM treatment was reflected in the 43% of patients who believed vitamin therapy helped their cancer and 58% who believed vitamins helped their overall health.

Banner et al. found that 28% of breast and cervical cancer patients in Hawaii used traditional Hawaiian remedies the year before the survey; 14% had sought help from a Hawaiian healer; and 6% said traditional therapy would be their first source of medical assistance. Further, Lerner and Kennedy performed a statistically valid sampling study using telephone interviews of 5047 patients with cancer, almost all of whom were treated with conventional medicine, including surgery (69%), radiation therapy (33%), and chemotherapy (33%). Of these, 9% used at least one type of CAM. Women and men used CAM about equally, 9.2% and 8.7%. CAM usage rose proportionately with increased wealth, age less than 49 years, increasing education, and larger size of the household. Patients generally learned of these alternative methods of treatment from physicians, but the news media and television were also instrumental, along with word of mouth from family and friends. Some types of cancer were associated with CAM more often, including central nervous system (21%), lymphoma (14.5%), and ovarian (16%). The longer the patient had a malignancy, the more likely the patient was to seek alternative therapy. If the cancer was still in evidence at 5 years, 10% were using alternative therapy, and 6% with no evidence of disease used CAM. Diet therapies were more often used by women, mind-body therapies by men, and drug therapies equally.

More recently a survey of 453 outpatients at a comprehensive cancer center indicated that 69% of cancer patients used CAM treatment, excluding spiritual practices and psychotherapy. Further, of 100 adult cancer patients in a private nonprofit south Florida hospital, 80% reported using some type of CAM. The International Union Against Cancer (UICC) e-mail survey has also shown a large and heterogeneous group of CAM remedies used to treat cancer in both developed and developing countries worldwide.

Lerner and Kennedy reported that 44% of patients were using CAM after conventional therapy, presumably because of residual disease; 20% were using CAM simultaneously with conventional medicine; and 17% were using CAM before conventional therapy, possibly leading to delayed treatment and reduced chance of cure.
from the conventional approach. The authors found that patients rarely discontinued their visits to their conventional therapist once they started CAM; 58% of these CAM users believed they were likely to be cured by the therapy, and 25% of CAM costs was covered through third-party health insurance.

Lerner and Kennedy concluded that “it is evident that physicians must become familiar with questionable cancer therapies, must make it known to patients that they are available to discuss questionable methods, and must then, without criticism, direct patients to appropriate sources of care and additional information.” They added the following:

Whereas some questionable therapies are harmless or inexpensive, others have toxic effects and may be costly, and none has scientifically proven efficacy. Although the percentage of usage reported is relatively low, overall large numbers of patients are involved, especially in certain groups. The physician plays a key role in encouraging or preventing the use of questionable methods, and substantial improvements in public and professional education are needed.

Cancer patients may use CAM more frequently than what standard history and physical examination might record. Because these therapies may interact with conventional treatments and cause significant side effects, it is crucial for medical oncologists to inquire with explicit questions about the use of CAM in order to guide patients using these therapies.

The use of CAM in children with cancer reveals that 10%, presumably through their parents, had previously consulted CAM practitioners, most often using chiropractic, homeopathy, naturopathy, hypnotherapy with relaxation, and acupuncture. They were generally older children with better-educated mothers. Some children were given megavitamins, which could have serious negative consequences. The most common cancer-related medical conditions were respiratory illness, musculoskeletal problems, dermatologic conditions, gastrointestinal problems, and allergies. A recent study in Saskatchewan indicates that 36% of participating families reported using CAM for their child’s cancer and that another 21% considered CAM.

CAM is used worldwide for cancer treatment (Table 4-1).

PHYSICIAN AND PATIENT ISSUES

The most common reasons that people with cancer seek CAM treatment are the (1) appeal of natural holistic remedies, (2) possibility of improving quality and quantity of life when the allopathic community says “nothing can be done,” (3) need to have a sense of control over own life, (4) pressure from family and friends, and (5) mistrust of the conventional medical establishment and authority figures in general. Further, allopathic medicine can be expensive. Scientific cancer medicine demands an appropriate, clear diagnosis, which requires a biopsy. Testing often includes costly radiographic imaging studies and laboratory evaluation. The therapy itself, including surgery, chemotherapy, and radiation therapy, can be very costly.

CAM, with its stress on natural products, teas, herbs, electric stimulation, massage, and so forth, often is much less expensive per treatment. Cancer patients often
<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Patients</th>
<th>CAM Usage</th>
<th>Specific Findings</th>
<th>Most Common Therapies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Downer et al.87</td>
<td>Great Britain</td>
<td>415</td>
<td>16%</td>
<td>—</td>
<td>Healing, relaxation, diet, homeopathy, vitamin</td>
</tr>
<tr>
<td>Lerner, Kennedy211</td>
<td>United States</td>
<td>5047</td>
<td>9%</td>
<td>—</td>
<td>Diet, mind/body, drug</td>
</tr>
<tr>
<td>Begbie et al.26</td>
<td>Australia</td>
<td>335</td>
<td>21.9%</td>
<td>Young adults, women, married/single, well educated, desire for “natural” therapies</td>
<td>Diet, psychologic, herbal remedies</td>
</tr>
<tr>
<td>Cassileth, Chapman53</td>
<td>United States</td>
<td>660</td>
<td>54%</td>
<td>—</td>
<td>Metabolic, diet, megavitamin, imagery, spiritual, ”immune”</td>
</tr>
<tr>
<td>Fisher, Word67</td>
<td>England</td>
<td>Not given</td>
<td>16%</td>
<td>—</td>
<td>Acupuncture</td>
</tr>
<tr>
<td>Sawyer et al.323</td>
<td>Australia</td>
<td>48</td>
<td>46%</td>
<td>Positive imagery, hypnosis, relaxation, exercise, diet, vitamin, herbal</td>
<td>—</td>
</tr>
<tr>
<td>Morant et al.359</td>
<td>Switzerland</td>
<td>160</td>
<td>53%</td>
<td>Younger/older</td>
<td>Herbal teas, beetroot extracts, laying on hands, homeopathy, Iscador, magnetic, diet, acupuncture, psychologic</td>
</tr>
<tr>
<td>Pawlitschek et al.360</td>
<td>Poland</td>
<td>70</td>
<td>25%</td>
<td>Caused delay in conventional medicine usage</td>
<td>—</td>
</tr>
<tr>
<td>Munstedt et al.259</td>
<td>Germany</td>
<td>206</td>
<td>39%</td>
<td>—</td>
<td>Mistletoe, trace minerals, megavitamin, enzyme</td>
</tr>
<tr>
<td>Helany31</td>
<td>France</td>
<td>—</td>
<td>52%</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Study</td>
<td>Country</td>
<td>Sample Size</td>
<td>CAM Use</td>
<td>CAM Methods</td>
<td></td>
</tr>
<tr>
<td>----------------------------</td>
<td>------------------</td>
<td>-------------</td>
<td>---------</td>
<td>-----------------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>Dady et al.</td>
<td>New Zealand</td>
<td>464</td>
<td>32%†</td>
<td>Diet, vitamin, Laetrile, magnetic resonance, faith healing</td>
<td></td>
</tr>
<tr>
<td>Richardson et al.</td>
<td>United States</td>
<td>453</td>
<td>83.3%</td>
<td>Improve patient-provider communication and research to reduce potentially harmful drug-herb-vitamin interactions.</td>
<td></td>
</tr>
<tr>
<td>Bernstein et al.</td>
<td>United States</td>
<td>100</td>
<td>80%</td>
<td>Health care professionals must be educated about most common therapies as more patients use CAM remedies.</td>
<td></td>
</tr>
<tr>
<td>Cassileth et al.</td>
<td>33 countries</td>
<td>83</td>
<td></td>
<td>Large heterogeneous group of CAM remedies is used to treat cancer in both developed and developing countries.</td>
<td></td>
</tr>
<tr>
<td>Metz et al.</td>
<td>United States</td>
<td>196</td>
<td>40%</td>
<td>Of 79 patients using CAM, 84% were identified by directed questioning and 16% by standard history and physical examination.</td>
<td></td>
</tr>
</tbody>
</table>

*Cancer in women.
† CAM advised generally along with conventional treatments.
seek an integrative approach to treatment, using both conventional medicine and CAM simultaneously. A huge amount of money is spent on CAM, but much less per treatment; exceptions include megavitamin therapy, chiropractic, antineoplastons, and dietary therapy in specialized spas, all of which may cost more than allopathic treatment. However, naturopathic treatment seems to be a small expense compared with allopathic medicine.92–94

Montbriand252 found that 75% of her 300 informants did not tell their physician they were using some type of alternative therapy for treatment of cancer. With such a high prevalence of alternative treatments, it is important for conventional medical practitioners to know which therapies their patients are using. There is significant risk of product interactions,79 such as interactions between herbal medicines and prescribed drugs,169 and of clinical effects, which could confuse the patient’s diagnosis. Some CAM treatments have potentially harmful effects173 (Table 4–2).

<table>
<thead>
<tr>
<th>Plant/Plant Product</th>
<th>Active Ingredient</th>
<th>Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Comfrey*</td>
<td>Pyrrolizidine alkaloids</td>
<td>Hepatic; primary pulmonary hypertension</td>
</tr>
<tr>
<td>Senecio/Crotalaria spp.</td>
<td>Pyrrolizidine alkaloids</td>
<td>Venocclusive disease</td>
</tr>
<tr>
<td>Heliostropium</td>
<td>Unknown</td>
<td>Hepatic failure</td>
</tr>
<tr>
<td>Pa sea tea corylifolia (babchi)</td>
<td>Pyrrolizidine</td>
<td>Ascites, hepatic disease</td>
</tr>
<tr>
<td>Piper methysticum (kava,97 kovakova)</td>
<td>Psoralen</td>
<td>Photosensitivity</td>
</tr>
<tr>
<td>Cantha edulis (khat)</td>
<td>Unknown</td>
<td>Stimulates then depresses central nervous system</td>
</tr>
<tr>
<td>Datura (thornapple, jimson weed)</td>
<td>Hyoscyamine</td>
<td>Psychosis, optic atrophy, pharyngeal cancer</td>
</tr>
<tr>
<td>Valerian, skullcap†</td>
<td>Unknown</td>
<td>Hallucinations</td>
</tr>
<tr>
<td>Taheoba</td>
<td>Unknown</td>
<td>Liver damage</td>
</tr>
<tr>
<td>Aloe vera</td>
<td>Unknown</td>
<td>Bleeding</td>
</tr>
<tr>
<td>Arnica</td>
<td>Unknown</td>
<td>Laxative: low vitamin K levels</td>
</tr>
<tr>
<td>Alfalfa</td>
<td>Canavanine</td>
<td>Cardiac</td>
</tr>
<tr>
<td>Aristolochia (Virginia snakeroot)</td>
<td>Unknown</td>
<td>Nephrotoxicity; squamous cell carcinoma of stomach in rats</td>
</tr>
<tr>
<td>Coffee enemas</td>
<td>Unknown</td>
<td>Fluid/electrolyte imbalance</td>
</tr>
<tr>
<td>Ginseng</td>
<td>Sugars, steroids, saponins</td>
<td>Swollen tender breasts, vaginal bleeding, hypertension</td>
</tr>
<tr>
<td>Fungi (Psilocybe spp.)</td>
<td>Psilocybin, psilocin</td>
<td>Hallucinations</td>
</tr>
<tr>
<td>Lawsonia alba (henna dyes)</td>
<td>Unknown</td>
<td>Edema of face, lips, epiglottis, pharynx, neck, bronchi; anuria; acute renal failure</td>
</tr>
<tr>
<td>“Black powder” † (phenylethlyamine)</td>
<td>Unknown</td>
<td>Skin irritation, eczematoid dermatitis, vertigo; anemia, gastritis</td>
</tr>
<tr>
<td>Lasthile (vitamin B₁₂)</td>
<td>Hydrogen cyanide</td>
<td>Cyanide poisoning</td>
</tr>
<tr>
<td>Glycyrrhiza glabra (licorice)</td>
<td>Unknown</td>
<td>Hypokalemia, ventricular fibrillation</td>
</tr>
<tr>
<td>Mangosteen oil</td>
<td>Unknown</td>
<td>Fatty infiltration of liver, vomiting, drowsiness, metabolic acidosis</td>
</tr>
</tbody>
</table>


* Data also from Couet et al.,59 Betz et al.,51 and D’Ancy.79
† Data also from MacGregor et al.,227 Chan et al.,60 and Willey et al.402
Physicians also need to incorporate the beneficial effects of all types of treatments into their patients’ treatment. Lerner has delineated the following guidelines for an effective physician role:

1. Avoid patient abandonment, which drives patients to the alternative medical practitioner completely.
2. Adopt a strategy of preemptive discussion, making it clear that this discussion is desired and valuable for the patient and the physician.
3. Clearly indicate that the physician is a valuable source of information about CAM practices.
4. Know the specific questionable methods that have been shown to be at best useless and at worst fraudulent.

Physicians should be clear in their goals of treatment and in the promise that conventional therapy offers, but brutal honesty and fearful predictions only tend to drive the patient to other sources of potential help, often promised without statistical validity. Approximately 5% of cancer patients abandon conventional therapy and pursue alternative methods. Knowing about CAM therapies and discussing these alternative therapies early in the patient’s treatment, and being honest about the patient’s goals and the likelihood of help from conventional medicine and CAM enhance the physician-patient relationship. Seeking to help the whole patient, to look at patients in a humanistic way, is good medicine, whether practiced by the conventional therapist or the alternative practitioner.

Unfortunately, a recent survey indicates that although physicians may be aware of different forms of CAM treatments, they are still unaware of the existence of readily accessible reference materials on CAM remedies, such as Physicians’ Desk Reference for Herbal Medicines and CAM journals (see Appendix B). In addition, physicians’ knowledge of the side effects and contraindications of 10 commonly used herbs was very limited. Recently the two journals Scientific Review of Alternative Medicine (http://www.hcrc.org) and FACT: Focus on Alternative and Complementary Therapies (http://www.ex.ac.uk/FACT/) were launched to cover scientific reports of CAM.

The goals of studies on CAM treatments are often complex and blurred. Standard chemotherapy, surgery, and radiation therapy studies hinged on measurements of disease-free survival and longevity. Although there were always questions about quality of life, these were often asked secondarily. In CAM studies, however, quality of life often becomes the key question, especially when treatments are given with only palliative intent. It will always be difficult to measure quality of life, and studies will need to be ever more carefully designed to use measurement and survey instruments that can accurately reflect differences across groups.

**CLINICAL RESEARCH ISSUES**

Cancer therapy involves three types of specific multipatient studies. As discussed in Chapter 2 and previously, different phases of preclinical studies include techniques required to evaluate or synthesize a potential new drug molecule as well as conduct pharmacologic studies (safety and toxicity tests) and preclinical toxicologic studies.
(acute and chronic toxicity, teratogenicity, carcinogenicity, and mutagenicity). Phase I studies are performed to determine the appropriate dose of a given material for study, not to seek anticancer effects of these therapies. Phase II studies are performed to seek potential clinical usefulness of a new drug or new drug combination. A number of patients, often with varying types of malignancies, are given a treatment at an acceptable dose level, as determined from Phase I studies. When greater than 20% potential response occurs, these drugs can then be entered into controlled Phase III studies. The newer agent or combination is compared with a control group using the best treatment to date, which might be another single agent, combination of treatments, or placebo.

There are very few controlled scientific studies of CAM related to cancer treatment, and many CAM therapy practitioners are reluctant to conduct such research. However, some are actively engaged in careful clinical studies, which can be costly if controlled and well documented using high-level statistical analysis. Also, it is often difficult to control clinical studies in a double-blind format, although good records of quantifiable data should be kept, including tumor size and laboratory work. CAM practitioners often rely on the subjective views of the patient rather than objective evidence such as radiographs, laboratory work, and clinical measurement. Clear survey instruments can be developed to obtain subjective information in a reproducible way from patients about their lifestyle and quality of life, and future health care providers should obtain such data. (For a preliminary discussion of requirements of research design, see Chapter 1.) The following criteria should warn of questionable practices in the use of CAM, particularly for the treatment of cancer:

- Lack of studies on effectiveness
- Practitioners who claim the medical community is keeping the cure from the public
- Treatment that primarily relies on diet and nutrition
- Claim that the “curative” treatment is harmless, painless, and without side effects
- Treatment with a “secret formula” that only a small group of practitioners can use
- Treatment by an untrained person

Since 1991 the National Cancer Institute (NCI) has had a process for evaluation of data from CAM practitioners. The Best Case Series Program provides an independent review of the medical records and primary source materials, including medical imaging (e.g., radiographs, ultrasound) and pathology (cytology, surgical), as well as an overall assessment of the evidence for a therapeutic effect. To date, only one study provided sufficient data to carry forward to Phase III analysis. Unfortunately, only a few patients enrolled in the randomized trial.

In general, limited number of cases and limited data from medical records are the primary reasons preventing comparison of CAM to conventional treatment. The NCI established the Office of Cancer Complementary and Alternative Medicine (OCCAM) in October 1998 to coordinate and enhance the activities of the NCI in the arena of CAM.

In 2001 the National Institutes of Health (NIH) funded more than $220 million in CAM research and training. The lead agency, the National Center for Complementary and Alternative Medicine (NCCAM), has an $89 million budget and funds more than 50 CAM projects on cancer treatment. Two research centers, Johns Hopkins University and the University of Pennsylvania, have been funded for $8 million over 5 years to study CAM cancer therapies. The NCI funded almost $50 million in CAM and CAM-related cancer research.

Although CAM cancer research has grown substantially over the last few years, more information concerning CAM is needed. Without formal standardization and regulation of CAM products and practitioners, while emphasis focuses on the individualized treatment, it will take more time and effort to carry out research in CAM modalities and incorporate them into standard care. Therefore the major obstacles to integrate CAM into medical science are still the burden of proof and standardization.

Efforts are increasing to integrate CAM into established research institutes. Tagliaferri et al. reviewed potential methods to integrate certain CAM modalities into conventional adjuvant therapy for early-stage breast cancer. DiPaola et al. describe research efforts in both conventional and CAM areas to improve the prevention and treatment of prostate cancer at the Cancer Institute of New Jersey. In collaboration with the NCCAM, the first OCCAM initiative provided supplemental funds to six NCI-designated cancer centers: Johns Hopkins Oncology Center, Wake Forest School of Medicine, University of Medicine and Dentistry of New Jersey, University of Colorado Cancer Center, University of California at San Francisco Cancer Center and Cancer Research Institute, and the University of Chicago Cancer Research Center. A total of $6 million has been funded over a 3-year period to stimulate CAM cancer research between CAM practitioners and researchers at the six cancer centers.

**CAM and Prevention of Cancer**

Cancer prevention is a major subspecialty of conventional oncology. The search for genetic predispositions and carcinogens is very active, but preventive activities are most useful in the area of personal behavior modification. Because these modifications, usually in the form of diet and specific chemical use, are being made in otherwise healthy individuals, such changes must be safe.

A growing body of literature involves cancer prevention and CAM. Although common lore indicates that civilization and pollution (i.e., the industrial world) are major causes, cancer is often found in less polluted areas. In fact, 56% of the world’s 5 million cancer deaths in 1985 occurred in the developing world. Three approaches for prevention of cancer are delineated by Reizenstein, Modan, and Kuller: (1) control of environmental sources of carcinogens; (2) modification of personal habits, including cigarette smoking and diet; and (3) identification of specific genotypes. Of these, only personal habit modification is under the individual’s direct control. It is also thought that this one approach would lead to the greatest potential decrease in cancer incidence.
A particularly novel approach to the prevention of cancer is by teaching personal habit modification through what might be called "cyberprevention." Shinke, Moncher, and Singer described using interactive, culture-sensitive computer software to reduce risks of carcinogens, mainly cigarettes and poor diets, in a small study in one Native American population. Longer-term follow-up data were not available.

An ongoing study to determine the potential benefit of changing behavior is the Working Well Trial, which is being done at worksites across the United States under NCI auspices. Because 80% of cancers may be attributable to lifestyle or environmental exposure, including smoking, diet, and occupational exposures, the focus is to change motivational factors and social norms in a more widespread way than would be possible in the clinical setting. Also, the American Cancer Society (ACS) has developed seven general recommendations to reduce cancer risk or diagnose the disease early, when it is most treatable:

1. Choose most of the products from plant sources; that is, obtain vitamins, minerals, and other nutrients from food sources rather than from dietary supplements.
2. Choose foods low in fat, particularly from animal sources.
3. Reduce or eliminate sun exposure.
4. Be physically active, and stay within a recommended weight range for your age, height, and gender.
5. Reduce or eliminate consumption of alcoholic beverages.
6. Eliminate smoking and chewing tobacco.
7. Obtain a cancer-related checkup: every 3 years for people ages 20 to 40 and every year for people 40 and older.

Diet

A potential link between cancer and diet has been suggested for more than 50 years. As early as 1933, a supposition was voiced that overweight people had a higher cancer risk than people of normal weight. The active study of this potential relationship began in the 1960s when the World Health Organization (WHO) concluded that the majority of human cancers may be preventable largely through dietary modification. The Surgeon General’s Report on Nutrition and Health in 1988 showed a straight-line relationship between estimated daily dietary fat intake and breast cancer death rate. Colon cancer was correlated with dietary fiber intake and overall body weight. Several cancers were correlated with vitamin A or alcohol intake. Esophageal cancer was correlated with vitamin C intake, and both stomach and esophageal cancers were associated with poor nutritional status.

International surveys, migration studies, cohort studies, case control studies, and clinical trials data have all shown a relationship between diet and cancer, especially of the colon and rectum, breast, prostate, esophagus, lung, stomach, and liver. A high-calorie, high-fat, low-fiber diet may increase the risk of cancer. However, the fat intake by the general U.S. population is decreasing,
Colon cancer has been positively correlated with fat intake in a number of studies. Potentially premalignant adenomatous polyps are more common in countries of high animal fat consumption. In an epidemiologic study of 24 European countries using mortality data, a direct correlation was shown between the consumption of animal (but not vegetable) fat and colon and breast cancer and an inverse relationship with fish oil consumption. The authors surmised that fish oil is protective against these cancers and that animal fat is carcinogenic in colorectal and breast cancers.

Fish oils are potent modulators of eicosanoid production. Eicosanoids are derived from arachidonic acid and include prostaglandins, thromboxanes, leukotrienes, and various hydroxy and hydroperoxy fatty acids. These substances have effects on inflammation, immune function, and tumor cell division. Recent epidemiologic and clinical studies indicate a potential role for treatment with eicosanoids in cancer prevention. Some eicosanoids activate protein kinase C and may have potential action in animals, retarding tumor growth and inhibiting metastasis production. Increased dietary fat leads to certain eicosanoids that result in increased levels of cytochrome-c oxidase II (COX-II), which may play an active role in the production of breast and prostate cancer.

Controversy is ongoing over the role of dietary fat, cancer production, and cancer recurrence or spread. There are marked differences in prevalence rates of breast cancer and prostate cancer in various parts of the world that correlate with increasing dietary fat intake, and these rates are changing with increasing dietary fat intake over time. In Japan, dietary fat intake and breast and prostate cancers have risen significantly. Interestingly, Eskimos, with their high fatty intake—predominantly omega fatty acids—still have a very low incidence of breast cancer.

The blood levels of estrogenic compounds can be altered by diet. Fiber binds estrogen in the gastrointestinal tract, resulting in lower blood levels. The hypothesis that endogenously produced estrogen is related to the development of breast cancer is at least partly substantiated by the finding that tamoxifen, an estrogen blocker, reduces recurrence rates when used as adjuvant therapy after “curative” surgery and reduces occurrence of breast cancer in the contralateral breast when used in cases of carcinoma in situ.

Estradiol and estrone blood levels were related to dietary fat intake in several studies and directly correlated with the prevalence of breast cancer. Women who decreased the percentage of fat in their diet for 3 months lowered their circulating estrogen, estrone, and estradiol levels, whereas progesterone, luteinizing hormone, and follicle-stimulating hormone levels remained unchanged. It remains to be determined, however, whether fat intake leads to lower cancer rates.

Fat intake may influence breast cancer prevalence through mechanisms other than hormonal. Fat-rich linoleic acid, an omega-6 fatty acid, enhances rat mammary carcinoma, whereas olive oil, containing oleic acid, an omega-9 fatty acid, has no such effect. Epidemiologic studies in humans appear to be consistent with these findings in animals, and similar results are obtained with fish oil ingestion. Eicosanoids produced by lipoxygenase activity have an enhancing role in growth, invasion, and...
metastases of cancers. Similar harmful effects were seen in prostate cancer cell growth. A low-fat diet may decrease the production of these eicosanoids and thus inhibit growth, invasion, and metastases of breast or prostate cancer.

The nuclear grade of carcinoma in situ of the breast and of the prostate is also found to be proportional to the fat intake, being less aggressive in Japan with its low-fat diet than in the United States. Akazaki and Stemmermann reported that first-generation Japanese immigrants in Hawaii have a higher tendency for latent carcinoma to become invasive and aggressive compared with Japanese in Japan.

Total fat consumption from meat is directly related to risk of advanced prostate cancer. In a population-based, case-control nutrition intake study in Utah of 358 patients with prostate cancer surveyed and matched with 679 controls, West et al. found that dietary fat was the strongest risk factor to explain the aggressiveness of this cancer. Other factors that had no significant effect on the study population included the intake of protein, vitamin A, beta-carotene, vitamin C, zinc, cadmium, and selenium. Fat intake from dairy products or fish was free from correlation. Heinonen et al. reported the significant reduction in prostate cancer incidence and mortality in male smokers in a large, long-term study in Finland. Further studies are needed to corroborate this finding.

Recent clinical results indicate potential applications of polyunsaturated fatty acids (PUFAs) to cancer treatment. A double-blind study at the Harvard and Deaconess Medical Centers suggested a significant effect of postsurgical adjuvant supplementation with eicosapentaenoic acid (EPA) in limiting recurrence of colon cancer. Twenty-seven patients with stage I or II colon carcinoma or potentially premalignant adenomatous polyps were randomly selected to consume 9 g daily of either fish oil with high EPA content or corn oil after excision of detectable lesions. S-phase labeling of tissue from proctoscopic mucosal biopsies, a predictor for incidence of new neoplasms, dropped from its baseline in the treated group but rose in the control group. The rate of metastases after curative breast cancer surgery also suggested a clinical benefit with the use of adjuvant supplementation with omega-3 PUFA. Nanji et al. offer a potential mechanism of action for these findings.

VITAMINS

Observational epidemiologic studies have suggested a possible decrease in the prevalence of cancer in people who consume higher amounts of fruits and vegetables, which are foods high in beta-carotene. This decreased prevalence may result from these foods’ antioxidant effect. Research literature is replete with anecdotal reports of antioxidant properties of many foods or food additives. For example, the spice turmeric has been found to exhibit such properties in vitro.

Animal studies suggest the value of vitamin A and retinoids in regulating epithelial cell differentiation and maintenance. Animals receiving a vitamin A–deficient diet develop keratinization, squamous metaplasia, and gross tumors, with subsequent regression of this metaplasia on reintroduction of vitamin A into the diet. Retinoids also inhibit tumor angiogenesis. Chemoprevention of mammary carcinoma in some strains of rats and mice by vitamin A and retinoids has been shown, but hepatic
toxicity may be significant, as well as dermatologic toxicity. Metastases also decrease if retinoids are used as adjuvant treatment after removal of the primary tumor.

Further animal studies revealed that combining retinoids with oophorectomy, using dehydroepiandrosterone (DHEA), or with 2-bromo-alpha-ergocryptine (an inhibitor of pituitary prolactin secretion), had an additive effect. For example, in N-methyl-N-nitrosourea-induced rat mammary carcinoma, the combination of retinoids and selenium had an additive effect in cancer prevention. However, clinical studies in humans are needed to confirm these effects.

Although vitamin K is necessary for blood clotting, a possible link between the development of childhood cancers (leukemia) and injections of vitamin K supplements in newborns was suggested but not confirmed by subsequent studies.

Matthew reported that the blue-green microalgae of Spirulina, rich in carotenoids, reversed oral leukoplakia in tobacco chewers. Complete regression of lesions was observed in 45% of the 44 evaluable patients, with no toxicity, compared with only 7% of the placebo-treated patients. However, almost half the responders developed a recurrence within 1 year of discontinuance of Spirulina use.

Torun et al. reported that compared with normal control subjects, patients with cancers from many different sites, including breast, head/neck, genitourinary, lung, and gastrointestinal, had a significantly decreased level of beta-carotene, vitamin E, and vitamin C. There was significantly increased level of malondialdehyde, a product of arachidonic acid metabolism and a potential mutagen and carcinogen whose increased level in serum may indicate increased lipid peroxidation in tissues.

The 1995 Western Electric Study, which evaluated 1556 employed middle-aged men over 37 years, is an example of how a large longitudinal analysis can produce useful information. Men who ate a diet rich in vitamin C and beta-carotene fared better, with less heart disease and possibly less cancer. The correlation persisted after adjustment for age, cigarette smoking, blood pressure, serum cholesterol values, alcohol consumption, and other factors.

In 1996, Henneckens et al. reported on 22,071 male physicians 40 to 84 years of age in the United States who were evaluated in a randomized, placebo-controlled, double-blind study to determine the potential effectiveness of alternate-day beta-carotene as a cancer preventive. Of the subjects, 11% were active smokers and 39% were former smokers when the study began in 1982. (A second part of this study, designed to determine the effectiveness of aspirin as a cardiac disease preventive, was discontinued before the study’s predetermined end point because the aspirin had a statistically significant preventive effect.) The study was continued for more than 12 years. No differences were found in the overall incidence of early or late malignant neoplasms or in overall mortality, and no significant harmful effects were reported. In addition, no decrease in specific types of cancer was observed, including lung, colon/rectum, prostate, brain, and melanoma.

Omenn followed 18,314 people at high risk for lung cancer because of their past or present smoking or exposure to asbestos. That study also showed no beneficial effect and, in fact, revealed an increase in lung cancer prevalence and death from lung cancer in the antioxidant-treated group. A randomized study of 755 former asbestos
workers at high risk for cancer failed to find a decrease in sputum atypia between the beta-carotene or retinol arm and the placebo arm.266

In a double-blind controlled study, Albanes et al.5 followed 29,133 eligible male cigarette smokers, randomly selected to receive beta-carotene, alpha-tocopherol, both, or placebo, for more than 5 years. The beta-carotene–treated group was observed to have no decrease in cancer but an increase in lung, prostate, and stomach cancer. Although the alpha-tocopherol–treated patients had a decrease in prostate and colorectal cancer and no change in lung cancer, they had an increase in stomach cancer and an increase in stroke, an unexpected finding, considering vitamin E’s usual effect on platelets.

Greenberg and Sporn131 followed 1805 patients who had had a recent nonmelanomatous skin cancer and were randomly selected to receive 50 mg of beta-carotene daily or placebo. With yearly evaluations to detect new skin cancers, no reduction in the number of new nonmelanomatous skin cancers was detected.

In recent years, cruciferous vegetables, notably broccoli, have been touted as beneficial. Although rich in antioxidants of vitamin C and beta-carotene as well as folacin, cruciferous vegetables are also a source of hundreds of phytochemicals, which may stimulate the production of anticancer enzymes and chemicals that may block the effects of estrogen, among other, still-unidentified mechanisms.221

The craze to add antioxidants to treatment methods must be balanced by the need for scientifically valid studies. In two complex, nonrandomized, single-arm studies using beta-interferon, retinoids, and tamoxifen as maintenance therapy in patients with metastatic breast cancer, Recchia et al.301 concluded that the combination as maintenance “is feasible and shows activity in metastatic breast cancer with an acceptable toxicity,” but that further controlled studies would be needed to be able to confirm this statement.

In a randomized comparison of fluorouracil, epidoxorubicin, and methotrexate plus supportive care versus supportive care alone in patients with nonresectable gastric cancer, Pyrhonen et al.300 showed that the chemotherapy-treated group had a better response rate and prolonged survival. Subjects in both arms of the study received vitamins A and E, however, so no conclusions can be drawn on the effectiveness of these antioxidants.

Studying chemoprevention by retinoids in the upper aerodigestive tract and lung carcinogenesis in a Phase II study, Lippman et al.216 found a significant improvement in leukoplakia (67% in treated versus 10% in control group) with the use of high-dose isotretinoin in a short-term study. Because of the significant mucocutaneous toxic effects and short duration of remission of this isotretinoin treatment, the authors’ subsequent study employed prolonged low-dose treatment. After a 3-month induction phase with high-dose isotretinoin, patients were randomly selected to receive either 9-month low-dose isotretinoin or beta-carotene. With follow-up to 5 years, the authors showed highly significant results, with progression of disease in only 8% of the isotretinoin–treated group versus 55% in the beta-carotene–treated group.

Pastorino et al.283 reported a Phase III controlled study of retinyl palmitate compared with placebo used as adjuvant therapy in patients who had undergone curative surgery for stage I, non–small cell lung cancer. Although there was a decrease in
second primary cancers in the retinyl palmitate–treated group and an increase in dis-
ease-free interval, no 5-year survival difference was found. The latter finding may be a 
result of the vigorous treatment received by the individuals who developed the second 
primary cancers.

Trace elements may have an antioxidant effect. Copper is required to maintain 
antioxidant defenses in vivo. Low copper states may produce prooxidant effects. 
Copper complexes have been shown to have anticancer, anticarcinogenic, and 
antimitogenic properties in vitro. Zinc has potential antioxidant effects as well, but its 
role in disease is unclear.324 Zinc-deficient rats have an increase in single-strand 
deoxyribonucleic acid (DNA) breaks in the liver, and zinc leukocyte or plasma levels 
have been low in cancer patients, although little evidence suggests a zinc deficiency in 
these patients. The finding of decreased cancer rates in people who eat greater quanti-
ties of fruit may be related to their intake of these trace elements, which are found in 
these foods along with vitamins and beta-carotene.

Van Zandwijk389 reported the use of \( \text{N} \)-acetylcysteine and glomerulus-stimulat-
ing hormone as antioxidants with potential antimutagenic and anticarcinogenic 
properties for prevention of lung cancer, as evidenced in a large European chemopre-
ventive study. Ongoing European studies may determine the effectiveness of these 
agents and delineate possible toxicities.

**SOYBEANS**

Several review articles36 have suggested that multiple soy products may suppress 
carcinogenesis, including a protease inhibitor called the \( \text{Bowman-Birk trypsin } \underset{\text{inhibitor (BBI), also found in other beans and peas; inositol hexaphosphate (phytic }}{\text{inhibitor}}} \rightleftharpoons \text{acid;} \) and the sterol \( \text{beta-sitosterol}.109,146,184,242,250 \) Soybean isoflavones also appear to 
suppress carcinogenesis in animals. Other trypsin inhibitors with evidence of poten-
tial preventive effects on cancer include \( \text{saponins} \) and the phytoestrogen \( \text{genistein} \), 
which may inhibit neovascularization and tumor cell proliferation.22,109 BBI did not 
confer resistance on lung cancer cells in culture to irradiation or cisplatin-induced 
cytotoxicity but did confer such protection on mouse fibroblasts treated with both 
these methods.186 Several NCI-sponsored human studies on individual soy compo-
nents as potential chemopreventive agents in breast and prostate cancer are in 
progress.

The cancer-preventive effects of soybean products were reversed in animal 
studies by feeding the animals \( \text{methionine} \). This finding may indicate that methionine 
deficiency in these animals is the cause of the decreased cancers.195

**OTHER DIETARY PREVENTIVES**

Recent studies indicate that high-fiber and high–folic acid intake is protective against 
colon cancer. Other cancers whose prevalence is inversely related to vegetable and fruit 
intake include those of the oral cavity, larynx, pancreas, bladder, and cervix. Whole-
grain products seem to reduce the rate of colon cancer, possibly because of their 
increased fiber content.
Animal protein intake may increase urinary calcium loss, contributing to homocysteinemia, leading to an increase in the risk of various cancers, whereas low calcium intake has been associated with a risk of colon cancer.401

**Folic Acid**

A high dietary intake of folate appears to exert a protective action against adenomatous polyps in the colon.172 A deficiency of folate appears to be correlated with cervical dysplasia (see earlier discussion).

**Selenium**

Garlic, which is high in selenium, has been found to inhibit colon cancer in mice,396 possibly through its action as an antioxidant. Garlic inhibits skin tumor growth,269 inhibiting carcinogenesis, and appears to have an immunostimulatory effect.27 An epidemiologic study revealed that the prevalence of stomach cancer in the area of Georgia where there is the highest level of production of Vidalia onions, high in selenium, is significantly lower than in other parts of the state.416 However, in one area of Japan where gastrointestinal tract carcinoma is common, high levels of selenium in the soil were not associated with a significantly high cancer mortality.261

Gupta et al.139 studied plasma selenium levels in cancer patients and found that mean plasma selenium levels fell with increasing extent of disease and that patients with recurrent cancers had lower levels than those without recurrence. The authors believed that the low level is a causative factor in the cancer. One NCI study reported a 16% decrease in incidence of gastric cancer, a 4% reduction in esophageal cancer, and an overall 20% reduction in other cancers in a large group of Chinese adults taking vitamin E, beta-carotene, and selenium compared with a control group.221 Because the study did not compare single variables, it is impossible to determine the role of each of the three additives. Clark, Combs, and Turnbull71 reported a decrease in cancer incidence in patients with a history of basal cell or squamous cell carcinoma of the skin with supplementation with selenium. Goodwin, Lane, and Bradford129 found that mean plasma selenium was elevated in 50 patients with untreated cancer of the oral cavity and oropharynx. On the other hand, mean erythrocyte selenium and glutathione peroxidase were depressed compared with age-matched controls. Additional research is needed to determine the role of selenium as a potential chemopreventive agent for head and neck cancer.

**Molybdenum**

Nakadaira et al.241 found a correlation between molybdenum concentrations in soil sediment samples and death resulting from pancreatic cancer in women.

**SUMMARY**

Familiar drugs such as tamoxifen and aspirin have been found useful as chemopreventive agents for breast and colorectal cancer, respectively. Similarly, daily intake of folate supplement for 15 years may decrease the incidence of colorectal cancer. However, the
pros and cons of each chemopreventive agent must be weighed against the risk of cancer for each individual.332

Treatment of Cancer

The therapies described in this section have been reported in the literature as showing evidence of possible effectiveness. The listing is not meant to be all inclusive. Table 4–3 provides information on CAM in the treatment of specific malignancies.

ACUPUNCTURE

After being employed for thousands of years in China,304 acupuncture is rapidly gaining popularity in the United States. Despite this long-term usage, there is no evidence of its effectiveness as treatment for cancer itself. Most claims for effectiveness are as a

<table>
<thead>
<tr>
<th>Malignancy</th>
<th>Treatment</th>
<th>Results</th>
<th>Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Superficial bladder cancer</td>
<td>Keyhole limpet hemocyanin</td>
<td>Increased activity of natural killer cells</td>
<td>Kalilé, Otto143</td>
</tr>
<tr>
<td>Cervical dysplasia and cancer</td>
<td>NS</td>
<td>Low levels of beta-carotene, vitamins A and C</td>
<td>Lamm et al.211</td>
</tr>
<tr>
<td>Cervical cancer</td>
<td>NS</td>
<td>Deficiency of folate, beta-carotene, vitamin C, riboflavin</td>
<td>Orr et al.203</td>
</tr>
<tr>
<td>Cervical smears abnormal</td>
<td>NS</td>
<td>Folic acid deficiency in Bantu women, corrected with folic acid treatment</td>
<td>Niekerk347</td>
</tr>
<tr>
<td>Cervical dysplasia</td>
<td>NS</td>
<td>Low levels of vitamin A, selenium</td>
<td>Dawson et al.92</td>
</tr>
<tr>
<td>Colorectal adenomas</td>
<td>NSAIDs or diet high in fresh fruits and vegetables</td>
<td>Lower incidence of adenomas</td>
<td>Janne et al.172</td>
</tr>
<tr>
<td>Esophageal cancer</td>
<td>Animal protein supplements in Chinese diet</td>
<td>Decreased rate of occurrence</td>
<td>Herbert160,168</td>
</tr>
<tr>
<td>Gastric cancer</td>
<td>Increased garlic and onion intake</td>
<td>Decreased rate of occurrence</td>
<td>You et al.414</td>
</tr>
<tr>
<td>Acute promyelocytic leukemia</td>
<td>Co-oxide in culture cells</td>
<td>Apoptosis, morphologic changes</td>
<td>Chen et al.177</td>
</tr>
<tr>
<td>Melanoma</td>
<td>Sesame/safflower oil in culture</td>
<td>Inhibited cell growth</td>
<td>Sun et al.361</td>
</tr>
<tr>
<td>Nonmelanoma skin cancer</td>
<td>Beta-carotene treatment</td>
<td>No change in number of new lesions over 5 years</td>
<td>Greenberg et al.132</td>
</tr>
<tr>
<td>Oral leukoplakia</td>
<td>Spirulina fusiformis vs. placebo</td>
<td>45% regression vs. 7% with placebo</td>
<td>Matthew232</td>
</tr>
<tr>
<td>Pancreatic cancer</td>
<td>Mistletoe extract</td>
<td>No improvement in tumor size or survival</td>
<td>Friess et al.112</td>
</tr>
</tbody>
</table>

NS, Nonspecific; NSAIDs, nonsteroidal antiinflammatory drugs.
treatment for the side effects of cancer, such as emesis associated with treatment or for control of pain. For the control of pain, acupuncture may activate "endogenous pain inhibitory systems" by the production of beta-endorphins and neuropeptides, which bind to opioid receptors, increase interleukin-2 (IL-2) levels, and increase natural killer (NK) cell activity.12,24,35,48

Measurements of CD3, CD4, and CD8 cells as well as soluble IL-2 receptor and beta-endorphin levels in the peripheral blood of patients with malignancies revealed an increase in CD3, CD4, and CD4/CD8 ratio and an increase in the beta-endorphin level after acupuncture, with a concomitant decrease in soluble IL-2 receptor levels.34,35 Theoretically these findings might lead to clinical treatments for cancer patients, but further studies are needed. A preliminary review of electroacupuncture with imagery has revealed some potential usefulness.362

According to the 1997 NIH Consensus Development Conference on Acupuncture, acupuncture is an effective treatment for nausea and vomiting caused by chemotherapy drugs. A small clinical trial recently reported that acupuncture was also effective in reducing the number of hot flashes men experienced after hormonal therapy for prostate cancer.142 Although generally considered safe, acupuncture performed improperly can cause fainting, local internal bleeding, convulsions, hepatitis B, dermatitis, nerve damage, and infection from contaminated needles at insertion sites. WHO publishes several guidelines on acupuncture, including research, training, safety, and nomenclature.*

**ANTINEOPLASTONS**

Antineoplastons are derived from glutamine, isoglutamine, and phenylacetate salts; antineoplaston AS5 is phenylacetate itself.46 These chemicals inhibit incorporation of glutamine292,344 into the proteins of tumor cells, which may cause G1-phase arrest. Antineoplaston A10 is thought to interfere with intercalation with DNA. Other antineoplastons inhibit methylation of nucleic acids; hypomethylation may activate tumor suppressor genes.46 Antineoplaston A10 and AS2-144 have been shown to produce a deleterious effect on cell proliferation, cell morphology, cell cycle, and DNA in human hepatocellular carcinoma cell culture lines and in one patient with hepatocellular carcinoma.377 Burzynski46 stated that “it can be clearly observed that antineoplastons induce abnormal cells to undergo terminal differentiation and die.”

Many Phase I trials on antineoplaston treatment have been performed in the United States and Japan. Tsuda et al.294,377 reported responses in patients with ovarian cytoadenocarcinoma, anaplastic astrocytoma, recurrent renal cell carcinoma, brain metastases from prostate carcinoma, brain metastases from breast cancer, lymphoma, and brain stem glioma. Their overall response rate was reported to be 32%. Sugita et al.360 reported treatment success in a few patients with antineoplastons. Side effects included weakness, drowsiness, febrile reactions, nausea/vomiting, skin rash, and leukopenia/thrombocytopenia. Phase I studies of phenylacetate in patients with cancer have been performed,291 and clinical Phase II studies would be needed to

---

determine the likelihood of clinical usefulness. Although an NCI study was begun to
determine the usefulness of phenylacetate treatment in patients with brain tumors,
after a very slow accrual of patients, disagreements over study design prohibited the
study from moving forward. (See Appendix B for websites presenting additional clin-
cal trial data.)

AYURVEDA

Ayurveda (Sanskrit for “that which has been seen to be true about long life”)374) treatment has been used in India for thousands of years. Smit et al.341 found cytotoxicity in
the flowers of Calotropsis procera and the nuts of Semecarpus anacardium. However,
there are no randomized studies in humans to show the clinical effectiveness in cancer
treatment.

Over the past 10 years, a form of Ayurveda medicine promoted vigorously
through the Maharishi Mahesh Yogi has become quite popular,145 with animal experi-
ments showing cytotoxicity of Maharishi-4, a mixture of low-molecular-weight subst-
ces, including antioxidants such as alpha-tocopherol, ascorbate, beta-carotene,
catechins, bioflavinoids, and flavoproteins in the treatment of 7,12-dimethylbenz
[a]anthracene (DMBA)–induced mammary tumors in rats331 and in the treatment of
lung metastases in Lewis lung carcinoma in mice.284 MAK-A, one such compound,
induced biochemical and morphologic differentiation in murine neuroblastoma cells
in culture.295 MAK-4 and MAK-5 may have antioxidant properties.89,101,270

Ayurvedic healing techniques are based on the classification of people into one
of three predominant body types, with specific remedies for disease and regimens for
health promotion for each group. Ayurveda emphasizes regular detoxification and
cleansing through all physiologic systems of elimination and all orifices. Toxicity has
been reported with ayurvedic remedies. Hepatic venoocclusive disease was reported in
patients taking Heliostropium species, causing rapidly progressive hepatic failure lead-
ing to death. A recent review of 166 species of plants used in the ayurvedic phar-
macopoeia suggests that certain species may have some positive effects, at least in
palliative care, and deserve further studies.188

CHIROPRACTIC

Chiropractic is generally reserved for the treatment of pain related to nonmalignant
causes. Of concern is the possibility of negative outcomes resulting from manipula-
tive treatments of patients with undiagnosed cancer. Few published studies are avail-
able on the complications of chiropractic manipulation. In one study, however,
miagnosis of the patient’s condition accounted for 26 of 135 complications after
chiropractic treatment, 16 of which were in patients with neoplasms.201 Because of
the potential of paraplegia resulting from spinal manipulation in patients with can-
cer, malignancy is at the least a relative contraindication to chiropractic manipula-
tion.333 For example, a case of quadriplegia after chiropractic manipulation in a
4-month-old infant with congenital torticollis caused by a spinal astrocytoma has
been reported.329
DIET AND NUTRITION

Diet is discussed earlier in relation to cancer prevention, but several diets are also used as treatment. So-called metabolic diets include anticancer diets with digestive enzymes; high-dose vitamin therapy, including vitamins A and C; pangamic acid (so-called vitamin B15); amygdalin (Laetrile), or so-called vitamin B17; an alleged vitamin preparation (“Plus 198”); and vitamin E and mineral supplements, with ancillary injections of intratumoral enzymes. Raw food consumption is increased, protein intake is decreased, and refined foods and additives are eliminated. Coffee enemas are used. Hair and blood analyses are also performed routinely. The ACS has published its findings of serious risks to patients resulting from these “metabolic diets.”

Macrobiotic diets were developed by Michio Kushi, based on the yin-yang principle. These two elementary and complementary forms of energy are present within all people, according to ancient Asian spiritual traditions. For a person to achieve health and vitality, these two forces must be in equilibrium. A macrobiotic diet is considered a part of a whole-body regimen and philosophy, a more comprehensive way of life rather than just a diet. This diet obtains 50% to 60% of its calories from whole grains, 25% to 30% from vegetables, and the rest from beans, seaweed, and vegetarian soups. These strictly vegetarian diets have been touted as successful for the prevention of cancer, as well as its treatment. Although conventional medicine has recognized the potential benefit of increasing vegetables in the diet for prevention, there is no compelling evidence that this diet overall has a beneficial effect for prevention or treatment of cancer. No controlled trials of these diets have been made. The diets are potentially significantly deficient in vitamins D and B12, as well as in protein, iron, and calories.

Many anticancer diets have been described; they tend to be especially popular in Europe. A partial listing follows:

- “Kousmine diet”: raw vegetables and wheat that are “rich in vital energy”
- “Instinctotherapy”: only raw products, including raw meat; no milk products
- “Moerman diet”: lactovegetarianism plus “the eight essential substances: vitamins A, B, C, and E, iodine, sulfur, iron, and citric acid”
- “Breuss cancer cure”: up to 1 L of vegetable juice daily and different teas for 42 days
- “Budwig’s oil-protein diet”: curd cheese/flaxseed oil mixture, with fruits/fruit juices
- “Anthroposophic diet”: lactovegetarianism, unrefined carbohydrates, sour milk products
- “Bristol diet”: raw and partly cooked vegetables, soybeans, peas, and beans
- “Gerson therapy”: crushed fruits and vegetables, coffee enemas, nutritional supplements

Only the Bristol diet has been studied in a prospective, controlled trial. Breast cancer patients attending a Bristol diet center showed no benefit compared with a control group. For cancer patients who were metastasis free at entry into the center, metastasis-free survival was, in fact, significantly worse than in the control group. Survival in patients with relapse was also poorer compared with controls. However, preentry differences in clinical staging, conventional treatment, and selective self-referral confuse and weaken the reported results.
Hoxsey herbal treatment includes an antimony-zinc-bloodroot paste, arsenic, sulfur, and talc as external treatments and a liquid mixture of licorice, red clover, burdock root, Stillingina root, barberry, Cascara, prickly ash bark, buckthorn bark, and potassium iodide for internal consumption. A mixture of procaine hydrochloride and vitamins, along with liver and cactus, is prescribed. The U.S. Congress Office of Technology Assessment (OTA) found that “taken together, the data indicate that many of the herbs used in the Hoxsey internal tonic or the isolated components of these herbs have antitumor activity or cytotoxic effects in animal test systems.” The OTA indicated that a paste made from these herbs had reliable beneficial effect on the treatment of basal cell carcinoma of the skin. Austin, Dale, and DeKadt did find cures for patients placed on the Hoxsey regimen but did not find such responses for patients treated at the Gerson clinic. Review by the NCI of the “cures” from these treatments failed to reveal any evidence of effectiveness for these patients with cancer.

The Gerson diet is a no-sodium, high-potassium diet rich in carbohydrates and defatted liver capsules, with injections of liver extract and coffee enemas. The treatment has led to serious infections from the poorly administered liver extracts, as well as electrolyte imbalance resulting from the coffee enemas. No study published in the peer-reviewed literature has indicated any beneficial effect of this diet.

The Kelley diet employs enemas, diuretics, nasal irrigation, Sitz baths, deep-breathing exercises, and external body cleansing to rid the body of toxins; an expensive, restrictive diet generally follows. There have been no carefully performed studies to show any benefit. Gonzales in New York follows a similar system (although Kelley apparently disagrees) and has produced a best-case series for the NCI. The hair analysis for nutritional assessment is believed to be of no value. Metabolic therapy, coffee enemas, laxatives, juices, “antineoplastic” enzymes, amygdalin, pangamic acid, and dozens of other products, including vitamins C and E, selenium, zinc, ribonucleic acid (RNA), DNA, and ground-up animal organs all have been used, and no studies have indicated effectiveness.

Essiac (“Caisse” when spelled backwards; named after Rene Caisse, a Canadian nurse who popularized its use) is a combination of four herbs: burdock, Turkey rhubarb, sorrel, and slippery elm. Researchers at the NCI and Memorial Sloan-Kettering Cancer Center have found that essiac has no anticancer effect.

Cancell therapy is particularly popular in Florida and the Midwest. Through these medications, the practitioners claim to return the cancerous cell to a “primitive state,” from which it can be rendered inert. U.S. Food and Drug Administration (FDA) laboratory studies revealed that these are common chemicals, including nitric acid, sodium sulfite, potassium hydroxide, sulfuric acid, and catechol. The FDA found no basis for the claims of effectiveness of the Cancell treatment. In 1989, the FDA was granted a permanent injunction against both principal manufacturers of Cancell/Entelev, prohibiting them or their agents from distributing the mixture across state lines and classifying the therapy as an unapproved new drug.

Table 4–4 summarizes a recent ACS publication and a review of additional diet and nutrition substances in cancer; appropriate references are listed in the ACS book.
### Table 4-4: American Cancer Society and Other Reviews of Diet and Nutrition in CAM Cancer Research

<table>
<thead>
<tr>
<th>Common Name</th>
<th>Scientific Name</th>
<th>Evidence</th>
<th>Conclusion</th>
<th>Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>714-X&lt;sup&gt;19, 20, 21&lt;/sup&gt;</td>
<td>Trime thylbicyclo-nitramine-heptane chloride</td>
<td>Laboratory/animal studies on camphor, a 714-X component; appears to promote immune response</td>
<td>More research needed to determine activity in cancer prevention/ treatment</td>
<td>Potential side effects unknown, except local redness, tenderness, and swelling at injection site</td>
</tr>
<tr>
<td>Lactic acid bacteria</td>
<td>Lactobacillus acidophilus</td>
<td>Varied results in animal studies No formal human study</td>
<td>More research needed to determine activity in cancer treatment/ prevention</td>
<td>Possibly serious infections Questionable product quality</td>
</tr>
<tr>
<td>Amino acids</td>
<td>Arginine, alanine, aspartic acid, etc.</td>
<td>One small human study needs further investigation Conflicting results in laboratory/ animal studies</td>
<td>More research needed to determine activity in cancer treatment/ prevention</td>
<td>May interfere with effectiveness of chemotherapy drug asparaginase</td>
</tr>
<tr>
<td>Cassava, tapioca, manioc</td>
<td>Manihot esculenta, Crantz</td>
<td>No scientific evidence in cancer treatment/prevention</td>
<td>Gene therapy studies using linamarase gene from cassava plant require further investigation</td>
<td>Cassava plant may produce cyanide, which can be deadly to humans</td>
</tr>
<tr>
<td>Coenzyme Q10</td>
<td>Ubiquinone</td>
<td>Laboratory/animal studies show some antioxidant and anti cancer activities Human studies inconclusive because of design flaws or small number of patients</td>
<td>More studies needed with larger number of subjects to determine activity in cancer treatment</td>
<td>Headache, heartburn, fatigue involuntary muscle movements, diarrhea, skin reactions with high dose Anticoagulant interactions</td>
</tr>
<tr>
<td>Ellagic acid:</td>
<td>Ellagic acid</td>
<td>Laboratory/animal studies show promising results Human studies in progress</td>
<td>Human studies using berries containing ellagic acid needed to verify absorption and distribution into various human tissues</td>
<td>Raspberry leaf or its extraction may induce labor.</td>
</tr>
<tr>
<td>Grapes</td>
<td>Vitis vinifera, vitis coignetiae</td>
<td>Laboratory/animal studies show some protective effects One human trial shows some antioxidant activity in grape seed extract</td>
<td>More research needed to determine if resveratrol, active ingredient in red grape skin, may benefit cancer treatment/ prevention</td>
<td>Increased consumption of wine to increase resveratrol intake may increase risk of certain cancers</td>
</tr>
<tr>
<td>Supplement</td>
<td>Description</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>------------</td>
<td>-------------</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Juicing</td>
<td>No scientific evidence in cancer risk outweighs benefit. Possibly severe diarrhea.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kombucha, Manchurian, Kargasok tea</td>
<td>No scientific evidence in cancer risk outweighs benefit. Death possible from acidosis and other complications.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lycopene</td>
<td>Laboratory/animal studies show promising protective effects. Population studies and a human trial appear to show lower risk in certain types of cancer. More research needed to determine if lycopene or other antioxidant may benefit cancer treatment/prevention. No known side effects from lycopene. Supplement side effects unknown.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maitake mushroom</td>
<td>Laboratory/animal studies show promising results. More research needed to determine if maitake D fraction (active ingredient) may benefit cancer treatment/prevention. No known side effects from mushroom itself. Effects from maitake D fraction unknown.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Modified citrus pectin (MCP), Pecta-sol</td>
<td>Laboratory/animal studies show potential inhibition of spread of prostate and melanoma cancer cells. More research needed to determine activity in cancer treatment/prevention. MCP may cause stomach discomfort.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Noni plant, Indian mulberry, Morinda, hog apple, etc.</td>
<td>Laboratory/animal studies show some positive effects in various compounds in noni juice. More research needed to determine activity of noni juice in cancer treatment/prevention. Side effects unknown.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Selected vegetable soup (SV), sun soup</td>
<td>Small human trial by soup developer found some positive effects in conjunction with conventional treatment. More research needed to determine activity of SV with conventional cancer treatment. Insufficient data.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shiitake mushroom</td>
<td>Animal studies show some positive effects of compounds. Human study of lentinan (one compound) showed positive effect on advanced/recurrent stomach/colon cancer. More research needed to determine activity of mushroom and compounds in cancer treatment/prevention. Allergic reaction affecting skin, nose, throat, and lungs.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Common Name</td>
<td>Scientific Name</td>
<td>Evidence</td>
<td>Conclusion</td>
<td>Complications</td>
</tr>
<tr>
<td>-------------</td>
<td>-----------------</td>
<td>----------</td>
<td>------------</td>
<td>---------------</td>
</tr>
<tr>
<td>Vitamin D</td>
<td></td>
<td>Laboratory/animal studies show reduced proliferation on certain tumor cell lines and inhibited metastasis in breast cancer models. Preliminary human studies show some promising effects.</td>
<td>More research needed to determine effectiveness and amount in cancer treatment/prevention</td>
<td>Overdose may lead to anorexia, nausea, vomiting, polyuria, polydipsia, weakness, pruritus, nervousness, and irreversible calcification of soft tissue in kidney and liver.</td>
</tr>
<tr>
<td>Wheatgrass</td>
<td>Agropyron</td>
<td>No scientific evidence in cancer treatment/prevention</td>
<td>Insufficient data</td>
<td>Insufficient data</td>
</tr>
<tr>
<td>Willard water</td>
<td></td>
<td>No scientific evidence in cancer treatment/prevention</td>
<td>Insufficient data</td>
<td>Insufficient data</td>
</tr>
</tbody>
</table>

HERBAL REMEDIES

Plant products have been used for centuries as medicines. At present, in most countries of the developing world, plant remedies are the most prevalent treatments, with recipes handed down from generation to generation. These remedies are readily available and are less costly than allopathic medicine, and practitioners are accessible and generally have a more culturally sensitive attitude. Much of allopathic medicine is derived from plant product. An estimated 20% to 25% of U.S. prescriptions contain natural plant products. Oncology drugs are no exception. Taxol and Taxotere are derived from the Western yew tree, epipodophyllotoxins from the mandrake plant, camptothecin from the bark of a Chinese tree (bought at the rate of approximately $35,000/kg), and vinca alkaloids from periwinkle plants.

Approximately 114,000 plant extracts from 35,000 species were screened for anticancer activity between 1960 and 1981 in a mouse leukemia model. None proved effective in clinical trials during that time; therefore interest diminished. Other countries, notably Japan, France, and China, continue to screen new plant materials. With the advent of newer models of evaluation, including cell culture lines, a screening program at the NCI has been renewed. The NCI maintains a repository of 22,000 samples of natural products, primarily higher plants, adding about 6000 new samples yearly.

Any study of herbal products carries significant problems. First, standardization of dosage and formulation is generally lacking. The plant contains many potentially effective compounds, with their inherent synergistic and competitive possibilities making it difficult to determine which products are beneficial and which are potentially harmful. Often, naturopaths employ several such plants simultaneously, making determination of effects of any one plant impossible. The studies are frequently poorly controlled, and scientific method is seldom employed. Biopsy proof of malignancy is often absent, as is direct clear measurement of end points. Careful, well-controlled statistical studies are needed.

Currently, hundreds of herbal remedies purported to have anticancer benefits are available over the counter. Most of them have no such demonstrated benefit. Many are not reliably formulated in available products, and some are toxic (see later discussion). Nevertheless, a few remedies have demonstrated indications of potential anticancer activity, including polysaccharide krestin, which has demonstrated such activity in Phase III studies. Herbal agents that merit closer study as potentially beneficial complementary treatments for cancer are described separately in the following sections.

POLYSACCHARIDE KRESTIN

Polysaccharide krestin (PSK) is a polysaccharide preparation isolated from the mushroom *Coriolus versicolor* (family Basidiomycetes), which consists predominantly of glucan and approximately 25% tightly bound protein. PSK has been heavily reported in the medical literature and studied in vitro, in vivo in animal studies, and in
controlled human clinical trials.\textsuperscript{70,268} PSK is administered orally and has shown no toxicity. Murine colon cancer studies showed a suppression of growth of these cancers and augmentation of tumor-neutralizing lymph node activity of draining mesenteric nodes by PSK.\textsuperscript{144}

PSK has shown significant effectiveness as clinical treatment as well as adjuvant therapy. In colon cancer as adjuvant therapy, PSK-treated patients had a 30\% 8-year disease-free survival versus 10\% for the control group. When added to radiation therapy as treatment for stage III non–small cell lung cancer, the 5-year survival was 22\% versus control survival of 5\%.\textsuperscript{147} An 8-year disease-free survival for women with breast cancer with demonstrated vascular invasion was reported to be 75\% with combination chemotherapy plus PSK, compared with 58\% for those with only the chemotherapy.\textsuperscript{143,144} As adjuvant therapy added to adjuvant chemotherapy of 5-fluorouracil plus mitomycin for gastric cancer, the 5-year disease-free survival was 71\% versus 59\% for the adjuvant chemotherapy alone.\textsuperscript{365} Fukushima\textsuperscript{147} reviewed the Japanese experience with gastric carcinoma treatment and concluded that PSK and other biologic response modifiers may have a role. In patients with colorectal cancer, PSK increased disease-free survival.\textsuperscript{372}

In a randomized study of 158 patients with esophageal cancer treated with radiation therapy, a statistically significant improvement in survival was seen in those treated with PSK as well.\textsuperscript{277} On the other hand, Suto et al.\textsuperscript{364} found no survival benefit to PSK in hepatocellular carcinoma patients after treatment with various standard therapies. PSK greatly increased the motility and phagocytic activity of polymorphonuclear leukocytes, which may be significant based on other findings that the prognosis of cancer patients correlated positively with the degree of cellular infiltration around tumor sites.\textsuperscript{372}

**CHLORELLA**

*Chlorella pyrenoidosa* is a one-celled green alga rich in proteins, vitamins, nucleic acids, and chlorophyll used extensively as a food supplement worldwide. *Chlorella* has not exhibited toxicity at any dose. The components with identified anticancer activity are water-soluble polysaccharides in the cell wall\textsuperscript{352,383,391} and glyceroglycolipids.\textsuperscript{256,257}

*Chlorella* has been shown to have antitumor activity in association with immune activation.\textsuperscript{195,248,369} A study at the Medical College of Virginia of 15 patients with glioblastoma treated with *Chlorella* with or without other therapies, including radiation therapy or chemotherapy, resulted in a 2-year survival of almost 40\%, with four of these six patients showing no tumor progression during that time.\textsuperscript{241} Potential mechanisms of actions for *Chlorella* include (1) polysaccharide ingredients binding to tumor cell membranes, with subsequent effects on tumor cell growth, adhesion, invasion of normal tissues, metastasis, and vulnerability to immune attack; (2) increase in NK cell activity; (3) increase in helper-suppressor T cell ratio; and (4) stimulation of macrophage activity.\textsuperscript{141,352}

WHO guidelines and standards on herbal/traditional medicine include research methodologies, uses, assessment, good manufacturing practices, safety, and efficacy.\textsuperscript{*}

\textsuperscript{*At http://www.who.int/medicines/library/trm/guidelinesdocs.shtml.}
Chinese herbal remedies form a subset of herbal medicine. Several of these have been studied in vitro for cytotoxic activity (Table 4-5). Ko has reviewed the clinical diagnosis and evaluation of Chinese herbal toxicity and has suggested methods to identify suspected herbs that cause adverse reactions. Although some studies indicated benefits from traditional medicines, Ernst emphasized the risk of heavy metal content (e.g., arsenic, cadmium, mercury, lead) in traditional Chinese medicines as well as in other traditional medicines. Therefore it is important that regulators, pharmacists, practitioners, and physicians as well as consumers are familiar with these risks and attempt to minimize them.

One specific Chinese herbal preparation deserves specific mention. PC SPES consists of reproducible extracts of seven different Chinese herbs and one American herb. The major component of PC-SPES, baicalin, inhibits the proliferation of human cancer cells by apoptosis and cell cycle arrest. Specific studies in prostate cancer cell lines have revealed that exposure to PC SPES resulted in decreased secretion of prostate-specific antigen (PSA), as well as a less prominent decrease in intracellular PSA. Preliminary study with SPES indicates a potential beneficial effect on metastatic growth and on pain resulting from cancer.

Currently, clinical studies are under way to validate the anecdotal reports from patients taking PC SPES who have significantly decreased PSA and symptomatic improvement in patients with advanced prostate cancer. Side effects of high doses of the herbs must be evaluated in patients with advanced disease. Some evidence indicates an estrogenic effect. However, preliminary observations indicate some effectiveness in patients in whom diethylstilbestrol (DES) treatment failed previously. Because PC SPES contains concentrated phytoestrogenic components, precautions against thromboembolic phenomena may be appropriate. Several NCCAM-sponsored trials are in progress. Nonetheless, as a result of an investigation and laboratory analysis, the California State Health Director warned consumers to stop using the dietary supplement/herbal products PC SPES and SPES capsules due to their contamination of warfarin and alprazolam, respectively. The manufacturer of the products, BotanicLab, has

<table>
<thead>
<tr>
<th>Plant Source</th>
<th>Chemical Found</th>
<th>Cytotoxic Assay Cell Line</th>
<th>Study</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Pteris multifida</em>, <em>Poir</em></td>
<td>Deterpins</td>
<td>Ehrlich ascites tumor cells</td>
<td>Woerenbag et al.</td>
</tr>
<tr>
<td>Guava leaf, mango stem peel, pomegranate leaf</td>
<td>Unknown</td>
<td>Human cell lines</td>
<td>Setheetham, Ishida</td>
</tr>
<tr>
<td><em>Antrodia cinnamomea</em></td>
<td>Zhanxuic acid (steroid)</td>
<td>P-388 murine leukemia</td>
<td>Chen et al.</td>
</tr>
<tr>
<td><em>Trichosanthes</em></td>
<td>Triterpenoids</td>
<td>B-16 melanoma</td>
<td>Takada et al.</td>
</tr>
</tbody>
</table>
voluntarily recalled PC SPES and SPES nationwide. Subsequently, on June 1, 2002, BotanicLab officially closed.

**CAPSAICIN**

The use of hot peppers is common around the world. Often considered a food preservative or a sweating agent for people in hot climates, peppers are thought to be beneficial. Capsaicin (8-methyl-N-vanillyl-6-nonenamide), a major ingredient of these peppers, is used specifically for topical treatment of pain. It has also been shown to improve symptoms and reduce the size of the polyps associated with nasal hyperactivity. However, the burning sensation caused by oral or topical use has caused some patients to stop using capsaicin, making it difficult to conduct placebo studies of the drug.

In mouse and human melanoma lines, capsaicin has been shown to inhibit plasma membrane–reduced nicotinamide adenine dinucleotide (NADH) oxidase and cell growth, leading to apoptosis. Capsaicin also has potential carcinogenic activity as a result of its covalent modification of protein and nucleic acids, and it may possess chemoprotective activity against some chemical carcinogens and mutagens. On the other hand, in a case control study in Mexico, chili pepper consumers were at a significantly higher risk of developing gastric cancer than non-consumers.

Capsaicin is among a host of chemical compounds, including sulfides, indoles, and vitamins, that have significant influence on the cytochrome P-450 enzymes, which are responsible for the bulk of oxidation of xenobiotic chemicals.

**EVENING PRIMROSE OIL**

In 1987, Van der Merwe and Booyens reported gamma-linolenic acid (GLA) treatment of 21 patients with advanced malignancies. This therapy was based on the finding that GLA suppresses the proliferation of malignant cells in tissue culture and on the observation that evening primrose oil, containing a high level of GLA, reduces the rate of growth of transplanted mammary carcinoma in rats. Subjective improvement was observed in almost all 21 patients, and a survival benefit was reported in hepatocellular carcinoma patients, increasing from a mean of 40 days to 90 days, but using historical controls. Ongoing studies in Europe sponsored by Scotia Pharmaceuticals will help answer the question of clinical benefit. A single-course, 10-day infusion of lithium GLA for nonresectable pancreatic cancer is said to have significantly prolonged survival. Intratumoral GLA is reported to shrink lesions significantly without toxicity.

**GARLIC**

Garlic extract has been reported to inhibit the first stage of tumor promotion in a two-stage mouse skin carcinogenesis model in vivo, to inhibit dimethylhydrazine-
induced colon cancer in mice,\textsuperscript{396} and to inhibit growth of Morris hepatomas,\textsuperscript{76} possibly as a result of diallyl sulfide, a thioether. Although no clinical study in humans has been reported, recent comparative epidemiologic studies with ecologic and case control approaches in high-epidemic and low-epidemic areas of China\textsuperscript{368} suggest that frequent vegetable and garlic consumption contributes to low mortality rates for esophageal and stomach cancers in a low-epidemic area. Unfortunately, a recent study by Hoshino\textsuperscript{160} suggests that some garlic preparations may cause undesirable effects, including gastrointestinal problems. Two recent reviews suggested that garlic might stimulate the immune response and therefore reduce the risk of cancer.\textsuperscript{7,204} This inconsistency in the efficacy of garlic supplements may be a result of active compounds not being accurately identified and standardized. Song and Milners,\textsuperscript{345} studies illustrate that the benefits of garlic may be lost because of the preparation or processing methods, such as heating.

**GINSENG**

Yun and Choi\textsuperscript{418} found a lower overall rate of several cancers, including lung, hepatoma, and head/neck, in people who took extracts or powdered ginseng but not in those who used fresh ginseng or ginseng tea. Ginseng can cause swollen and tender breasts, headaches, tremors, manic episodes, insomnia, vaginal bleeding, and hypertension. In a more recent systematic review of 16 randomized clinical trials, Vogler et al.\textsuperscript{392} concluded that ginseng root extract did not show effect on physical performance, psychomotor performance, cognitive function, the immune system, diabetes mellitus, or herpes simplex II infections. Efficacy of ginseng is either not known or unquestioned, and adverse reactions are not accurately described due to variation in production and potential ingredient contamination.\textsuperscript{212}

**MISTLETOE**

Without empiric evidence of benefit, Steiner considered mistletoe a future cancer therapy but thought its spiritual quality would help integrate patients’ “four different entities.”\textsuperscript{114} Mistletoe is commonly used in Europe, especially in Germany, where yearly expenditure is more than $750,000. It has been used as a sedative and for treatment of epilepsy, headache, paralysis, hypertension, lung ailments, and debility. Mistletoe is so popular that a stamp picturing the plant was issued in Guernsey, England, in 1978.

Animal studies in India have shown that *Iscador*, an extract from the semiparasitic plant *Viscum album*, was found to exhibit a dose-related inhibition of 20-methylcholanthrene–induced carcinogenesis in mice.\textsuperscript{200} Yoon et al.\textsuperscript{415} reported the inhibitory effect of Korean mistletoe (*Viscum album coloratum*) extract on tumor angiogenesis and metastasis of hematogenous and nonhematogenous tumor cells in mice, which he believed to be a result of the induction of tumor necrosis factor alpha\textsuperscript{405} (TNF-\(\alpha\)).

Further studies with mistletoe (*Viscum album*) lectins revealed that using the purified proteins from this plant induced apoptosis in lymphocytes in culture, as measured by the appearance of a hypodiploid DNA peak using flow cytometry.\textsuperscript{47}
Mistletoe lectins have also been shown to have cytotoxic effects on breast cancer in cell culture. In addition, it was postulated that cell killing may have been accomplished indirectly by damaging the cell membranes, with subsequent influx of Ca\(^{2+}\) and of DNA intercalating the dye propidium iodide and with cell shrinkage.

Although mistletoe has been regarded as a potentially dangerous plant, with the ability to cause seizures and even death, Spiller et al. surveyed 92 people who had used this treatment and found that 11 were symptomatic from the mistletoe. The symptoms included gastrointestinal tract upset (six patients), mild drowsiness (two), eye irritation (one), ataxia (one child), and seizure (one child). Medical intervention was required in only one of these patients. Mistletoe preparations vary substantially depending on how they are prepared, which species they were obtained from, and the harvest season.

Numerous controlled clinical studies show no significant antitumor activity from mistletoe. Most treatment or prevention studies that have shown positive results are not considered scientifically dependable. A recent European Phase III trial on the effect of an adjuvant mistletoe extract treatment in 477 patients with head and neck squamous cell carcinoma showed that 5-year survival of patients from the mistletoe group was no better than that in control patients. In addition, no stimulation of the immune system or improvement in quality of life could be detected. A similar conclusion was drawn in an earlier Phase III trial of patients with high-risk melanoma.

HERBAL REMEDY TOXICITY

As with synthesized drugs, plant products taken in excessive amounts may cause toxicity. Even prune juice, a natural laxative, may cause diarrhea if taken in excess. Licorice may cause hypertension as well as potassium loss. A recent review suggests that in high dosages for long periods, licorice can trigger pseudoaldosteronism, which may lead to hypokalemia, heart failure, and cardiac arrest. However, Wang and Nixon suggest that licorice might be a candidate in cancer chemoprevention studies when used with other botanicals such as green tea.

Many products can cause an allergic reaction, and many plants are carcinogenic in animals. Many herbal products are collected in their plant form, which may be contaminated with toxic insecticides, fertilizers, or infectious agents. Herbal remedies may contain lead, mercury, tin, zinc, or arsenic, which can be toxic in their own right.

Herbal remedies are often believed to be harmless because of the “natural” characteristics. Although this is generally true, potential and demonstrated toxicities occur. Because these herbs are often prescribed in otherwise healthy people and are presumed to be safe, it is of particular importance to delineate some of these side effects (Table 4–2).

Two herbal products deserve specific mention. First, chaparral tea can cause severe liver toxicity with cholestasis and hepatocellular injury, which resolved with discontinuation but recurred with challenge in one reported case, leading to fulminant hepatic failure requiring a liver transplant. Renal disease may also result from chronic chaparral tea ingestion. The FDA has cautioned against the internal use of chaparral.
Second, short-term use of the Chinese herb *Jin bu huan* has been found to produce life-threatening neurologic and cardiovascular effects requiring intubation in children. Long-term treatment causes liver injury from a poorly defined hepatotoxic mechanism. The chemical L-tetrahydropalmatine, a potent neuroactive substance, may play a role in this toxicity because it is 34% by weight, whereas in the natural plant it is only 1.5%. This product is sold without childproof packaging. *Jin bu huan* has been banned in the United States but apparently is still available. A recent study also shows hepatotoxic effects for additional Chinese herbal medicines (e.g., *Ma Huang*, *Sho-saiko-to*), pyrrolizidine alkaloid–containing plants, *germander* (*Teucrium chamaedrys*), *Atractylis gummifera*, and *Callilepsis laureola*. The recent ACS publication and reviews* provide an updated list of unsafe and potentially safe herbal therapies (Table 4–6). The authors emphasize that an increase in public education, physician/pharmacist awareness, and patient-physician/pharmacist communication is needed to protect consumers from potential herbal remedy toxicity and herb-drug interactions. In addition, the lack of reliable research data, well-designed clinical trials, quality control, standardization of products, and postmarketing surveillance studies, as well as the increase in unregulated licensing, are key issues in the use of herbal therapies.

**OTHER TOXICITIES**

Supplementation in healthy individuals can be problematic because of the toxicities for these products, even if they are rare. Vitamin toxicities are uncommon but well defined, including vitamin A’s side effects of increased intracranial pressure and vomiting in children and its chronic use in adults potentially leading to hypercalcemia, teratogenic abnormalities, and rheumatologic complications. Pennes et al., in a prospective study of patients receiving 13-cis-retinoic acid therapy, described the skeletal hyperostoses. The most common site of extraspinal hyperostoses is the knee. Such arthropathies with arthralgias and myalgias may appear, often disappearing even with continued use.

*Vitamin B complex* overdose can lead to cardiovascular toxicities, including arrhythmias, edema, vasodilation, and allergic reactions. Megadoses of niacin can cause cardiac toxicity with arrhythmias and infarction, as well as liver toxicity and peptic ulceration. Long-term high-dose toxicities include gouty arthritis, hyperglycemia, hyperkeratosis, dry skin, and rashes. Vitamin B₆ in megadose levels has caused peripheral neuropathies, with resulting numbness lasting up to 3 years.

*Vitamin C* toxicities include the development of renal stones and a risk of rebound scurvy when high-dose treatment is discontinued. Ascorbate has been found to inhibit mitoses and to induce chromosomal aberrations in cultured Chinese hamster ovary cells. The addition of copper and manganese enhanced both actions. Iron in both the ferrous and the ferric states also enhanced the chromosome-damaging capacity of ascorbate.

*References 63, 97, 174, 182, 192, 193, 286, 290.*
<table>
<thead>
<tr>
<th>Common Name</th>
<th>Scientific Name</th>
<th>Evidence</th>
<th>Conclusion</th>
<th>Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Milk vetch, Huang qi/ch'i</td>
<td>Astragalus membranaceus</td>
<td>Laboratory/animal studies suggest enhancement of immune response. No human study.</td>
<td>More research needed to determine activity of Astragalus with conventional cancer treatment.</td>
<td>Abdominal bloating, low blood pressure, loose stools, dehydration.</td>
</tr>
<tr>
<td>Kilwart, milkbush, pencil tree</td>
<td>Euphorbia tirucalli, E. insulana</td>
<td>Laboratory/animal studies suggest promotion of tumor growth and suppression of immune system.</td>
<td>Risks outweigh benefit.</td>
<td>Burning of mouth and throat, skin inflammation, conjunctivitis, diarrhea, nausea, vomiting, stomach cramps.</td>
</tr>
<tr>
<td>Betulinic acid, Butalin, Bet A</td>
<td>—</td>
<td>Laboratory studies show antitumor activity in melanoma and nervous system tumors.</td>
<td>More research needed to determine if betulinic acid is potential antitumor drug.</td>
<td>Side effects are being studied.</td>
</tr>
<tr>
<td>Cat's claw, una de gato</td>
<td>Uncaria tomentosa</td>
<td>Laboratory/animal studies suggest alkaloids (active ingredients) may increase immune response. Human study in progress.</td>
<td>More research needed to determine activity in cancer treatment. Contains tannins, which can cause gastrointestinal problems and kidney damage. Potentially serious drug-herb interactions.</td>
<td></td>
</tr>
<tr>
<td>Ginger root</td>
<td>Zingiber officinale</td>
<td>Laboratory/animal studies suggest some antitumor promotional and antiproliferative effects. No human study; ability to reduce nausea/vomiting has mixed results.</td>
<td>More research needed to determine effectiveness, amount, and specific ingredients of ginger in cancer treatment/prevention and in treating nausea/vomiting.</td>
<td>Interference with blood clotting; prolongation of bleeding. Allergic reaction, upset stomach. Potentially serious drug-herb interactions.</td>
</tr>
<tr>
<td>Product</td>
<td>Primary Active Ingredients</td>
<td>Research Studies</td>
<td>Potential Interactions</td>
<td></td>
</tr>
<tr>
<td>---------------------------------</td>
<td>-------------------------------------------------------------------------------------------</td>
<td>-----------------------------------------------------------------------------------</td>
<td>---------------------------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>Ginkgo biloba</td>
<td>Ginkgo biloba</td>
<td>Laboratory/animal studies show some positive antioxidant and chemopreventive effects.</td>
<td>More research is needed to determine effectiveness of ginkgo in cancer treatment/prevention.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>No human study.</td>
<td>Potentially serious drug-herb interactions.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Headache, seizure (children), dizziness, upset stomach, bleeding.</td>
<td></td>
</tr>
<tr>
<td>Golden seal, eye balm,</td>
<td>Hydrasis canadensis</td>
<td>No scientific evidence on effectiveness.</td>
<td>Testing needed for developmental problems and cancer of reproductive system.</td>
<td></td>
</tr>
<tr>
<td>eye root, goldsiegel,</td>
<td></td>
<td></td>
<td>High doses can lead to death from highly toxic effects.</td>
<td></td>
</tr>
<tr>
<td>ground raspberry, Indian</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>dyes, Indian turmeric,</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>jaundice root, yellow paint,</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>yellow puccoon, yellow root</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Green, black, and Chinese tea</td>
<td>Camellia sinensis</td>
<td>Laboratory/animal studies show some positive antioxidant and chemopreventive effects.</td>
<td>Clinical trials needed to determine effectiveness of green tea in cancer prevention.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Human studies have mixed results.</td>
<td>Allergic reactions.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Nutritional and other problems with large amounts of tea due to its caffeine content and polyphenol activities.</td>
<td></td>
</tr>
<tr>
<td>Marijuana (pot,grass, cannabis,</td>
<td>Cannabis sativa, delta-9-tetrahydro-cannabinol (THC)</td>
<td>Synthetic THC may be used to control chemotherapy-induced vomiting and nausea when other antiemetic drugs are useless.</td>
<td>More and better studies needed to evaluate use of marijuana as supportive care for cancer patients.</td>
<td></td>
</tr>
<tr>
<td>weed, hemp)</td>
<td></td>
<td>Additional studies sponsored by NCI are in progress.</td>
<td>Smoking/eating raw marijuana may cause euphoria, low blood pressure, tachycardia, and heart palpitations.</td>
<td></td>
</tr>
<tr>
<td>Milk thistle, Mary, Marian,</td>
<td>Silybum marianum</td>
<td>Laboratory/animal studies show some positive antioxidant and chemopreventive effects.</td>
<td>More research needed to determine effectiveness of silymarin in cancer treatment/prevention and in reducing chemotherapy side effects.</td>
<td></td>
</tr>
<tr>
<td>and Holy lady thistle, silymarin</td>
<td></td>
<td>No human study.</td>
<td>Allergic reactions.</td>
<td></td>
</tr>
<tr>
<td>Oleander, dogbane, Louvier rose,</td>
<td>Nerium oleander, Oleandri potum, Thevetia peruviana</td>
<td>No scientific evidence on effectiveness of oleander.</td>
<td>Nutritional and other problems with large amounts of tea due to its caffeine content and polyphenol activities.</td>
<td></td>
</tr>
<tr>
<td>rose, rose bay, andrzel</td>
<td>T. ipe, T. heptaphylla, T. ipe, T. tubebu a impetiginosa, T. avallanectae</td>
<td></td>
<td>May lead to fatal respiratory paralysis and cardiac effects.</td>
<td></td>
</tr>
<tr>
<td>Pau D’Arco, lapacho;</td>
<td>Laboratory/animal studies show some effects on certain tumor cells (sarcoma)</td>
<td>Should not be used.</td>
<td>Vomiting, diarrhea.</td>
<td></td>
</tr>
<tr>
<td>lapacho marado, Colorado; lapacho</td>
<td>Few studies of lapacho in humans show serious risk of side effects.</td>
<td>Should not be used.</td>
<td>High doses: interference with blood clotting.</td>
<td></td>
</tr>
<tr>
<td>raso, raso, raso, tahuari,</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>trumpet bush, trumpet tree</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Common Name</td>
<td>Scientific Name</td>
<td>Evidence</td>
<td>Conclusion</td>
<td>Complications</td>
</tr>
<tr>
<td>---------------------</td>
<td>-----------------</td>
<td>---------------------------------------------------------------------------</td>
<td>-----------------------------------------------------------------------------</td>
<td>--------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Saw palmetto</td>
<td><em>Serenoa repens</em></td>
<td>Scientific evidence shows relief of symptoms in benign prostatic hyperplasia (BPH). NCCAM co-sponsoring clinical trial for BPH.</td>
<td>More research needed to determine effectiveness of saw palmetto on BPH complications.</td>
<td>Headache, nausea, vomiting, upset stomach, dizziness, constipation, diarrhea, difficulty sleeping, fatigue, heart pain, hepatitis, and fibrosis.</td>
</tr>
<tr>
<td>St. John’s wort, goatweed, amber, Klamath weed, Tipton weed, Kira, Tension Tamer, Hypercalm</td>
<td><em>Hypericum perforatum</em></td>
<td>Scientific evidence shows effectiveness in treating mild to moderate depression. NIH sponsoring multicenter clinical trial using hypericin.</td>
<td>More research needed to determine effectiveness of St. John’s wort as effective antidepressant, especially in cancer patients.</td>
<td>Interactions with alcohol, narcotics, amphetamines, anticoagulants, antibiotics, cold/flu medicine (pseudoephedrine), antidepressants, warfarin, indinavir, cyclosporine, digoxin, oral contraceptives, antiretrovirals. *</td>
</tr>
</tbody>
</table>

NCl, National Cancer Institute; NCCAM, National Center for Complementary and Alternative Medicine; NIH, National Institutes of Health; PSA, prostate-specific antigen.

*Interactions may result from induction of P450 enzyme system. Serious adverse effects include photosensitization and induction of manic symptoms.*
Vitamin D overdose becomes evident in elevated blood calcium levels and may cause symptoms of anorexia, nausea/vomiting, polyuria, polydipsia, weakness, pruritus, and nervousness, potentially with irreversible calcification of soft tissue in the kidney and liver. As newer, more highly active forms of vitamin D are developed, it becomes imperative to monitor even more carefully for this potential toxicity.

High-dose vitamin E therapy can interfere with blood coagulation by antagonizing vitamin K and inhibiting prothrombin production. As discussed earlier, in a recent study of vitamin E an increased number of strokes were observed in the vitamin E treatment group compared with the control group.5

**IMMUNOAUGMENTATIVE THERAPY**

As proposed by Burton, immunoaugmentative therapy (IAT) is based on balancing four protein components in the blood and relies on strengthening the patient’s immune system.39,40 The use of various organ extracts from cows and pigs is claimed to suppress tumors selectively, stimulate defense cells, and revitalize several tissues. No studies have shown clinical effectiveness.5,33,364 Popularity of IAT has apparently declined.56 Based on data from 79 patients who received IAT, the University of Pennsylvania Cancer Center researchers could not make meaningful comparisons between IAT patients and those treated with conventional treatment.317 The FDA banned the import of IAT drugs in 1986.

Another approach may be to simply replace immune system function (immunotherapy) with T cells that are taken from each patient’s tumor, grown in the laboratory, and then readministered with protein (interleukin-2 [IL-2]) for continued stimulation. The technique, known as adoptive transfer, has recently been shown in preliminary studies to shrink metastatic melanoma in a small number of patients.87a

**MIND-BODY TECHNIQUES**

A number of laboratories have documented that psychologic techniques have affected the immune system of specific people with a high absorption ability. The response purportedly is based on an ability to concentrate so intently that physiologic action results from mental events such as fantasies or memories.370 Screening for these inclusionary personal characteristics may be helpful before prescribing a particular adjunctive technique, such as relaxation or imagery.135

Prayer, meditation, biofeedback, t’ai chi,52 Qi Gong,323,322,394 and yoga are all being used with increasing frequency in the treatment of cancer. Anecdotal cases of tumor regression in juxtaposition with prayer have been discussed, as has the role of prayer in lessening anxiety.86 Biofeedback has been beneficial in treating cancer pain as well as in regaining both urinary and fecal continence after cancer surgery.58,197,330 Visualization of the cancer so that the body can fight the disease may help patients regain control of their health care and may help with stress reduction,107 but failure of the method to change the course of cancer puts the blame squarely on the patient’s shoulders.
The use of mind-body approaches as a primary cancer treatment has not been studied in a controlled way. Anecdotal reports of response, for example, in “Bob Brody’s Athlete’s Edge against Cancer,” implies that the mind of the athlete is particularly conducive to “fighting” against cancer and that others can learn to do this as well.53

**DISTRACTION, COGNITIVE-BEHAVIORAL, AND GROUP THERAPY**

Distraction therapies involve pleasant thoughts or activities that distract the patient from the unpleasant effects of cancer such as pain. Cognitive-behavioral therapies involve the patient making an active effort to view the cancer in the best possible light (e.g., “taking one day at a time”). Both forms of therapy may have a role in the overall care of the cancer patient.

A 1989 report showed a survival advantage for women who were randomly assigned to a weekly talk and support group, including training in self-hypnosis for pain, compared with control patients.346 A second study failed to replicate such an advantage.117 More recently, Goodwin et al.128 reported that “supportive-expressive group therapy did not prolong survival in women with metastatic breast cancer,” although it did improve mood and pain perception. These other end points in addition to survival (satisfaction with treatment, coping skills) are important when designing studies. Also, combining methods such as nutrition with relaxation or other mind-body therapies can lead to additive effects.397 A greater self-awareness in one arena may potentiate good health practices in another area.

**AROMATHERAPY**

Aromatherapy is becoming more popular in the United States. Wilkinson400 described 51 patients in a hospice who were divided into two massage therapy groups, one using standard massage oil alone and one group with 1% essential oil, Roman chamomile, added. Although both groups showed a decrease in anxiety, the experimental aromatherapy group exhibited even lower anxiety, fewer physical symptoms, and a better quality of life. Although no scientific evidence indicates that aromatherapy cures or prevents disease, a few clinical studies suggest aromatherapy may be a beneficial complementary therapy in reducing stress, pain, and depression as well as enhancing quality of life.73,190,317

**MEDITATION**

Transcendental meditators have been found to have higher daytime levels of the serotonin metabolite 5-hydroxyindole-3-acetic acid (5-HIAA) compared with control subjects, and these levels increased with meditation. Serotonin is a precursor of melatonin (see later discussion). Meditation and melatonin have some similar effects: analgesia, antistress effect, antiinsomnia/hypnotic effect, and decreased heart rate and blood pressure.233
MUSIC THERAPY

Some studies have found that music therapy can lower heart rate, blood pressure, and breathing; alleviate insomnia and depression; and relieve stress and pain. Music therapy may help reduce pain and ease physical symptoms of chemotherapy-induced nausea and vomiting.

HEAT THERAPY (HYPERTHERMIA)

Heat therapy involves exposing part or all of the body to high temperatures (up to 106°F). External and internal heating devices are used to enhance other treatments, such as radiation therapy, biologic therapy, and chemotherapy. A potential hypothesis is that heat may help shrink tumors by damaging cells or depriving them of substances they need to live. The effectiveness of laboratory and animal studies on heat therapy led to numerous clinical trials using whole-body heat therapy, and NCI is currently sponsoring several studies using whole-body heat therapy. With the high mortality and labor-intensive methods associated with whole-body heat therapy, more research is needed before hyperthermia can be considered as a permanent element in a multimodal therapeutic concept in cancer treatment (see Chapter 2).

BIOELECTRIC TREATMENTS

Nordenström described electric stimulation treatment for cancer. Electroporation, a new technique to enhance antitumor effects of chemotherapeutic agents, has been expounded recently by a number of researchers. They report that electric current delivered to the tumor reversibly increases permeability of the cell membranes, allowing intracellular concentrations of chemotherapy to increase significantly, up to 700 times with some agents.

Chou et al. reported beneficial treatment of fibrosarcomas in mice and rats with direct current (DC) through apoptosis. A number of reports on small studies indicate the potential of electrochemotherapy in several types of cancer, including salivary gland and breast, lung, hepatocellular carcinoma, and others. A clinical study of two patients with basal cell carcinoma used untreated nodules as controls while applying DC to other nodules simultaneously with systemic bleomycin chemotherapy. Improvement with DC was significantly greater than with bleomycin alone. Mir et al. found that the addition of IL-2 to bleomycin/electrochemotherapy increased cure rates in mice with subcutaneously implanted cancer.

Seven patients with squamous cell carcinoma of the head and neck were treated with electroporation and very low dose bleomycin. Of the 34 treated nodules in these seven patients, 14 showed a complete remission and nine showed partial regression. Multiple nodular disease is an unusual presentation for head and neck carcinomas, and questions surround the natural history of these patients. The results indicate a need for randomized studies with clear measurements and follow-up.
HYDRAZINE SULFATE

Claims that hydrazine sulfate is a cure for cancer and a treatment of its devastating effects, including cachexia, have been made for several decades. The potential mechanism of action was said to be hydrazine’s monoamine oxidase–like effect. Many anecdotal and some controlled studies were reported throughout the 1970s and 1980s indicating effectiveness of hydrazine as a cancer treatment* and as treatment for the abnormal glucose tolerance of cachectic cancer patients.67 Other studies, however, failed to confirm these findings.299,276,350

Recently, several randomized, well-controlled studies showed no beneficial effect of hydrazine sulfate in lung cancer or colorectal cancer.196,223,224 The double-blind study by Kosty et al.196 included 291 newly diagnosed, untreated patients with non–small cell cancer of the lung randomly selected after optimal treatment with cisplatin and etoposide to receive hydrazine sulfate or placebo. There was no evidence of increased response rate or survival difference as a result of the hydrazine, but evidence did show a poorer quality of life in the treated group. There was no difference in the two groups of this double-blind study with regard to anorexia, weight gain, or nutritional status. In the study by Loprinzi et al.,223 127 assessable patients with advanced colorectal cancer were randomly selected to use hydrazine sulfate or placebo. The hydrazine-treated patients showed trends for poorer survival and poorer quality of life. There were no differences in the two arms of this randomized study relating to anorexia or weight loss. Chlebowski et al.66 reported a randomized study of non–small cell lung cancer patients treated with bleomycin, vincristine, and cisplatin followed by either observation or hydrazine sulfate. Neither response rate nor survival was statistically different in the two arms of this randomized study. Caloric intake and albumin maintenance levels were improved in the hydrazine-treated patients.

A further double-blind, randomized study of patients with colorectal cancer receiving hydrazine sulfate had to be discontinued early because the mortality in the treated arm was higher than predicted. However, proponents of hydrazine sulfate therapy continue to claim its value and report further noncontrolled studies to support their claims.105 In the treatment of 200 patients with lung cancer and 55 patients with colorectal cancer, proponents claimed “positive” results when 6 of 740 patients were said to have a complete remission, although no clear evidence of measurable, biopsy-proven disease was provided.

Much discussion has surrounded the increased feeling of wellness and the improvement in cachexia of cancer patients.65–67 Chlebowski and Grosvenor48 described the abnormal glucose tolerance and increased glucose production frequently seen in cancer patients, as well as the improvement in these measurable parameters seen with hydrazine sulfate treatment, thought to result from the inhibition of gluconeogenesis. In the first of these “randomized” studies, however, the control group of 30 had an addition of 40 nonrandomized treated patients, a serious flaw in the study’s design. Furthermore, the results of these studies were not confirmed in the well-designed study by Kosty et al.196 and in the previously cited studies. A recent case study reported fatal hepatorenal failure in a 55-year-old man with maxillary sinus cancer resulting from self-medication with hydrazine sulfate.140

AMYGDALIN (LAETRILE)

No discussion of CAM and cancer would be complete without a mention of the drug amygdalin (Laetrile), derived from apricot and other fruit pits. Although amygdalin had been used for centuries, it was elevated to new heights under the trade name Laetrile by Ernest Krebs, Jr., in 1952, and it totally eclipsed all other unorthodox treatments. A review was undertaken that revealed six cases in which there was a possible Laetrile effect. Based on these findings, Moertel et al. treated 178 previously untreated patients with good performance status with Laetrile; vitamins A, C, E, and B complex; and minerals, as well as with pancreatic enzymes. Only one patient, who had a gastric carcinoma with cervical lymph node metastases, had a possible short-lived, partial remission of 10 weeks. All others showed no response. No evidence indicated stabilization of disease. Blood cyanide levels were high and often in the toxic range, at levels known to kill animals and humans. In addition, the Laetrile was generally available from Mexican suppliers and was found to be contaminated with infectious agents and endotoxin.

Deaths attributable to Laetrile have been reported. Laetrile use is not approved in the United States.

MELATONIN

The pineal gland appears to have an important role in regulating the body's circadian rhythm. In animal studies, pinealectomy has been reported to cause a proliferation of cancers, and physiologic concentrations of melatonin, a hormone synthesized in the pineal gland, inhibit growth in vitro of some breast cancer cell lines. Epithalamin, a low-molecular-weight, pineal-derived peptide, prolonged the life of various strains of mice and rats. Epithalamin decreased the incidence of spontaneous tumors and radiation-induced mammary carcinoma in rats, inhibited the growth of N-nitrosoethylurea (NEU)-induced transplacental carcinogenesis in rats, inhibited the growth of transplanted tumors and their metastases, and increased tumor sensitivity to cytotoxic therapies. One explanation for these actions may be the observed increase in the night peak of melatonin with epithalamin treatment.

Melatonin levels rise to a plateau between midnight and 3 AM in people who have a standard work-sleep lifestyle, then fall to low levels after light appears. The pineal gland and melatonin are involved in regulation and timing of reproduction, in development, and in the aging process. Possible mechanisms for melatonin activity are as (1) an anti–physical stress hormone, (2) an immunomodulatory agent through the release of opioid peptides and IL-2 by T helper cells, (3) a scavenger of endogenous hydroxyl radicals, (4) an oncostatic agent inhibiting proliferation of estrogen-responsive cells (e.g., MCF-7 human breast cancer cells), and (5) an endogenous antiestrogen inhibiting breast cancer growth in vivo and in vitro. Studies indicate that melatonin may act synergistically with tamoxifen.

Melatonin level has a suppressed nighttime rise in patients with breast cancer. Patients who exhibited a twofold rise in peak levels were associated with a low proliferative index, possibly indicating a more favorable outcome. A depressed or absent nocturnal peak level has also been reported in men with prostate cancer when
compared to men with benign prostatic hypertrophy or normal control subjects. Also, melatonin has resulted in a survival advantage and an improvement in quality of life indicators in patients with brain metastases from solid tumors.\(^\text{217}\)

It has been suggested that melatonin is a gonadal inhibitor and that the loss of this function with the decrease of melatonin could be related to the development of hormonally sensitive cancers, such as those of the breast and prostate. Melatonin also appears to antagonize the immunosuppressor effects of corticosteroids, to increase the cytotoxic activity of NK cells, and to interact reciprocally with beta-endorphins. There has been evidence of in vitro cytotoxic effects on cell culture preparations of breast, ovarian, and bladder cancers. Lissoni et al.\(^\text{218}\) reported on preliminary work in which melatonin appeared to enhance the effect of IL-2 in patients with solid tumors other than renal cancer and to ameliorate the IL-2 toxicity. Evidence also indicates that melatonin blocks macrophage activation of IL-2, producing a possible beneficial effect in the treatment of cancer-related thrombocytopenia.\(^\text{219,220}\)

The melatonin cycle may be abnormal in some cancer patients. High rather than low levels of melatonin have been reported in the morning in women with breast cancer. Abnormal levels in the cycle of melatonin have been reported in men with prostate cancer.\(^\text{233}\)

Based on a very small, noncontrolled trial using subjective end points related to performance status, Braczkowski et al.\(^\text{40}\) reported that “melatonin has to be considered as an essential drug in the curative or palliative therapy of human neoplasms and as a drug that plays an important role in reducing the administration toxicities of some cytokines.” Further studies are needed to draw such a conclusion. Maestroni and Conti\(^\text{228}\) reviewed the published literature on the effects of melatonin on tumor growth and quality of life. They concluded that “melatonin protects against IL-2 and synergizes with the IL-2 anticancer action. This combined strategy represents a well-tolerated intervention to control tumor growth. In most cases performance status and quality of life seem improved.” However, these reviewed studies were noncontrolled and often anecdotal, with subjective measurements.

Lissoni et al.\(^\text{220}\) reported a study of 100 people with solid tumors who were to have no further conventional chemotherapy and were randomly selected to receive either IL-2 plus melatonin or supportive care. There was no single drug arm of the study. The investigators found a 17% response rate in the immunotherapy group and the expected “no response” in the supportive therapy arm of the study. In addition, 1-year survival was significantly improved, as was the experimental arm’s performance status.

The circadian timing of chemotherapy may play an important role.\(^\text{161}\) The timing of the doxorubicin (Adriamycin) dose when given in combination with cisplatin in the treatment of 31 ovarian cancer patients was a determinant in the toxicity, with a morning dose being less toxic. This finding again points to a potential influence of the circadian rhythm system.

**SHARK CARTILAGE**

The use of shark cartilage as a potential treatment of cancer has become so well known that, according to one oncologist, 80% of cancer patients in that practice had asked
about this treatment in the preceding several months.231 The scientific basis for the use
of shark cartilage is based on the findings that (1) sharks infrequently develop cancer
(but in fact they have been shown to develop melanomas and brain malignancies225)
and most of the shark’s bulk is cartilage, which may be protective, and (2) cartilage
from calves as well as other animals contains substances that decrease angiogene-
sis.12,208 Cartilage itself is resistant to invasion by most tumors.390 Cartilage is vascular-
ized in its embryonal form, then loses this vascularization, which led Brem and
Folkman42 to postulate the production of a factor from cartilage that inhibits vascular-
ization and that could inhibit tumor angiogenesis. Such a cartilage-derived factor has
been discovered, purified, and found to be a protein with an approximate molecular
weight of 24,000 and potent antiprotase properties. This factor is very similar to a
collagenase inhibitor isolated from cultured human skin fibroblasts.

McGuire et al.238 reported that shark cartilage produced a concentra-
tion-dependent decline in endothelial cell 3H-thymidine incorporation using a human
umbilical vein cell proliferation assay. Gomes, Souto, and Felzenszwalb127 reported
that shark cartilage was instrumental in protecting cells against lesions induced by
hydrogen peroxide in normal and low iron conditions, suggesting a possible scavenger
role against free radicals.

A small study conducted in Cuba was reported in a segment of the television
show “60 Minutes” in 1993. In 29 patients receiving shark cartilage, three of 15 “evalu-
able” patients were said to have responded to treatment. No further information was
given regarding the types of cancer, the definition of response, or the reason for deem-
ing the other patients not evaluable. A further study of 70 patients was reported as
ongoing, but no results have been generated.164

Even if cartilage has antitumor properties, the likelihood of the ingested mate-
rial reaching the tumor at all, and in an active state, would be unlikely.231 Further, toxic-
ity appears to be rare, although one case of presumed hepatitis attributable to shark
cartilage has been reported.14

More recently a study concluded that orally administered liquid shark cartilage
effectively inhibited the growth of new blood vessels in healthy men, suggesting that the
active ingredients in liquid shark cartilage were available for use by the body.29 On the
basis of laboratory, animal, and human data, two randomized Phase III trials of shark car-
tilage along with conventional therapies have been approved by the FDA in patients with
stage III non–small cell lung cancer and patients with metastatic renal cell carcinoma.

BOVINE TRACHEAL CARTILAGE

Bovine tracheal cartilage (BTC) is an acidic glycosaminoglycan complex containing
20% chondroitin sulfate and lesser quantities of dermatan sulfate, heparan sulfate,
hyaluronic acid, and other polysaccharides. Human tumor stem cell assays have
shown antitumor effect in vitro.29 In 1985, Prudden280 reported a significant response
rate to BTC of 10% to 15% in various tumor types, including pancreatic, non–small
cell lung, gastric, and colon cancers and glioblastoma, but with no follow-up series. In
1994, Puccio et al.299 reported three responders in 20 patients with metastatic renal cell
cancer receiving the same BTC agent. No toxicity has been reported.
HYPERBARIC OXYGEN THERAPY

Hyperbaric oxygen therapy (HBOT) is an emerging specialty of medicine that uses oxygen at greater (1.5 to 3 times) than atmospheric pressures. HBOT has been used as an additional therapy for the prevention and treatment of osteoradionecrosis and clostridial myonecrosis and for assisting skin graft and flap healing and other cancer treatment complications.\textsuperscript{33,35,264} NCCAM is currently funding a specialized center to study the mechanisms of action, safety, and clinical efficacy of HBOT for head and neck tumors. HBOT side effects include claustrophobia, fatigue, headache, and myopia. Complications may result in convulsions and respiratory failure, as well as death from fires and explosions in hyperbaric chambers.

HOMEOPATHY

Homeopathy\textsuperscript{30} is based on the assumption that a substance that causes symptoms of illness can relieve those same symptoms when used in very small amounts. German physician Samuel Hahnemann developed homeopathy in the 1800s. A randomized controlled study with 32 patients ages 3 to 25 years suggests that TRAUMEEL S may reduce the severity and duration of chemotherapy-induced stomatitis in children undergoing stem cell transplantation.\textsuperscript{275} Additional studies with large sample sizes are needed to confirm this finding. Several reviews of homeopathy suggest that some individualized homeopathy remedies may have some effects over the placebo, possibly in palliative care.\textsuperscript{77,98,100,213,324}

However, the evidence is not convincing because of methodologic shortcomings and inconsistencies, such as poor sampling and measurement techniques as well as no replication. Furthermore, studies with better methodologic quality tended to yield less positive results. Scheen and Lefebvre\textsuperscript{214} even questioned the validity of a meta-analysis of controlled studies, concluding that the clinical effects of homeopathy are not completely caused by a placebo effect.\textsuperscript{25} Therefore it is still questionable whether homeopathy has a role in palliative cancer care.

NEWCASTLE DISEASE VIRUS

Newcastle disease virus (NDV) is a paramyxovirus that causes Newcastle disease in a variety of birds but only minor illness in humans. The two strains of NDV are lytic and nonlytic. Lytic NDV is used for its ability to kill cancer cells directly, but both strains have been used to make vaccines to stimulate the immune system to fight cancer. Although several clinical studies report the benefit of NDV-based anticancer therapy, their results are questionable due to their poor designs, incomplete reporting, and small number of patients. Future studies should explore the possibility that the immune system may produce virus-neutralizing antibodies by repeated administration and may defeat the underlying vaccine mechanism.\textsuperscript{286}
Side Effects of Cancer and Cancer Treatment: Palliative and Supportive Care

Cancer and its treatment cause many types of symptoms. Pain, nausea, and weakness are all potentially disabling. Patients' perceptions of their discomfort are so different that health care providers must treat patients individually with varying methods. Physical suffering, or pain, is the most common and the most quantifiable, although imprecisely and subjectively, of these side effects (see Chapters 10 and 12).

Ahmedzai et al. define supportive care for cancer patients as the “multi-professional attention to the individual’s overall physical, psychosocial, spiritual and cultural needs, [which] should be available at all stages of the illness, for patients of all ages, and regardless of the current intention of any anti-cancer treatment.” Palliative care is the achievement of the best possible “quality of life” for the patient. It focuses on the palliation of physical symptoms such as pain, nausea, vomiting, constipation, and fatigue as well as psychologic symptoms such as anxiety, depression, and spiritual distress.

A nonrandomized controlled trial compared one group who heard a personal tape-recorded message from the patient’s physician at chemotherapy with a control group who heard no recording. The study found a reduction in overall anxiety levels in patients who heard the personal message but found no difference in specific side effects of chemotherapy.

An independent NIH panel found strong evidence for the use of hypnosis in reducing pain associated with cancer. Wong et al. provided preliminary evidence suggesting how Chinese medicine modalities such as herbs, acupuncture, meditation, Qi Gong, and t’ai chi can be integrated into the supportive cancer care. Ernst provided some evidence indicating that complementary therapies such as acupuncture, acupressure, aromatherapy, massage, reflexology, and relaxation have potential in palliative and supportive cancer care. However, due to the lack of well-designed and large-scale studies, the evidence is still preliminary. More rigorous clinical research in these CAM modalities is required before they can be fully integrated into standard care of cancer patients.

Breathlessness

Breathlessness in cancer patients is a common finding and a late sign of disease. The first treatment is for the underlying disease entity, such as a mass lesion (primary lung cancer, metastasis from other cancers, finding of a pleural effusion), and if that fails, treatment of the symptom itself. Treatment is often chest physiotherapy (to remove secretions), bronchodilators, oxygen, and respiratory sedatives (e.g., opioids), frequently with little benefit. Other symptoms are controllable; pain generally improves, but breathlessness does not improve.

Filshi et al. found significant improvement in 14 of 20 patients with various cancer types who received treatment with sternal and hand acupuncture. This beneficial result lasted over the next 1½ to 6 hours and was independent of the patient’s anxiety index. The authors acknowledged that the placebo effect could have played a
significant role and that a controlled study is needed. Bailey discussed breathing control techniques and nursing therapy to alleviate loss of function and to ease the psychologic burden through an integrative model. The aims of these techniques are to promote a relaxed and gentle breathing pattern; minimize the work of breathing; establish a sense of control; improve ventilation at the bases of the lungs; increase the strength, coordination, and efficiency of the respiratory muscles; maintain mobility of the thoracic cage; and promote a sense of well-being. The authors reported preliminarily that their techniques are successful in enhancing a quality of life of patients with lung cancer experiencing breathlessness.

**MUCOSITIS**

A controlled clinical trial of 94 patients in the use of imagery and cognitive-behavioral training designed to reduce mucositis pain during cancer treatment was performed by Syrjala et al. Four groups of patients who had undergone bone marrow transplantation were compared: (1) treatment as usual to act as controls, (2) therapist support, (3) relaxation and imagery training, and (4) training in a package of cognitive-behavioral coping skills that included relaxation and imagery. The authors concluded that relaxation and imagery training reduced the cancer treatment–related pain of mucositis relative to the control arm but that adding cognitive-behavioral skills did not enhance this improvement.

**NAUSEA AND VOMITING**

Keller summarized several nonpharmacologic approaches to the treatment of nausea and vomiting resulting from cancer treatment in children. Distraction, including listening to music, was effective in decreasing the duration of the nausea but not its severity. Video games decreased both the anticipatory and the post treatment nausea. Hypnosis, used in children as young as 4 years old, resulted in decreased severity and duration of nausea. Progressive muscle relaxation with relaxation tapes appeared to decrease nausea. Diet modification also could be helpful. Acupuncture, acupressure, or transcutaneous electric stimulation of the P6 antiemetic acupuncture site seemed to have some effect, which was not found with treatment to a dummy acupuncture site.

Nausea resulting from chemotherapy can be ameliorated by hypnosis. Jacknow et al. reported a decrease in anticipatory nausea in children, a common and often treatment-limiting side effect of chemotherapy, that was sustained after only 2 months of treatment using self-hypnosis. Significantly fewer doses of as-needed antiemetics were used by the treatment group compared with a control group in this small, randomized study of 20 patients. Hypnosis also was found to improve coping skills in cancer patients, leading to decreased symptoms.

**RADIATION-INDUCED XEROSTOMIA**

Xerostomia is a common toxic effect of radiation therapy. Acupuncture was given to 41 patients with varying degrees of xerostomia. No explanation for the rationale for
this treatment was given. Classic acupuncture was used as the treatment arm, and superficial, subcutaneous acupuncture 1 cm from the classic site was used as a control. No difference in results was seen between the two arms, although some improvement occurred in both groups. Whether this improvement was normal healing or a result of the acupuncture could not be determined. The authors concluded that acupuncture might be helpful in xerostomia and that superficial acupuncture should not be the control.

SUMMARY
CAM is widely used in the treatment of cancer by all types of people and more often by educated and affluent patients. As insurance companies increase coverage, CAM use will rise. It is important for health care providers to be knowledgeable about these treatments and to discuss them openly with patients.

Diet has been implicated as a means of preventing cancer. Low-fat, high-fiber diets are associated with lower risks of colon, breast, and aggressive prostate cancer. The use of antioxidants (e.g., vitamins A, C, and E) is controversial as preventive treatment. No diets or herbal treatments have been shown to reliably achieve responses for active cancer, although the polysaccharide agent PSK prolonged survival in Phase III trial patients when used as an adjuvant agent. Melatonin, Chlorella, PC SPES, and other herbal agents have shown indications of anticancer activity in preliminary studies and merit closer investigation. Even with well-designed studies, however, the products' contamination, such as PC SPES with warfarin, is still one of the major obstacles toward integrating herbal remedies into standard care of cancer patients.

An important use of CAM in cancer patients appears to be in the treatment of side effects of the cancer and its treatment. The value of acupuncture, even in the treatment of pain, is still controversial. Mind-body methods such as hypnosis, relaxation, and imagery techniques seem to benefit patients with pain, anxiety, and nausea.

All alternative therapies, including diet, herbal products, and electric stimulation, must be studied in controlled, preferably blinded, randomized trials to prove effectiveness and to be included in the general armamentarium of treatments for patients with cancer.

REFERENCES


191. Kleeberg UR et al: Adjuvant trial in melanoma patients comparing rIFN-alpha to rIFN-gamma to Iscador to a control group after curative resection of high-risk primary (≥ 3 mm) or regional lymph node metastasis (EORTC 18871), Eur J Cancer 35(suppl 4):82, 1999.


**SUGGESTED READINGS**


American Cancer Society's *guide to pain control: powerful methods to overcome cancer pain*, Atlanta, 2001, American Cancer Society.
