

## Chapter 4

# Herbal Treatments

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## Herbal Treatments

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**The therapeutic use of plant products—herbal medicine—is among the oldest of medical practices. It is a central feature of many current forms of folk and traditional medicine, e.g., traditional Chinese medicine, Native American healing, and curanderismo, and is used in the treatment of a wide range of disorders, including cancer. More than 3,000 different plant species have reportedly been used to treat cancer in cultures worldwide, according to a survey of the international literature (through 1971) in scientific and folk medicine (382). Herbal products are also used in unconventional cancer treatment in the United States, drawing from traditional practices in most cases, but generally offered outside of the overall context of traditional medicine and folk healing.**

**Plant products are also the source of much of the mainstream pharmacopeia. The use of botanical products in drug development involves the identification and extraction of active components of whole plants or crude extracts and, in some cases, synthesis of equivalent active compounds. The rationale for this approach is that by reducing or eliminating the variability of chemical composition and concentration that exists in crude plants, precise doses of known compounds can be given to patients.**

**Several chemotherapeutic drugs used in conventional cancer treatment were developed from botanical sources. One of the best known examples is Etoposide, derived from the mayapple plant (*Podophyllum peltatum*). Prompted by a 1942 report of the treatment of venereal warts using a constituent (podophyllotoxin) of mayapple, Jonathan Hartwell and colleagues at the National Cancer Institute's (NCI's) Drug Research and Development Program identified the chemical structure for podophyllotoxin and isolated other constituents of the plant (719). NCI conducted tests of the constituents for antitumor activity in a mouse tumor model (the Sarcoma 37 test), and found that all were highly active in that test system (384). NCI initiated clinical trials of podophyllotoxin, which were later discontinued because of its toxicity. Clinical trials of the substance were continued by a private company (Sandoz Limited) in the 1960s, and semisynthetic compounds (etoposide and teniposide) were later developed from the substance. Etoposide was ap-**

**proved by the Food and Drug Administration (FDA) in 1983 for use in patients with refractory testicular tumors, small-cell lung cancer, nonlymphocytic leukemias, and non-Hodgkins lymphoma (424).**

**Two of the most important chemotherapeutic drugs currently used were originally developed from a folk remedy containing the rosy periwinkle plant (*Vinca rosea*), which was used in Madagascar for treatment of diabetes. Chemical constituents with antitumor activity were isolated from the plant and tested for antitumor effects in animal systems. The constituents were later approved as vinblastine, used to treat Hodgkins disease, and vincristine, used to treat acute childhood leukemia (826).**

**Traditional herbal practices, in contrast, involve the use of whole plants or crude extracts of whole plants, rather than purified active components. One of the central tenets of herbal philosophy is that constituents in botanical preparations other than the predominant active component may modify physiologic effects of the active component in beneficial ways (945). The effects of crude preparations are generally slower in onset and less dramatic than those of the purified active ingredient, which maybe considered advantageous in some instances (946).**

**In recent years, some aspects of traditional Chinese medicine involving herbal medicine, acupuncture, *Qi gong*, and other practices, have become more popular in the United States and are used to treat a wide variety of conditions. U.S. cancer patients who use traditional Chinese medicine do so mainly for pain control, reduction in side-effects of conventional treatment, and enhanced quality of life, in the opinion of several members of the Advisory Panel for this project (8). Some of the herbal products used in traditional Chinese medicine are sold in U.S. health food stores and by specialty supply companies (948). In China and Japan, where traditional chinese medicine and, particularly, herbal medicine, is used in primary antitumor treatment, herbal products are the subject of much scientific research concerning their role in host support, e.g., as enhancers of immune function (207). Most of the recent scientific literature on immune-stimulating effects and adjunctive therapeutic use of herbal**

medicine in cancer treatment has been published by researchers in China, Japan, and Korea.

Higher fungi, including both edible and inedible mushrooms, are some of the major sources of polysaccharides and other substances that have been studied for antitumor and immunologic activity and as potential sources of new anticancer drugs. Many types of fungus are used medicinally in China and Japan to stimulate host defenses and to enhance patients' overall health. One of the most extensively studied mushrooms is the shiitake (*Lentinus edodes*), a popular edible mushroom in Japan. Lentinan, a polysaccharide isolated from extracts of the shiitake, has shown antitumor activity in a variety of animal tumor tests and has shown a variety of immune-altering functions, e.g., as a restorer or potentiator of T-lymphocyte activity, with no direct cytotoxicity (182). Another example includes extracts from the underground tuberlike growths (sclerotia) of *Polyporus umbellatus*, an edible mushroom that grows wild on tree stumps. Studies have shown that a polysaccharide found in extracts of *Polyporus umbellatus* increases cellular and humoral immunities in experimental animals, is active in experimental tumor systems, and may potentate the effects of chemotherapy (375). Other fungi studied for immunologic and antitumor effects include *Coriolus versicolor*, from which the polysaccharide Krestin is derived, and the enokidake fungus (*Flammulina velutipes*). Clinical studies in Japan and China have also examined the potential for using extracts of some fungi in conjunction with conventional cancer treatment (207,375).

A small number of botanical preparations are currently being used to treat cancer in a way that is distinct both from the context of traditional herbal practices and from conventional drug development. Some of them may have had roots in traditional practices, but have since been removed from that context and offered independently or in conjunction with conventional cancer treatments by practitioners untrained in traditional medicine. These few herbal treatments can be included in this report, since in their present form, they are neither a part of conventional cancer treatment nor of traditional or folk medicine.

This chapter summarizes the available information on five of the most widely used unconventional treatments based on herbal substances (presented in alphabetical order). These include single agent treatments, such as teas brewed from chaparral and Pau d'Arco, and mixtures of herbal products sold as proprietary treatments—Hoxsey products, preparations of mistletoe, and Essiac treatments.

## CHAPARRAL

Chaparral is an herbal product commonly available in health food stores. There is little systematic information available on its use, but it is often singled out, along with Pau D'Arco and several others, as a widely used unconventional treatment for cancer. Chaparral tea has reportedly been used in folk remedies for leukemia and cancers of the kidney, liver, lung, and stomach (382). It is reported to have been popular among American Indians of the Southwest as a remedy for a wide variety of disorders in addition to cancer, such as arthritis, venereal disease, tuberculosis, bowel cramps, rheumatism, colds, and bronchitis (266). Chaparral tea is claimed to have a variety of medicinal qualities—it has been described as an analgesic, an expectorant, an emetic, a diuretic, and an anti-inflammatory substance (861).

Chaparral tea is prepared from the leaflets and twigs of *Larrea divericata* Coville and/or *Larrea tridentata* Coville, also known as the creosote bush (520), which is indigenous to the desert areas of the Southwestern United States. According to one report, the tea is made by steeping about 7 to 8 grams of dried leaves and stems of chaparral per quart of hot water (809).

A number of chemicals, e.g., gums and resins, have been isolated from the creosote plant. Studies of its biological activity have focused on one of its main components, nordihydroguaiaretic acid (NDGA), a chemical with antioxidant properties that has been used widely in the food industry as a preservative.<sup>1</sup> A 1969 report by Smart and colleagues (809) summarizing the available scientific data on NDGA noted that *in vitro* tests revealed a 'virtual complete inhibition of aerobic and anaerobic glycolysis and

<sup>1</sup>Among the biological properties of NDGA is that it inhibits respiration in certain types of cells; this antioxidant characteristic was, until 1967, used as the rationale for the food industry's using NDGA as a food additive to prevent fermentation and decomposition of commercial foods. In 1968, the FDA removed NDGA from its "generally recognized as safe" (GRAS) list, after the results from long-term feeding studies in rats showed that NDGA induced lesions in mesenteric lymph nodes and kidneys. The U.S. Department of Agriculture, however, still permits the use of NDGA in lard and animal shortenings (861).

respiration with dilute suspensions of Krebs 2 ascites, Ehrlich ascites, and leukemia L1210 cells. Some *in vitro* studies reported that NDGA was associated with stimulation of tumor cell growth and stimulation of respiratory enzyme activity at low concentrations, though those same processes were inhibited at higher concentrations of NDGA (810). It has also been reported that under certain conditions, NDGA can bind to DNA (932) and can suppress certain immune responses in cultured mouse cells (783).

NDGA had significant antitumor activity in one animal tumor model (Ehrlich ascites tumor) when given with high doses of ascorbic acid (vitamin C), but has shown no activity in several other animal tumor models (S180, mammary adenocarcinoma 755, and leukemia L1210 in mice). Additional tests of extracts of the crude chaparral plant and of NDGA for antitumor activity in animal models showed no significant antitumor effects, with the "possible exception of a flavonoid fraction of *L. divaricata* which had marginal activity in P388" (383). According to NCI, additional animal tumor tests carried out at the University of Utah reportedly showed that NDGA was active in the ependymoblastoma test system but not in Melanoma S91 tumors (810). NDGA has also been reported to inhibit the development (59 1) and promotion (57) of certain carcinogen-induced tumors in rodents.

Based on a 1969 case report (809) of a patient with recurrent malignant melanoma whose cancer reportedly regressed following treatment with chaparral tea, and on some of the experimental data cited above, NCI sponsored a clinical study of NDGA (810). It was reported that over a period of 1 year (November 1969 to November 1970), 59 patients with advanced incurable malignancy were treated with chaparral tea or NDGA at the University of Utah. The treatment examined in the study included both chaparral tea as used by cancer patients and its component, NDGA: some patients drank two to three glasses per day of chaparral tea, while others received oral doses of pure NDGA (250 to 3000 mg per day). It was not noted in the analysis which patients took which form of the treatment. The outcomes of 45 of these patients were considered evaluable (defined as having received at least 4 weeks of treatment or as having undergone a tumor regression of at least 25 percent or more), although few clinical details were given in the published report.

Tumor remissions were reported in four patients in that study. One was the case previously described of the man with recurrent melanoma (his inclusion in the results indicates that the study was not entirely prospective) (see ch. 3). Another was a second patient with melanoma (in these two cases of melanoma, the duration of response was noted as 3 months and 20 months). The third was a patient with choriocarcinoma of the testicle with pulmonary metastasis, whose regression lasted 2 months, and a fourth was a patient with lymphosarcoma, whose regression lasted 10 days. Little additional clinical information about these patients, e.g., previous treatment or stage of illness, is given in the report. It was noted that 27 of the patients had "subjective improvement" during the course of their treatment with chaparral tea or NDGA.

While the authors concluded that chaparral tea was not an effective anticancer agent (defined in the report as a substance that caused a significant regression of 20 percent of a specific cancer type lasting a minimum of 2 months), the report indicates that there could have been evidence of some antitumor activity. The lack of clinical detail in the published report makes the results difficult to interpret, but the observation that several patients with advanced disease had tumor regressions suggests that chaparral tea and NDGA as given were not necessarily inactive.

## ESSIAC

Essiac is an herbal preparation developed in Canada as a treatment for cancer, which is reported to have originated in Indian folk medicine. From the 1920s until the late 1970s, Essiac was made available to cancer patients by Rene M. Caisse, a nurse who developed the treatment while working at a medical clinic in rural Ontario and who became its sole proprietor. Shortly before her death in 1978, Caisse turned over the Essiac formula, along with rights to its name and manufacture, to the Resperin Corp. of Ontario, the company currently providing Essiac to patients in accordance with a special agreement with Canadian federal health officials.

### *Background and Early Use*

Rene Caisse began her career as a public health nurse in Haileybury, Ontario. In 1922, one of Caisse's patients told her that she had recovered from breast cancer some 20 years earlier after taking an Indian herbal tea. Caisse obtained the recipe for

the herbal tea and began administering it to cancer patients in 1924 following a reportedly successful treatment of a relative with cancer using the tea. She named the treatment *Essiac*, her name spelled backwards. She gradually modified the herbal formula, producing an injectable and an oral form of the treatment. One of the constituent herbs, which Caisse believed had antitumor effects, was used in the injectable form, while three other herbs, which she believed contributed to improvements in overall health rather than to tumor reduction, were used in the oral form (303). She never revealed the names of these herbs, nor any others she may have used. Throughout her career, Caisse insisted that the ingredients and formula remain secret, despite pressure from the public and medical profession to reveal the information (303).

From the late 1920s until 1942, Caisse operated a clinic in Bracebridge, Ontario (303), where she treated hundreds of cancer patients with *Essiac* (388). From the 1950s until her death in 1978, she provided patients with *Essiac* from her home in Bracebridge, except for a period of unknown duration beginning in 1959 when she worked at the Brusck Medical Centre in Boston (303).

OTA research did not turn up any papers by Caisse in the scientific or popular literature. Most of the available written information on *Essiac* comes from the press, which, since the 1920s, has periodically described certain aspects of Caisse's career, her advocacy of *Essiac* as a cancer treatment, and testimonials of patients treated with *Essiac*. Most of these articles have appeared in local Ontario newspapers.<sup>2</sup> In 1977, an investigative article entitled "Could *Essiac* Halt Cancer?" was printed in *Homemaker's*, a popular Canadian magazine (303). More recently, the identity of herbs used in *Essiac* has been reported (388,981), but few additional treatment details have come to light. No substantive information about the treatment regimen is available in the Archives of Ontario (Ministry of Culture and Communications, Toronto, Ontario), where copies of some of Caisse's personal correspondence between 1938 and 1959 are kept.

The description provided here is based on these few sources; most of these are secondary sources, since neither Caisse nor her supporters have appar-

ently provided any primary materials. OTA's requests for primary written information from the Ontario company currently supplying *Essiac* and from Canadian health officials now coordinating the provision of the treatment were refused.

#### *Rationale for the Treatment and Claims for Efficacy*

The 1977 *Homemaker's* article briefly described Caisse's view of how she thought *Essiac* affected the cancer process, based on her observations of patients who took the treatment:

Often patients would report an enlarging and hardening of the tumor after a few treatments; then the tumor would begin to soften, and if it was located in any body system with a route to the exterior, the patient would report discharging large amounts of pus and fleshy material. After this, the tumor would be gone. Rene reasoned that *Essiac* somehow caused all the cancerous cells to retreat to the site of the original tumor, then to shrink and discharge—often to vanish altogether. (303)

Caisse claimed that even in what she referred to as "hopeless" or "terminal" cases, *Essiac* benefited patients by relieving pain, reducing tumor size, and increasing survival. She claimed generally positive results with many types of cancer with no harmful side effects (303). She reportedly also believed that treatment with *Essiac* would reduce the risk of metastasis following surgery to remove tumor tissue (303). In a letter to the Deputy Minister of Health in Canada dated October 6, 1958, Caisse wrote:

My treatment consists of an intermuscular injection of herbs which causes the growth to localize. If there are secondaries, they recede into the primary growth, causing it to become larger, until it is all localized; then the mass starts to reduce in size. (148)

According to a current patient information sheet distributed by a cancer support group, *Essiac* increases appetite, "alleviates and can eliminate pain," and "gives a wonderful feeling of well-being." It is claimed to be nontoxic and to have no side-effects.

There is no available information to indicate how Caisse applied *Essiac* in specific cases, e.g., whether she gave all patients the same doses of the same formula or whether she modified the treatment

<sup>2</sup>Many of these are collected by Stan Darling, Member of Parliament, Ottawa, Ontario. One recent newspaper example is: J. Lund, "The Ojibway Wonder Drug, Can *Essiac* Cure Cancer?" *North Bay Nugget*, Apr. 9, 1988 (570).

regimen (ingredients, treatment schedules, oral v. injectable forms, etc.) for different patients. At present, Essiac is sold in 16 oz. bottles, with recommended doses of 2 oz. diluted in 2 to 3 oz. of warm water to be taken once a day for the first 10 days, later reduced to 1 oz. in the same dilution per day. This dose is recommended for 1 to 2 years or longer, with amounts eventually being further reduced to two or three times per week (449). The patient information advises that no other treatment, including chemotherapy and radiation, should be used while taking Essiac. It states that “any other treatment which causes change in the human immune system will prevent Essiac from doing its job.” If other medication must be taken, however, Essiac “will not conflict,” it just won’t “work as fast” (449), according to current patient information.

### Components of Essiac

Several reports specify four herbal ingredients in Essiac: **Indian rhubarb** (*Rheum palmatum*), **sheeps-head sorrel** (*Rumex acetosa*), **slippery elm** (*Ulmus fulva*), and **burdock root** (*Arctium lappa*) (388,392,981). None of these reports indicate how or when these ingredients were identified, although one (98 1) cites personal communication from the Resperin Corp. No information is available on the amount of each ingredient or the method of preparation, since Resperin considers the formula proprietary.

Some experimental antitumor data are available on the individual herbal ingredients reportedly present in Essiac mixture. As with the Hoxsey data described later in this chapter, OTA obtained information about antitumor testing of the Essiac ingredients from the Natural Products Branch at NCI (232)<sup>3</sup> and from the published literature (as collected by the NAPRALERT database,<sup>4</sup> various books, and scientific articles). The details are summarized below:

**Burdock**—Two studies reported antitumor activity of burdock in animal tumor systems (257,296), while two others reported no significant activity for this herb (451,969). NCI tested burdock 14 times, with one sample showing activity, though not considered significant, in the P388 mouse leukemia system. Benzaldehyde, which has been isolated from

burdock, has shown antitumor activity in some animal tests.

**Indian rhubarb**—This herb was found to have antitumor activity at one dose level in the Sarcoma 37 animal system but not at a higher dose in the same test system (72). Another group found Indian rhubarb inactive in two other animal tumor systems (485). NCI tested two samples of Indian rhubarb from Poland and found no antitumor activity in mouse leukemia systems. Another type of Indian rhubarb, *Peltiphyllum peltatum*, was tested three times at NCI using samples from California, and none was found active in mouse leukemia systems. Components of Indian rhubarb, e.g., aloe emodin, catechin, emodin, and rhein, have shown antitumor activity in some animal test systems.

**Sorrel**—NCI tested one sample of sorrel from Taiwan and found no activity in mouse leukemia systems. The compound aloe emodin and emodin have been isolated from sorrel and have shown activity in some animal test systems.

**Slippery elm**—NCI tested slippery elm seven times using samples from various parts of the United States and found no antitumor activity in mouse leukemia systems. Slippery elm contains beta-sitosterol and a polysaccharide, both of which have been reported to have antitumor activity in animal tumor models.

Unlike the Hoxsey treatment (see below), which has not been tested as a mixture for antitumor activity in animals, the presumably complete Essiac mixture has been tested for antitumor activity in a variety of experimental mouse tumor systems. These experiments were conducted at Caisse’s request by the Memorial Sloan-Kettering Cancer Center (MSKCC) in the mid- 1970s and again at MSKCC at the request of the Resperin Corp. in the early 1980s ((427). In 1983, Canadian federal health officials requested that NCI test Essiac for antitumor effects in animals (359,602).

Caisse submitted three samples of Essiac (two dried samples used to make an extract and one liquid sample), which MSKCC tested in the S-180 mouse sarcoma test system. This test is intended to detect immunotherapeutic effects (indicated by the occur-

<sup>3</sup>These data are unpublished, though publicly available from NCI on request.

<sup>4</sup>Natural Product Data Base, Program for Collaborative Research in the Pharmaceutical Sciences, College of Pharmacy, University of Illinois at Chicago. The NAPRALERT database systematically collects information about natural products from the published literature.

rence of tumor regression) or chemotherapeutic effects (indicated by a diminished tumor growth rate) (427). The results of six immunotherapy tests and two chemotherapy tests of Essiac samples using the S-180 system all showed no activity. MSKCC tested Resperin's sample of Essiac in a variety of other animal leukemia and solid tumor test systems in 17 separate chemotherapy experiments and found no antitumor activity in any of these tests. No evidence of acute toxicity was found in any of these tests, although some evidence of subacute toxicity (slight weight loss in treated animals) was found (427).

In 1983, the Resperin Corp. submitted a liquid Essiac sample to NCI, following a request from the Health Protection Branch, Health and Welfare Canada, that Essiac be tested in animal systems. The results of NCI's tests with Essiac showed no antitumor activity in the mouse lymphocytic leukemia P388 tumor system. In contrast to the MSKCC tests, however, NCI found lethal toxicity in the highest concentrations of Essiac given to the animals in these tests. It is not known how the composition of MSKCC's samples compared with NCI's samples, or how the concentrations used in the animal tests relate to those in the treatments given to patients.

#### *Attempts at Evaluating Essiac in Cancer Patients*

There have been no prospective clinical trials of Essiac to determine its safety and efficacy as a cancer treatment. In the early 1980s, however, Canadian health officials conducted a retrospective review of Canadian patients treated with Essiac using case summaries submitted voluntarily by the patients' physicians. In 1982, when the review began, about 150 physicians in Canada had reportedly requested supplies of Essiac on behalf of their cancer patients. On request from the government, approximately half of these physicians submitted summaries on a total of 86 patients to the Canadian federal health department (Bureau of Human Prescription Drugs, Health Protection Branch, Health and Welfare Canada). According to the former director of the Bureau of Human Prescription Drugs (392), the Bureau reviewed the physicians' reports and concluded the following:

47 patients received "no benefits" from Essiac treatment;  
8 of the patient reports were unevaluable;  
17 patients died;  
1 had a 'subjective improvement';  
5 required fewer analgesics;  
4 had an "objective response" to the treatment;  
4 were in "stable condition."

The Bureau's judgments were based on the written summary comments physicians submitted, not on a review of the original patient charts. The Bureau did solicit additional information on the four patients who reportedly had an objective response and the four who were in stable condition. Among these eight patients, three were then found to have had progression of disease, two had died, and three were still in stable condition. The latter three patients had received previous conventional treatment that, in the Bureau's judgment, was probably responsible for their stable condition. The Bureau concluded that this review provided no evidence that the progression of cancer in these patients had been altered by taking Essiac. It noted, however, the possibility that some of these patients might have benefited from the treatment psychologically or emotionally. The Bureau's summary of the safety data collected in that review noted that "with occasional batches there was some nausea and vomiting" and suggested that these reactions were probably due to "a variation in composition" of the herbal preparation. However, few patients reportedly experienced any serious side-effects from the treatment.

#### *Current Status of Essiac in Canada*

In 1978, Resperin filed a "preclinical new drug submission"<sup>3</sup> with the Health Protection Branch (HPB), Health and Welfare Canada. HPB officials allowed Resperin's application to proceed, authorizing the distribution of Essiac to "qualified medical investigators" for clinical trials designed to obtain scientifically valid data on Essiac's safety, dosage, and effectiveness in cancer treatment (392). In addition, it was expected that the Resperin Corp. "would maintain adequate manufacturing and quality control of the drug" and would "undertake appropriate scientific investigations to isolate and identify any active substances] in Essiac" (392).

<sup>3</sup>If approved, a preclinical new drug submission, like an IND application in the United States, permits clinical trials of new drugs in human subjects.

In September 1982, HPB suspended Resperin's preclinical new drug submission. An HPB official stated that Resperin had not fulfilled its commitment under the agreement "to maintain adequate manufacturing, to investigate the pharmacology of Essiac, and to arrange appropriate clinical trials" (392). During the same period in which the Canadian preclinical drug submission was in effect, Resperin applied to FDA for an NDA-permission to market Essiac in the United States-but this application was turned down (554). Details of the NDA submission are confidential, according to FDA rules, so no details on this application are available unless Resperin chooses to make them public.

Although Essiac is currently unapproved for marketing in Canada and cannot be used in clinical trials without a valid preclinical new drug submission, the Canadian Government allows Essiac to be manufactured and sold, and to be used by cancer patients under certain circumstances. A cooperative arrangement between Resperin and HPB authorizes the distribution and sale of Essiac to cancer patients "on compassionate grounds," i.e., when no other treatment is appropriate in the particular case (392). Patients who wish to obtain Essiac ask their physician to make a request to the Bureau of Human Prescription Drugs, which relays the order to the company, and the company ships Essiac directly to the patient. Physicians are asked to report to HPB the clinical details on each patient using Essiac. OTA requested details from HPB about its procedures for distributing Essiac and monitoring its use (e.g., the type of data collected, how many patients have requested and received Essiac from Resperin via HPB over the past 5 years, how many of these are U.S. patients, and the types of cancer for which treatment with Essiac is being sought), but was told that no more information could be given (480).

## THE HOXSEY TREATMENT

The Hoxsey treatment involves several herbal preparations, all of which are made from combinations of herbs and inorganic compounds. At present, this treatment is offered only at a clinic in Tijuana, Mexico, although from 1924 until the late 1950s (188) it was offered at a number of clinics in the United States under the direction of the late Harry Hoxsey (1901-1974). Awareness of the treatment was recently renewed by the release of *Hoxsey*:

*Quacks Who Cure Cancer?* (59), a documentary film on the history of the Hoxsey treatment and on Harry Hoxsey's personal role in its development and promotion.

According to Hoxsey's autobiographical book *You Don't Have To Die* (418), the herbal formula for the Hoxsey treatment was developed in 1840 by John Hoxsey, Harry Hoxsey's great-grandfather. It was derived from grasses and flowering wild plants growing in a pasture where one of John Hoxsey's horses, afflicted with a cancerous growth, grazed daily. The horse's cancer reportedly disappeared, and John Hoxsey surmised that the wild plants had caused the recovery. He gathered some of the plants from the pasture, and later added ingredients from old home remedies for cancer. He used the resulting herbal mixture to treat similarly afflicted horses near his farm in southern Illinois (418,938).

The herbal formula was bequeathed to John Hoxsey's son, then to Harry's father John, and finally to Harry Hoxsey in 1919, whose father charged him with using it to treat cancer patients "if need be, in defiance of the high priests of medicine" (418,984). Although Harry's father, a veterinary surgeon, was the first to use the formula to treat people with cancer, it was Harry Hoxsey who made it famous. The first clinic offering the Hoxsey treatment opened in the early 1920s and by the 1950s, the Hoxsey Outpatient Clinic in Dallas was reportedly one of the largest privately owned cancer centers in the world (188), with branches in 17 States (58). By Hoxsey's account, the clinic had at its peak of operation 10,000 patients "under constant treatment or observation" (418,582).

Hoxsey was widely known for his flamboyant and confrontational style (59,938,984). His reluctance to disclose the treatment formulas and his bold claims reportedly led Morris Fishbein, then editor of the *Journal of American Medical Association* (J.A.M.A.), to publish articles labeling Hoxsey and his late father as charlatans (938). Hoxsey sued for libel and won (984).<sup>6</sup> In 1956, the FDA Commissioner ordered that a "Public Beware!" warning against the Hoxsey treatment be posted in U.S. Post offices and substations across the country (518,984). Repeated clashes with FDA over violations, and a number of arrests eventually prompted Hoxsey to close his main Dallas clinic in the late 1950s.

<sup>6</sup>The history of Hoxsey's legal battles with the American Medical Association has been extensively reviewed elsewhere. See, e.g., (294,418,984).

Since 1963, the Hoxsey treatment has been offered at a clinic in Tijuana, Mexico, under the direction of Hoxsey's longtime chief nurse, Mildred Nelson (58). The herbal preparations Nelson uses to treat cancer patients are reportedly based on Hoxsey's herbal formulas and method of preparation (78,188).

### *Rationale for the Treatment*

In 1956, Hoxsey described his belief that cancer was a systemic disease, however localized its manifestations might appear to be. Although he did not "pretend to know its fundamental cause," he believed that "without exception it occurs only in the presence of a profound physiological change in the constituents of body fluids" and that it leads to a "chemical imbalance in the organism" (418). Hoxsey summarized the theory behind his approach this way:

We believe that the organism's attempt to adapt itself to the new and abnormal environment produced by the chemical imbalance causes certain changes (mutations) in newly born cells of the body. The mutated cells differ radically in appearance and function from their parent cells. Eventually a viciously competent cell evolves which finds the new environment eminently suitable to survival and rapid self-reproduction. These cells are what is known as cancer.

It follows that if the constitution of body fluids can be normalized and the original chemical balance in the body restored, the environment again will become unfavorable for the survival and reproduction of these cells, they will cease to multiply and eventually they will die. Then if vital organs have not been too seriously damaged by the malignancy (or by surgery or irradiation) the entire organism will recover normal health. (418)

He also did not claim to know how or why his herbal cancer treatment worked, but he maintained that it "corrects the abnormal blood chemistry and normalizes cell metabolism" by "stimulat[ing] the elimination of toxins which are poisoning the system" (418).

There are three external forms of the Hoxsey treatment used for tumors in or near the skin to 'halt the spread of the disease and speed the necrosis (death) of cancer cells' (418). Hoxsey reported that his yellow powder is "highly selective" for malignant tissue, leaving normal tissue undamaged. The paste and liquid forms, however, were not, by his

account, selective. He applied vaseline or zinc oxide around the perimeter of the affected area, a practice which he believed contained the corrosive action of the preparations (418). Hoxsey summarized the observed outcomes of his external treatment this way:

In practice we have found that a small amount of our compounds, when placed on a large cancerous mass, cause a chain reaction which extends an inch or two beyond the point of application. The mass dies, dries, separates from normal, healthy tissue and falls out. (418)

Nelson believes that the Hoxsey tonic "normalizes and balances the chemistry within the body," a process she believes results in tumor regression.

In a 1984 interview, Nelson said:

When you get everything normalized, the abnormal cells--the tumor cells--cease to grow. And very slowly the tumor is absorbed and excreted, and it's gone. (188)

In that same article, it was noted that the Hoxsey tonic is intended to help "eliminate toxins from the body." In addition, the Hoxsey powder and paste were described as "escharotic agents" that were commonly used by conventional physicians to treat cancer before radiation and chemotherapy were developed (188).

### *Components of the Treatment*

Hoxsey's treatment regimen included his internal and external preparations and "supportive treatment," although the components of the latter are not specified in his book (418). His preparations included a paste or salve applied topically for external cancers; a powder, pills, and a dark brown herbal tonic taken orally. Hoxsey adjusted the composition and dose of each patient's formula, depending on the individual patient's general condition, the location of the cancer, and the extent of previous treatment. The internal treatment was taken by mouth as a liquid tonic or in pill form (418).

Hoxsey's 1956 book *You Don't Have To Die* lists the ingredients of his internal treatment given in "all cases of cancer, both internal and external" (418) as potassium iodide combined with some or all of the following substances, on a case-by-case basis: licorice, red clover, burdock root (*Arctium lappa*), stillingia root (*Stillingia sylvatica*), berberis root (*Berberis vulgaris*), pokeroor (*Phytolacca ameri-*

*cana*), **cascara** (*Rhamnus purshiana*), **Aromatic USP 14 (artificial flavor)**, **prickly ash bark** (*Zunthoxylum americanum*), and **buckthorn bark** (*Rhamnus frangula*) (418). The last two substances in this list are not specifically mentioned in Mildred Nelson's list of ingredients used in the Hoxsey treatment she currently offers.

Hoxsey's escharotic preparations, which were applied locally in "external cases," included a yellow powder, a red paste, and a clear solution. He reported that his yellow powder contained arsenic sulfide, talc, sulfur, and what Hoxsey called a "yellow precipitate" (664).<sup>7</sup> The caustic red paste reportedly contained antimony trisulfide, zinc chloride, and bloodroot (*Sanguinaria canadensis*). The clear solution contained trichloroacetic acid (418).

The current Hoxsey treatment offered by Mildred Nelson at the Bio-Medical Center in Tijuana includes a liquid tonic, a salve, and a powder, all of which are reportedly based on Hoxsey's formulas. The current patient literature from Nelson's clinic lists the components of the liquid herbal tonic as: "potassium iodide and herbs, licorice, red clover, cascara, burdock root, barberis root (sic), poke root and stillingia root" (78). The ingredients of the salve and powder are not given. In addition, Nelson's treatment regimen specifically includes nutritional supplements and dietary restrictions. Nelson advises before-meal "tri-tabs," after-meal tablets, yeast tablets, vitamin C, calcium capsules, laxative tablets, antiseptic douches, and antiseptic washes. She also recommends that patients exclude certain foods that "nullify the tonic" (663), such as pork, tomatoes, pickles or other products with vinegar, salt, sugar, artificial sweeteners, alcohol, carbonated beverages, and bleached flour. All patients are tested for systemic infection with the fungus *Candida albicans* before treatment is initiated, although the reasons for such testing are not given in the patient literature (78). Treatment lasts up to 3 days at the clinic, with followup visits within 3 to 6 months after the initial visit.

#### *Antitumor Effects of the Hoxsey Components*

Many of the constituent herbs in the Hoxsey treatment have a long history of folk use in the treatment of cancer, as well as for a variety of other conditions (266,382). One of the constituents of the

**external treatment, bloodroot** (*Sanguinaria canadensis*), was used by Native Americans to treat cancer, warts, and nasal polyps.

The ingredients used in Hoxsey's external paste-zinc chloride, antimony trisulfide, and bloodroot (418)-were used by Frederic Mohs, M.D., of the University of Wisconsin Medical School in the 1930s and 1940s to treat nonmelanoma skin cancer, e.g., invasive basal cell carcinoma. The Mohs chemosurgical technique, as it came to be known, used the caustic paste to permit serial microscopic examination of excised tissue (625). Mohs' preparation, which he referred to as a zinc chloride fixative, reportedly contained 40 grams of stibnite (antimony trisulfide in a metallic base), 10 grams of powdered sanguinaria, and 34.5 cc of a saturated solution of zinc chloride (624). In this method, dichloroacetic acid was first applied to the skin covering the tumor, followed by application of the caustic paste to kill and fix the tissue, and left in place under a bandage for 24 hours, during which time the patient was given analgesics for pain. Twenty-four hours later, a layer of tissue approximately 5 millimeters thick could be excised with a scalpel, a procedure involving no pain or bleeding, and then examined microscopically. Several successive applications of fixative, excisions, and microscopic observation were performed until the tumor was removed.

Mohs reported high rates of success with this method-e. g., a 99 percent cure rate for all primary basal cell carcinomas he treated (625). He noted that the reliability of the method was due to the microscopic control that "makes it possible to follow out the irregular and unpredictable extensions from the main tumor mass" (624). In a 1948 paper in *J.A.M.A.*, he contrasted his use of the fixative paste with that of unconventional practitioners, who, according to Mohs, used the same fixative without microscopic control of excision, a procedure Mohs considered unreliable and excessively mutilating (624). In the early 1950s, Mohs and others abandoned the use of the fixative paste in this method and replaced it with surgical excision of fresh tissue specimens, which are then examined microscopically as before. This latter form of Mohs' method is currently used in conventional surgical treatment of some types of skin cancer, particularly

<sup>7</sup>This might correspond to the extra four ingredients in the book *New Cures for Old Ailments* (@~ on Hoxsey Medicines) (664), listed as: flower elder, magnolia flower, blood root, and antimony trisulfide.

basal cell and squamous cell carcinomas (845). Its advantages over the fixed tissue method reportedly include the avoidance of pain associated with tissue fixation, the ability to perform multiple stages of excision in one day, and the elimination of 'postfixation tissue slough,' permitting immediate reconstruction of the surgical wound when needed (845).

Over the past several decades, many of the botanical products reported to be present in the Hoxsey internal treatment have been tested individually for antitumor activity in animal systems (see ch. 12 for discussion of animal test systems). The complete Hoxsey tonic currently given to cancer patients has apparently not been tested for antitumor activity in animal systems.

OTA obtained results of testing for antitumor activity of the constituent Hoxsey herbs used in the internal tonic from NCI's Natural Products Branch,\* the NAPRALERT database,<sup>9</sup> an OTA contract report reviewing the history of the Hoxsey treatment (938), and other published sources. Details of the results in animal test systems are summarized below, giving results for NCI and non-NCI tests separately:

*Burdock*—Two studies reported antitumor activity (257,296) in animal tumor systems, while two others reported no significant activity for this herb (451,969). NCI tested burdock 14 times, with one sample showing activity, though not considered significant, in the P388 mouse leukemia system. Benzaldehyde, a constituent isolated from burdock, has been reported active in two test systems in rats (848).

*Buckthorn*—Antitumor activity of a component (aloe-emodin) of buckthorn has been reported in the P388 tumor system (495) and in the Walker 256 system (summarized in (384)) (the Walker 256 test was later withdrawn from use because of problems with its validity). Two other components, emodin and dihydroxyanthroquinone, may also have antitumor activity in animal systems. NCI tested buckthorn in animal systems three times, with no antitumor results.

*Cascara*—Also contains aloe-emodin and emodin, which have shown antitumor activity in animal test systems. No antitumor activity was found when a

powdered plant suspension of cascara was tested in the Sarcoma 37 system (72). NCI tested cascara 16 times and found no antitumor activity.

*Barber*—Two studies have reported antitumor effects of substances isolated from barberry (415,702). NCI reported one test of barberry, which showed no antitumor activity.

*Licorice*—one study reported that licorice was inactive in the Sarcoma 37 test system (72). NCI tested licorice 19 times, with one sample showing activity that was not considered significant. Benzaldehyde and a number of other components (e.g., fenchone, glycyrrhizin, indole, quercetin, and beta-sitosterol) have been isolated from licorice and found to be active in animal test systems.

*Red Clover*—Red clover showed no activity when tested in the P388 system (254). NCI tested red clover 94 times, with one test showing activity that was not considered significant.

*Pokeroot*—One published study reported no significant antitumor activity of pokeroot in three animal test systems (Ehrlich ascites, Leukemia SN36, and Sarcoma 180) (969). A component of pokeroot is well-known, however, for its ability to induce the proliferation and differentiation of lymphocytes in the blood (720), a property that might be relevant to an immunologic response to cancer but which might not be picked up as positive activity in these animal tumor models. NCI tested pokeroot for antitumor activity 43 times; in one of these tests, activity was reported in the Walker 256 system, but this test system was later withdrawn because of problems with its validity.

*Prickly Ash*—No tests for antitumor activity of prickly ash have been reported in the literature, although some of its components (e.g., chelerythrine and nitidine) have tested positive in animal systems. NCI tested this plant for antitumor activity five times, with no positive results.

*Stillingia*—No tests of stillingia have been reported, although one of its constituents (gnidilatidin) has tested positive in animal systems. NCI has no record of testing it for antitumor activity.

\*These data are unpublished, though publicly available from NCI on request.

<sup>9</sup>Natural Product Data Base, Program for Collaborative Research in the Pharmaceutical Sciences, College of Pharmacy, University of Illinois at Chicago.

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 complete Hoxsey herbal mixture has not been tested for antitumor activity in animal test systems, with human cells in culture, or in clinical trials, however. It is unknown whether the individual herbs or their components that show antitumor activity in animals are active in humans when given in concentrations used in the Hoxsey tonic. It is also unknown whether there might be synergistic effects of the herbs used together.

### *Adverse Effects*

Hoxsey's medical director stated in a 1952 publication that no toxic reactions had been seen in patients treated with the Hoxsey tonic, but he added that "the growth of a cancer can be stimulated if the treatment is used improperly" (664). No further information about this possibility was given.

No side-effects or toxicities specifically resulting from the Hoxsey treatment have been reported in the medical literature. Side-effects of some of the individual herbs taken alone, often in massive doses compared to the amounts present in the Hoxsey treatment, however, have been reported (67,179,487, 671,881). Pokerooroot, a reported component of the liquid tonic, contains toxic mitogenic substances (agents that induce cell division and proliferation), and has been linked with poisoning, including some fatal episodes, in children and adults (266). The relevance of these reports to possible toxicities of the Hoxsey mixture depends on the amount of each herb present in the mixture (which maybe unknown) and the total amount taken (which varies with each patient).

### *Claims*

Nelson claims that about 80 percent of the cancer patients who take her herbal treatment are cured (59). She believes that a "bad attitude" is usually responsible for her "20 percent failure rate" (663), and that she can tell who is going to get well and who is not from their attitude when they first arrive at the clinic; a patient's strong belief that the treatment is going to lead to recovery is the best predictor of success, she says.

Hoxsey's public claims of his treatment's effectiveness were similar to Nelson's present-day claims. Hoxsey presented numerous case histories of patients treated at his clinic in his 1956 book (418). Additional case histories supporting his claims are described in a 1954 publication by *Defender Magazine* (251). In his book, Hoxsey noted that cancer patients sought his treatment "as a last resort." He wrote:

We don't pretend to cure all of them. The vast majority are advanced and even terminal cases by the time we get them. Many come to us after the disease already has spread through the body; after surgery or irradiation has so impaired circulation of the blood to the affected areas that our treatment cannot reach them . . . Nevertheless we believe we cure a far greater percentage of cases treated than is cured by any other method at present known to science. (418)

In 1947, the medical director of Hoxsey's clinic stated it more specifically: he claimed they had been curing '85 percent of external cancers, and approximately 25 percent of internal cancers' (664). In particular, it was noted that the outcome of treatment was 'dependent to a great extent upon the lymphatic system, and our best results are in cancers that have a large lymphatic supply.' He stated that many of their patients had had "the limit of X ray and radium" and "in many of these, we cannot hope to cure the cancer itself because of the extensive prior destruction," but that the Hoxsey treatment might "limit the further extension of the cancer and keep the patient free from pain thereafter." This director noted, "in almost every case that the general health of the patient improves' as a result of the treatment. He concluded that "we know that the Hoxsey treatment cures cancer, and it is only reasonable to believe that we have within our grasp the cause, and eventually the complete solution, of the cancer problem" (664).

### *Attempts at Evaluating the Hoxsey Treatment*

No clinical trials of the Hoxsey treatment have been reported. Several record reviews, initiated in the 1950s, have been discussed in the literature, however. The first was based on a site visit in 1954 by a group of physicians, who, by Hoxsey's account, spent 2 days inspecting the clinic, reviewing patient records, and talking to patients. Although the data on which they made their conclusions are not given in Hoxsey's book where an excerpt of their statement appears, the group concluded that the Hoxsey Clinic

was “successfully treating pathologically proven cases of cancer, both internal and external, without the use of surgery, radium or x-ray” (quoted in (418)). Criteria for such successful outcomes reportedly included patients who remained “symptom-free in excess of five to six years after treatment.” They concluded that “the Hoxsey treatment is superior to such conventional methods of treatment as x-ray, radium, and surgery.”

In 1957, a committee of faculty members of the University of British Columbia conducted a review of the Hoxsey treatment and facilities (582). After visiting Hoxsey’s Dallas clinic, the committee described the overall treatment regimen, along with various other aspects of the treatment (the history of the treatment, Hoxsey’s claims for efficacy, and the history of Hoxsey’s litigation concerning the treatment). They were particularly interested in following up on patients from British Columbia who were treated at the clinic. The clinic gave the committee members records for 78 patients from their ‘active’ files (unbeknownst to the clinic, however, some of these patients had died). The committee was able to follow up on 71 of these patients, using British Columbia’s cancer registry, death registry, and physician records. Their detailed findings were summarized as follows:

For over one-half of the [cancer] patients from British Columbia, the result [of treatment with the Hoxsey method] has been either death or progression of the disease. In nearly one-quarter there was no proof that the patient ever had cancer. Nearly one in ten of the patients had curative treatment before going to the Hoxsey Clinic. In only one case, an external cancer, was there any evidence at all that the Hoxsey treatment had an effect on the disease; in that case, better results could have been obtained by orthodox means. (582)

The latter case to which they refer reportedly involved a woman with a “slow-growing cancer of the ear” who refused surgery and was treated with one of Hoxsey’s external treatments. The committee reported that the treatment “did, in fact, remove the cancerous growth, along with a good deal of normal tissue.” It did so “with needless pain and disfigurement,” given that it could have been treated with radiation or surgery, in the committee’s opinion (582). They also reported that of the 32 patients who died, “two-thirds were dead in less than six months, 90 per cent were dead within a year, and none survived two years” (582).

Hoxsey made attempts (in 1945 and 1950) to have NCI review his patients’ records. On both occasions, NCI determined that the records Hoxsey submitted did not meet NCI’s previously established criteria at that time for documenting treatment effects. In summary, these criteria required that Hoxsey:

- explain the composition of his herbal treatments and his regimen for treating patients;
- submit complete clinical and laboratory records of at least 50 patients with internal cancer to show conflation of the diagnosis by biopsy and objective evidence of regression of primary growth and metastasis by measurement, photographs, and x-rays; and
- provide proof that these patients had survived & least 5 years following treatment (418,582,984).

In 1945, Hoxsey reportedly submitted records for 60 patients, 40 of which were for cases of external cancer, and the remaining 20 were reportedly unevaluable by NCI’s criteria (582,984). In 1950, Hoxsey submitted an additional 77 case histories, all of which, he claimed, were “fully documented with clinical records and pathological reports” and some of which included “actual microscopic biopsy slide[s]” or details of where NCI could obtain such material. He added that all but a few of the cases we sent in had been cured more than five years, and those few were of a deadly type of cancer where survival for even three years was considered little short of miraculous” (418).

According to a discussion of the documentation Hoxsey submitted to NCI by the University of British Columbia committee, however, Hoxsey’s 77 records reportedly included only 6 biopsies; 2 of these were from patients with internal cancer and neither of these 2 biopsies confirmed the existence of malignant cells (582,984). It was also reported that 31 of the 77 patients were dead within 5 years of treatment and “in the remaining 46 cases, the criteria would have been met by 12 patients if suitable sections had been submitted” (582).

According to several sources, NCI concluded on the basis of Hoxsey’s data that no assessment of his treatment could be made (418,582,984). Hoxsey believed, however, that it was NCI’s responsibility to verify his case records; their failure to do so was deliberate, he believed, resulting from a widespread conspiracy organized against him by the AMA (418). Attempts were made to initiate investigations into Hoxsey’s treatment and his allegations against

NCI and AMA, but the investigations were never conducted. In 1947, Senator Elmer Thomas of Oklahoma asked the U.S. Public Health Service to investigate Hoxsey's treatment, and the Surgeon General refused the request (294,582,984). In 1951, Senator William Langer of North Dakota sponsored a resolution under which a subcommittee would have been authorized to study Hoxsey's treatment and claims for effectiveness, but this resolution was never reported out of committee (582,984).

Hoxsey's point of view was echoed by a 1953 report to the Senate Interstate and Foreign Commerce Committee by Benedict Fitzgerald, an attorney who examined records of Hoxsey's litigation with the AMA and the Federal Government. After reading about the circumstances of these attempted case reviews, Fitzgerald wrote that NCI "took sides and sought in every way to hinder, suppress, and restrict [the Hoxsey Cancer Clinic] in their treatment of cancer" (294). To date, no independent, comprehensive assessment has been made to resolve the many allegations and issues raised by Hoxsey's tumultuous career.

## MISTLETOE

Mistletoe has long been used in the treatment of a variety of acute and chronic conditions (302). It was not widely used for treating cancer, however, until the 1920s, during the early development of Anthroposophy, a modern "spiritual science" applied to medicine and a variety of other disciplines. At present, mistletoe is given to patients either as the central component of a complex, broader treatment regimen in the practice of Anthroposophic medicine mainly in Europe (277) or as a single agent partially or completely removed from the overall context of Anthroposophic care (e.g., in the United Kingdom and other countries). At present, mistletoe preparations are advocated mainly by Swiss and German physicians practicing Anthroposophic medicine, but are also used by other European physicians not necessarily associated with Anthroposophy. A larger group of researchers in Europe, and to a lesser extent in the United States, has focused on the study of mistletoe's biological properties in various experimental systems.

Mistletoe preparations are available in a variety of forms (413,753), including a preparation by the trade name Plenosal (208), but the oldest and most widely used is a product marketed by Weleda AG (Switzer-

land and West Germany) under the trade name Iscador, which consists of fermented extracts of mistletoe, some forms of which are combined with small amounts of various metals (e.g., silver, copper, and mercury). Iscador is listed in the German Rote Liste (1989) and is registered with the Swiss Inter-Cantonal Office for drug control (847), but is not listed in the Swiss Compendium of pharmaceutical drugs (224). Some commercial preparations of mistletoe are licensed in West Germany, but are not held to the same standards of efficacy as other medical drugs (422), according to a 1976 West German drug law (789) allowing for different standards for unconventional treatments.

Approximately 40,000 patients worldwide were receiving Iscador treatment in the early 1980s, according to the Society for Cancer Research, a Swiss Anthroposophic organization (8 16). Mistletoe treatment is reportedly available in Switzerland, West Germany, the Netherlands, the United Kingdom, Austria, and Sweden, at clinics and private practices specializing in Anthroposophic or in various types of "holistic" medicine. Commercial preparations of mistletoe can be legally prescribed by licensed physicians in these countries (726). The Weleda company, which makes a range of drug and household products, also has branch operations in several other European countries, as well as in Canada, the United States, India, South Africa, Argentina, and Brazil (746). Although Iscador is not commonly used in the United States, some U.S. physicians have been trained in Anthroposophic medicine and incorporate aspects of its practice into patient care (953). The U.S. branch of Weleda does not sell Iscador, as the product is not approved for sale in the United States, but U.S. physicians can order Iscador directly from European manufacturers (952). Some U.S. patients may also travel to specialized clinics or hospitals in Europe to receive Iscador treatment.

Mistletoe achieved prominence as a cancer treatment through the work of Rudolf Steiner, Ph.D. (1861 -1925), who founded Anthroposophy (598). Working with Ita Wegman, a Dutch physician, Steiner applied the principles of his "spiritual science," which combined spiritual and scientific thought, to the practice of medicine and to the treatment of cancer in particular. In the decades since Steiner's death, physicians and researchers have continued developing his ideas (423) and have established a network of clinics and hospitals in

Europe, North America, and South Africa designed to put his principles into medical practice. The first Anthroposophic clinics opened in Arlesheim, Switzerland, and Stuttgart, West Germany, in 1921. A group of physicians following Steiner's philosophy founded the Society for Cancer Research in 1935. In 1949, that group founded the Hiscia Institute, whose main purpose was to develop Iscador for therapeutic use and to conduct research. The Lukas Klinik, specializing in the Anthroposophic treatment of cancer, was opened in 1963 in Arlesheim. At present, the Society for Cancer Research supports two research institutes (the Hiscia Laboratory, where Iscador is manufactured, and the Widar Research Center, where biochemical studies of mistletoe are carried out), in addition to the Lukas Klinik and a postgraduate training facility for physicians specializing in Anthroposophic medicine.

#### *Steiner's Approach to Cancer Treatment*

Steiner's work led him to believe that cancer results from imbalances in certain forces affecting the human body. He believed that some of these forces are responsible for cell division, growth, and expansion ("lower organizing forces") and others ("higher organizing processes" or "formative forces" are responsible for limiting and organizing that growth, controlling cell differentiation, and producing overall body form; it is the balance of these two types of force that influences the strength or weakness of one's individuality. Steiner believed that in healthy people, such forces are balanced and act in harmony, whereas in people with cancer or in people "susceptible" to cancer, the higher organizing forces are weak, relative to the lower organizing forces. The resulting imbalance would lead to excess proliferation of cells, loss of form, and eventually tumor production (477). Steiner believed that cancer involved not only physical disorder in the body, but also disruptions among "different levels of matter, life, soul, and spirit" (726).

In the early 1920s, Steiner proposed mistletoe as a therapeutic agent capable of correcting the imbalance he believed was ultimately responsible for the development of cancer. In general, his proposal was based on the process of what he called "spiritual science," in which he combined spiritual and scientific thought as "complementary" modes of insight. Anthroposophic literature refers to his

reportedly extraordinary mental capabilities ("higher faculties of perception," extrasensory perception, or inner knowledge) as the key element underlying his novel proposal to use mistletoe therapeutically in cancer (277).

Contributing to Steiner's proposal to use mistletoe were his detailed analyses of the plant's botanical characteristics, which are described in many Anthroposophic accounts of the origin of this treatment. Steiner examined the growth and development of the semiparasitic mistletoe plant and noted, e.g., that its morphology is spherical rather than vertical; its growth is not influenced by the force of gravity; it grows on different species of host trees, taking water and minerals from the tree sap and supplying the tree with sugars made via photosynthesis; it avoids direct contact with the earth and makes no roots in the ground; it produces berries all year long; and it flowers in the winter. Steiner concluded from these characteristics that mistletoe develops independently from earth forces (e.g., gravitational, electromagnetic, chemical) and from seasonal cycles, opposite to the way in which he believed tumors develop (94,477). Steiner concluded that these characteristics made mistletoe uniquely valuable as a therapeutic agent. He believed that mistletoe could stimulate "higher organizing" or "individualistic" forces which he felt were relatively inadequate in cancer patients. He suggested that by taking mistletoe, such forces would be transferred from the plant to the patient and would result in an enhancement of host inflammatory defense mechanisms against cancer. The mistletoe treatment was named Iscador (94) and Steiner recommended that the mistletoe be combined with certain metals in high dilution that he believed would enhance the activity of the mistletoe preparation (847).

With Iscador as the central element, Steiner's cancer treatment regimen consisted of various medical and nonmedical interventions. Steiner developed and advocated specific artistic activities that he believed also contributed to recovery from cancer, such as clay modeling, eurythmy (or movement treatment), and speech formation. The overall aim of the regimen was to strengthen patients' "formative forces" or "organic self-supportive systems" and provide an opportunity for individuals to undergo inner change and to develop the soul and spirit (533).

The current Anthroposophic treatment for cancer consists of a similar, but expanded, combination of interventions intended to be used adjunctively with conventional care (726). Conventional medical treatment is recommended for some patients, although at the Lukas Klinik in Switzerland, patients are generally referred to other centers to obtain it. Treatment at the Lukas Klinik consists of some combination of the following, according to each patient's condition: conventional and homeopathic preparations for various medical problems associated with cancer (e.g., for hemorrhages, bone metastasis, effusions, pain, etc.); a vegetarian diet with restrictions on the consumption of mushrooms, hardened fats, refined sugars, new potatoes, and tomatoes; avoidance of alcohol and cigarettes; artistic activities such as eurythmy, painting, speech formation, light and color therapy, and music; light exercise; and hyperthermic baths, oil baths, and massage (277,533,534).

#### *Preparation and Administration of Iscador*

Iscador is made from a species of European mistletoe, *Viscum album*, which differs from mistletoe commonly found in the United States. The different preparations of Iscador are classified according to the type of tree on which the mistletoe grows and are chosen for use according to the sex of the patient and the location of the primary tumor. For instance, "Iscador M" refers to the preparation made from mistletoe growing on apple trees, and is used to treat women with cancer; "Iscador Qu," from oak trees, usually for men; "Iscador p," from pine trees, for men and women; and "Iscador U," from elm trees, for men and women (726,746).

The preparations are also distinguished by the type of metal added, e.g., silver, mercury, and copper, in concentrations ranging from  $10^8$ g silver/100 mg mistletoe to  $10^5$ g copper/100 mg mistletoe (746). The addition of these metals is believed to enhance the action of Iscador on particular organs and systems. An Iscador preparation with copper is used for primary tumors of the liver, gallbladder, stomach, and kidneys; Iscador with mercury is used to treat tumors of the intestine and lymphatic system; Iscador with silver is used to treat cancers of the urogenital system and breast; and Iscador without any added metals is used to treat tumors of the tongue, oral cavity, esophagus, nasopharynx, thyroid, larynx, and extremities (746). The rationale for

inclusion of metals with mistletoe preparations is not explained in the Iscador literature OTA reviewed.

Some aspects of the method by which Iscador preparations are made are proprietary, but it is known that the whole plant is used to make an aqueous extract, which is then fermented with the bacterium *Lactobacillus plantarum*. The fermented saps of summer and winter extracts of mistletoe are mixed and then undergo sterile filtration (413,955). It is packaged in small ampules containing different concentrations of mistletoe, ranging from 0.0001 mg mistletoe/ampule to 50 mg mistletoe/ampule, designed to be administered by subcutaneous injection at or near the tumor site. In some cases, Iscador is administered orally, e.g., in cases of primary tumors of the brain and spinal cord.<sup>10</sup> A typical course of Iscador treatment consists of 14 injections given in increasing concentrations. It is usually given in the morning, when body temperature is rising.

According to a report of the Swiss Cancer League (847), fermented Iscador products contain large numbers of both dead and live bacteria (mainly *Lactobacillus*) and some yeast (847). Proponents contest that assertion, noting that Iscador is filtered to eliminate bacteria and that routine testing is conducted for microbial contamination, as required by the Swiss International Office for Drug Control (723). Iscador preparations are also tested for endotoxin contamination (367). No cases of serious infection have been reported in the literature as a result of subcutaneous injection of Iscador.

#### *Indications for Use*

According to current information, Iscador preparations are used in several specific ways in cancer treatment. The main use of the treatment, and the one for which Anthroposophists claim the best results overall, is in the treatment of solid tumors before and after surgery and radiotherapy. It can be given in an intensive schedule 10 to 14 days before surgery "to activate the defensive functions," to "help prevent metastatic spread" due to surgery, and to promote rapid recovery. Alternatively, it can be given as followup treatment beginning immediately after surgery and continuing over several years in gradually decreasing doses and increasing intervals. Either way, Iscador is claimed to significantly

<sup>10</sup>Reportedly, parenteral administration of Iscador carries a risk of increased pressure in the cranial cavity due to swelling around the tumor.

improve survival rates, particularly in cancers of the cervix, ovaries, breast, stomach, colon, and lung.

A second indication claimed for Iscador is the treatment of advanced stage, inoperable solid tumors. Success in such cases is said to be dependent on the general condition of the patient when the treatment is started, but improvement in the patient's general condition, reduction of pain, cessation of tumor growth, and occasionally tumor regression are claimed.

In addition to treating solid tumors, Iscador is also used for cancers of the bone marrow, connective tissue, and blood-forming organs, specifically, lymphomas, sarcomas, and leukemias. Proponents state that Iscador is less effective with these cancers than with the solid carcinomas.

The fourth, and probably the most controversial, use of Iscador is for treatment of "precancerous states" (847). Recent anthroposophic literature states that cancer can start early in life and can be in "preparation" for several years, if not decades, before a tumor develops (533,847). It is believed that a variety of factors, including psychological damage, unresolved problems, incidents causing shock, "strokes of fate," individual predispositions, and environmental factors, can lead to an impaired metabolism and a gradual failure of the immune system, which, in turn, decrease the body's ability to identify and destroy malfunctioning cells (536).

Proponents cite a number of conditions, some of which are associated with an increased risk of cancer, that are treated with Iscador in an attempt to prevent their development into tumors; after treatment with Iscador, regression of these conditions is said to occur, along with improvement in a patient's general condition (e.g., as shown by the "blossoming of patients, who for example outgrow their repressed and depressed frame of mind, and develop new powers and initiative again" (109)). Such conditions are listed as the following:

- Ulcerative colitis-chronic inflammatory disease of the colon and rectum
- Cervical erosion (Papanicolaou III and IV)-dysplasia, carcinoma in situ, or invasive carcinoma of the cervix
- Kraurosis vulvae—primary atrophy of the vulva
- Leukoplakia-white lesions of the mucous membranes in various organs

- Proliferative mastopathy, stage III-abnormal growth of breast tissue
- Crohn's disease-chronic inflammatory bowel disease
- Papillomatosis of the bladder—abnormal growth of the mucosal lining of the bladder
- Intestinal polyposis-presence of multiple polyps in the intestine
- Chronic gastric ulcer-ulceration of the mucosa of the stomach
- Senile keratosis—scaly lesions of the skin (746).

In their 1984 statement on Iscador, the Swiss Society for Oncology noted that conventional surgical treatment for some of these conditions, e.g., cervical abnormalities, is likely to be simpler and easier for patients than long-term Iscador treatment would be, and that Iscador treatment for these conditions could "maintain the patient in a constant fear of cancer for many years" (847). According to information provided to OTA by the Physicians Association for Anthroposophical Medicine, surgery for these conditions is used "wherever possible" (726).

### *Effects of Iscador Treatment*

The immediate physiologic effects of Iscador reportedly include arise in body temperature and an increase in the number and activity of circulating white blood cells. Several clinical studies of the fermented form of Iscador have noted that patients experience moderate fever (arise of 2.3 to 2.4 °C) on the day of the injections and in some cases, also local reactions around the injection site (479), temporary headaches, and chills associated with the fever (367). Clinical effects of the unfermented form of mistletoe treatment have not been reported. Iscador treatment is also claimed to improve patients' general conditions, even after all other treatment options have been exhausted (109), and to enhance hormonal and enzyme activities (specifically, by improving thyroid and reproductive organ function), promote deeper sleep, improve appetite, relieve tension and depression, increase initiative, regulate bowel movements, and increase functional capacity (534,536).

In general, proponents claim that "in the majority of cases [Iscador] treatment has had positive results such as improved chances of survival, enhanced quality of life, extension of life and regression of

tumours" (530). Treatment with Iscador is generally not claimed to result in dramatic destruction of tumors. Instead, it is thought to slow the growth of tumors or even stop tumor growth altogether, and then lead to gradual tumor regression. It is believed that tumor cells may undergo a transformation from malignant forms to semimalignant forms, then to chronic inflammation, and finally to normal forms (533,534).

### *Mode of Action*

The current Anthroposophic literature describes Iscador as having a unique combination of cytostatic (suppression of cell multiplication and growth) and immune stimulating properties (533,534). Its cytostatic properties are thought to derive from its constituent proteins, some of which are reported to act specifically against malignant cells. One type of protein found in mistletoe (viscotoxin), for example, is reported to destroy cancer cell membranes in cell culture (753). Another type (lectin) is reported to inhibit the growth of proliferating cells by blocking the synthesis of particular proteins at the ribosomal level (301,536). Iscador's immune stimulating properties reportedly include the ability to increase the number and activity of certain types of immune cells and to promote specific immune defense mechanisms leading to increased production of lymphocytes (533,534).

### *Studies of the Biological Activity of Iscador*

The scientific literature contains a number of studies conducted during the 1970s and 1980s on the cytostatic and immunologic properties of mistletoe extracts. It is now well-established that crude mistletoe extracts contain a cytotoxic lectin<sup>11</sup> (695) (viscumin, also called mistletoe lectin I), several other similar lectins, and a few cytotoxic non-lectin proteins (viscotoxins) (413,511), among other components, such as polysaccharides (464) and alkaloids (475). The identity and characteristics of cytotoxic substances in the processed and fermented Iscador preparation, however, which differs from the crude mistletoe extract, have been less actively studied. One recent study (413) of the cytotoxic components of Iscador found that it does contain a substance

related to (though not the same as) mistletoe's viscumin, along with some additional cytotoxic material similar to the viscotoxins found in unfermented mistletoe (51 1).

Several studies have investigated the effects of Iscador, crude mistletoe extracts, and their constituents on the growth of rodent and human cell lines in culture. In most cases, these substances were found to inhibit the growth of cells in culture. The degree of inhibition was found to vary according to the types of cell used, the method of preparation of the extract, the subspecies of mistletoe used, and the type of host tree supporting the mistletoe plant (752,753).

Both crude mistletoe extracts and Iscador have been extensively tested for antitumor activity in various experimental animal systems (277,475). The results with Iscador preparations have been mixed. Significant antitumor activity of Iscador was found in some animal tests (Lewis lung carcinoma, colon adenocarcinoma 38, and C3H mammary adenocarcinoma C6/C) (475). No antitumor activity was found in other tests (leukemia L1210 (475,928), leukemia L5222 (75), leukemia P388 (928), Ehrlich ascites carcinoma of the mouse (475), B16 melanoma (475, 928), Walker 256 rat carcinoma (75), and a separate test of Lewis lung carcinoma (928)). In a test using autochthonous primary mammary carcinomas<sup>12</sup> in Sprague-Dawley rats (475), nonsignificant growth inhibition was observed 6 weeks after Iscador treatment, but no difference in median survival time was found.

Immunologic effects of Iscador in human cells in culture and in animals have also been investigated (208,367). In cell culture, for example, it was found that Iscador extracts increased the activity of natural killer (NK) cells (374). Several studies found that injections of Iscador in mice resulted in enlargement of the thymus (672), and one study found increased production of certain immune system cell types (745). It is not yet known which components of Iscador, e.g., the various proteins or the bacteria or a combination of several elements, are responsible for eliciting these reactions.

<sup>11</sup>Lectins are biologically active proteins or glycoproteins that cause agglutination, precipitation or other phenomena resembling an immune reaction without stimulating an antigenic response. Lectin can bind with red blood cells of certain blood groups and with malignant cells, but not their normal counterparts. Other lectins stimulate the proliferation of lymphocytes.

<sup>12</sup>These carcinomas resemble human tumors more closely than transplanted tumors with respect to growth behavior, antigenicity, and experimental sensitivity.

### *Clinical Studies With Iscador*

Although Iscador treatment is given along with other interventions in Anthroposophic medicine, proponents claim that Iscador itself has anticancer properties: it is believed to increase the length and quality of life, stabilize disease, cause regression of tumors, and improve the general condition of the patient (534). To support these claims, proponents cite their many years of clinical experience with Iscador during which individual doctor-patient encounters convinced them of its efficacy (534). Also cited are isolated case reports (935) of patients treated with Iscador and various clinical studies.

The clinical studies of Iscador published up to 1984, most of which are in German, were reviewed in the Swiss Society for Oncology's paper on Iscador (847). Included among these papers were individual case reports, retrospective clinical trials, and "controlled" and "uncontrolled" prospective studies. Among these, five studies described by their authors as controlled and prospective (386,771,772,773,774) were critiqued in the Swiss paper. The Swiss Society for Oncology study group found that major methodologic flaws in each of the five studies prevented valid conclusions about efficacy to be drawn from them.

Several additional clinical studies of Iscador have been published since the Swiss review. One recent report described a prospective, uncontrolled study of 14 patients with stage IV renal adenocarcinoma with measurable lung metastasis who were treated with subcutaneous injections of Iscador (479). Treatment was administered every second day in escalating doses over 3 weeks, followed by "maintenance" treatment on alternate days. The study reported no objective responses to Iscador treatment in these patients.

Other studies have examined various immunologic effects of Iscador treatment in patients with advanced breast cancer (367,368,369). A number of changes in immunologic function interpreted by the authors as immune enhancement were noted after intravenous infusion of Iscador. These studies did not examine antitumor effects or effects on survival.

## PAU D'ARCO

Pau D'Arco is one of several commonly available herbal products used for cancer treatment. Unlike the proprietary Hoxsey, Essiac, and Iscador prod-

ucts, Pau D'Arco is marketed by a number of different U.S. companies through local health food stores. It is available in the form of capsules, tea bags, or loose powder. Other terms used synonymously with Pau D'Arco include taheebo, lapacho, ipes, ipe roxo, and trumpet bush (521,861).

Pau D'Arco originates in South America, where it is said to be a popular treatment for cancer and a variety of other disorders (e.g., malaria). It is reportedly used in folk medicine for Hodgkins disease, leukemia, and cancers of the pancreas, esophagus, "head," intestines, lung, and prostate (266). According to catalogs from the U.S. companies that sell Pau D'Arco, the product is generally claimed to be a strengthening and cleansing agent, with antimicrobial properties. In the popular literature, anecdotal reports of its use by U.S. cancer patients link tumor regression with drinking Pau D'Arco tea (943).

The source of Pau D'Arco is the inner bark of the purple flowered *Tabebuia impetiginosa* tree in Argentina or the *Tabebuia heptaphylla* tree in Brazil. The method by which Pau D'Arco tea or powder is produced is not publicly known. However, efforts to study the effects of Pau D'Arco have focused largely on one of its chemical constituents, lapachol, a biologically active organic compound. Lapachol is said to be present, to varying degrees, in commercial preparations of Pau D'Arco, although a recent analysis found only trace amounts or no measurable amounts of lapachol in the bark of specimens of *Tabebuia impetiginosa* and other species collected for commercial purposes (61). Less attention has been paid to the biological properties of other constituents of Pau D'Arco, e.g., several naphthoquinone compounds (340), or to crude extracts of the whole product.

For many years it has been known that lapachol is a potent cytotoxic agent and is an active antimalarial agent in animal test systems (173). Lapachol has also been extensively tested for antitumor activity in a variety of animal tumor models. It has been found to have antitumor activity in two types of tests (Walker 256 system (736,737) and Sarcoma Yoshida ascites (285)), and no significant activity in other tumor models (Sarcoma 180 (352), L1210 leukemia (700), and Adenocarcinoma 755 (173)).

A recent unpublished study described the effects of crude extracts of Pau D'Arco, rather than lapachol alone, in mouse cells in culture and in the Lewis

**Lung Carcinoma system (626).** According to that study, the Pau D'Arco extract stimulated the activity of macrophages derived from mice, killed Lewis Lung carcinoma cells in culture, and in the animal model, reduced the occurrence of lung metastasis in mice following surgery to remove primary tumors. The authors suggested that the Pau D'Arco extract showed immune modulation and direct cytotoxic effects in these experimental systems. This study has not yet been confirmed by other investigators.

On the basis of the positive results with lapachol in the Walker 256 animal system cited above, lapachol has been examined in at least two clinical studies. Following toxicologic and pharmacologic studies of lapachol in animals (173), NCI sponsored a phase I toxicology study of oral doses of lapachol in human subjects (81). In that study, 19 patients with unspecified advanced non-leukemic tumors and two patients with chronic myelocytic leukemia in relapse were given oral doses of lapachol ranging from 250 to 3,750 mg per day. Although the study was designed only to measure pharmacologic and toxic effects of the drug, it was noted that one patient with metastatic breast cancer had a regression in one of several bone lesions, while none of the other patients was reported to have had objective responses to the drug.

The investigators also found that high oral doses of lapachol (1,500 mg or more per day) were associated with nausea, vomiting, and a prolongation of prothrombin time (an indicator of blood coagulation processes) that returned to normal when the drug was withdrawn. No myelosuppression, hepatic, or renal toxicity was seen among these

patients. Based on previous animal tests, it had been determined that a blood level of 30 ug/ml or more of lapachol would be necessary for physiologic activity of the drug, but the toxicities observed in the clinical study indicated that physiologic levels of lapachol, in the authors' opinion, could not be reached in patients without encountering anticoagulation reactions. As a result of this study, the IND for lapachol was closed in 1970 (231) and further study of lapachol as an antitumor agent was not pursued. In a recent paper, however, the authors noted that lapachol's anticoagulant effects maybe inhibited by the coadministration of vitamin K, allowing for future assessment of lapachol's antitumor effects alone (184).

In another uncontrolled study, nine patients, all of whom had received previous conventional treatment, were given oral doses (20 to 30 mg/kg/day) of lapachol for 20 to 60 days or longer (286). One complete and two partial tumor regressions were noted in three of the nine patients: one described as having hepatic adenocarcinoma, another with basal cell carcinoma of the cheek with metastasis to the cervix, and a third with ulcerated squamous cell carcinoma of the oral cavity. It was not indicated how the regressions were measured or their duration. Subjective improvements (e.g., reduction of pain) were noted in all nine patients. Some of the patients reportedly showed some signs of toxicity (e.g., nausea, dizziness, and diarrhea). Valid inferences about the efficacy of lapachol cannot be drawn from this study, since many of the clinical details are not given in the published report and the possible effects of previous treatment were not accounted for.