Unconventional Cancer Treatments

September 1990

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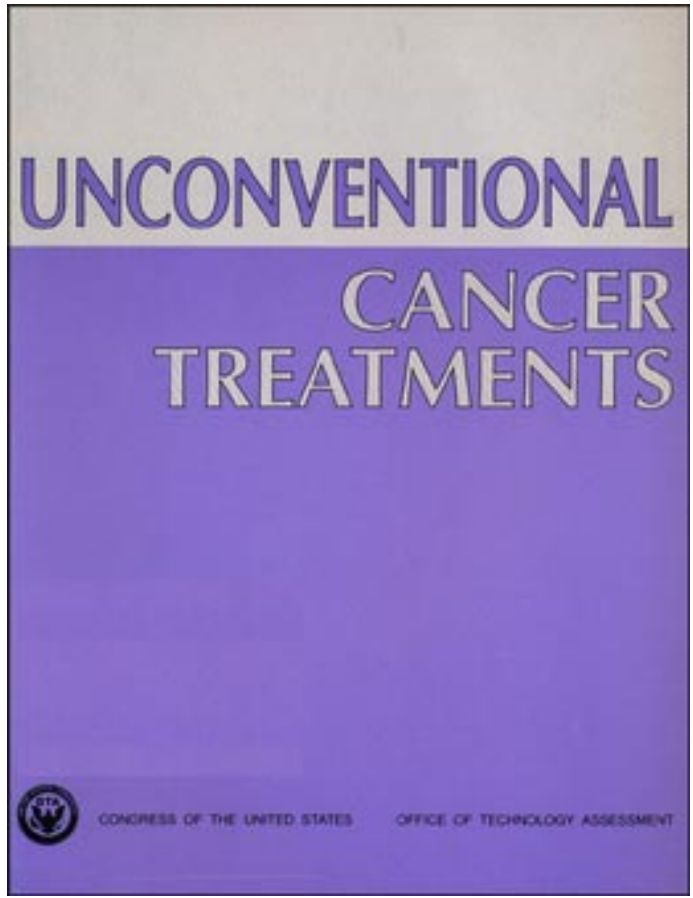

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Foreword

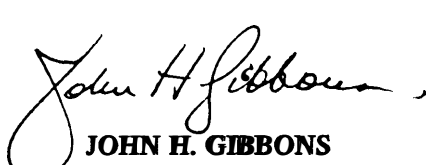
A diagnosis of cancer can transform abruptly the lives of patients and those around them, as individuals attempt to cope with the changed circumstances of their lives and the strong emotions evoked by the disease. While mainstream medicine can improve the prospects for long-term survival for about half of the approximately one million Americans diagnosed with cancer each year, the rest will die of their disease within a few years. There remains a degree of uncertainty and desperation associated with "facing the odds" in cancer treatment.

To thousands of patients, mainstream medicine's role in cancer treatment is not sufficient. Instead, they seek to supplement or supplant conventional cancer treatments with a variety of treatments that exist outside, at varying distances from, the bounds of mainstream medical research and practice. The range is broad—from supportive psychological approaches used as adjuncts to standard treatments, to a variety of practices that reject the norms of mainstream medical practice. To many patients, the attractiveness of such unconventional cancer treatments may stem in part from the acknowledged inadequacies of current medically-accepted treatments, and from the too frequent inattention of mainstream medical research and practice to the wider dimensions of a cancer patient's concerns.

Unconventional cancer treatments have received only cursory examination in the research literature, making an objective assessment of their efficacy and safety exceedingly difficult.It. Recognizing this, the Chairman of the U.S. House of Representatives Committee on Energy and Commerce, John Dingell, asked OTA to review the issues surrounding unconventional treatments: the types of unconventional cancer treatment most available to American citizens and how people access them, costs and means of payment, profiles of typical users of unconventional treatments, legal issues, and the potential for enhancing our knowledge about the efficacy and safety of these cancer treatments. A group of Members of Congress, led by then-Congressman Guy Molinari, also asked OTA to examine a particular unconventional treatment—Immuno-Augmentative Therapy-and to design a clinical trial protocol to permit valid evidence of efficacy and safety to be gathered. All these topics are covered in this report.

The debate concerning unconventional treatments is passionate, often bitter and vituperative, and highly polarized. To ensure that all relevant voices were heard and that OTA was accessible, particularly to advocates of unconventional treatments, OTA took several unusual measures during the course of this assessment in addition to its normal process of analysis and review. The project advisory panel, representing a diversity of views, played an important role. Under its Chairperson, Professor Rosemary Stevens of the University of Pennsylvania, the panel persevered through diffilcult discussions and provided valuable counsel. Much of the final meeting of the advisory panel was organized to hear from critics of the draft report, who were invited by OTA to present their concerns to the advisory panel and OTA staff. OTA's standing Technology Assessment Advisory Council devoted a meeting to this assessment, discussing the science and policy issues related to unconventional cancer treatments and providing counsel to OTA. Many other individuals and groups in the public and private sectors also contributed their ideas and criticism, for which they are gratefully acknowledged. As with all OTA assessments, however, responsibility for the content of the report is OTA's alone and does not necessarily constitute the consensus of the advisory panel, the Technology Assessment Board, or the Technology Assessment Advisory Council.

If history in this area is predictive, some few unconventional treatments may be adopted into mainstream practice in the years ahead, others will fade from the scene, and new ones will arise. The ways described in this report to stimulate the valid assessment of unconventional treatments could give the medical community and patients the means to make more informed decisions about their use.



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NOTE: OTA appreciates and is grateful for the valuable assistance and thoughtful critiques provided by the advisory panel members. The panel does not however, necessarily approve, disapprove, or endorse this report. OTA assumes full responsibility for the report and the accuracy of its contents.

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*From December 1987 until April 1989.
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Contents

Boxes

Tables

Chapter 1

Summary and Options

CONTENTS

Chapter 1
Summary and Options

INTRODUCTION

Each year, thousands of U.S. cancer patients use treatments that fall outside the generally understood bounds of mainstream medicine. While the majority of cancer patients do not use such treatments, those who do represent a visible minority (though the exact numbers are unknown). Additional thousands may be interested in such unconventional treatments and seek information about them.

Although any examination of unconventional cancer treatments will fall short of capturing all the reasons for cancer patients' interest in them, certain factors seem clear. Effective treatments are lacking for many cancers, especially in advanced stages; many mainstream treatments entail considerable toxicity; and long-term survival may be uncertain even after apparently successful treatment. These realities of mainstream treatment, coupled with explicit or implicit promises of effective, nontoxic cancer control by unconventional means, and the strong support of cancer patients for them, motivate new patients to seek treatments outside the mainstream.

Unconventional treatments vary greatly in content, and range from some that may be used easily along with mainstream treatment to those that, either because of the nature of the treatment, or because of the stance of the practitioner offering them, are used exclusive of mainstream medicine. They also range from those that are entirely within legal rules and ethical assumptions to practices that rely on drugs and biologics that are not approved and are not within the bounds of U.S. law.

Additionally, regardless of the nature of the approach taken, patients seek not only a hopeful prognosis, but also treatment perceived as humane and caring and psychological support from caregivers and fellow patients. These are elements that at least some patients believe are missing from mainstream medicine. Another important aspect is the sense of personal control that may be gained from deciding on a course of treatment and pursuing it, sometimes in defiance of physicians, family, and friends.

"Unconventional treatments"—the phrase chosen for this report to describe treatments outside of mainstream medical practice and research-are not limited to treatments for cancer. They are of considerable public interest in the United States, but their use has received little formal study. The range of treatments offered, the people who offer them, the number and types of patients who use them, and their costs are largely undocumented. The reliability of information on the effectiveness and safety of these treatments is questioned by most mainstream medical authorities, in part because most reports are anecdotal or represent unsupported claims of practitioners. Research and clinical studies of unconventional cancer treatments generally have not been well designed and have not met with the approval of academic researchers. Supporters of unconventional treatments tacitly approve these reports in the absence of anything better. Thus, one of the major rifts separating supporters of unconventional treatments from those in mainstream medical care and research is a distinct difference in what they accept as evidence of benefit.

Objective, informed examination of unconventional treatments is thus difficult, if not impossible, in the United States today. Acrimonious debate between the unconventional and mainstream communities reaches well beyond scientifc argument into social, legal, and consumer issues. Sides are closely drawn and the rhetoric is often bitter and confrontational. Little or no constructive dialog has yet taken place. In the course of this study, OTA involved individuals with a wide spectrum of views about unconventional and mainstream treatments, and went to great lengths to open the process to allow all viewpoints to be aired. This spectrum was represented on the advisory panel as well as among the hundreds of outside providers of information and reviewers who took part in the study. It is fair to say, however, that, while OTA heard and reported the viewpoints, the process did not bridge the gulf between two highly polarized positions.

This report describes the unconventional cancer treatments that are most used by U.S. cancer patients; it describes the way in which people find out about them and how much they pay for them; reviews the claims made for them and the informa-

tion base in support of the claims; suggests possible ways of generating valid information about their safety and effectiveness; and presents the legal issues surrounding unconventional treatments that have brought civil and criminal litigation to bear on the subject.

We focus on unconventional cancer treatments, and not on the successes and failures of mainstream medicine, either in general or in treating cancer. To help describe the context in which unconventional treatments exist, however, a brief summary of the status of mainstream cancer treatment is included later in this chapter. But this report is neither a comparison of mainstream and unconventional treatments nor an equal critique of both. In many places, the discussions of unconventional treatments in the report are quite critical, e.g., of the quality of evidence offered to support the treatments, of the claims that are made, etc.

In addition, adverse effects are pointed out when there is information about them. These points are not intended to suggest that mainstream medicine is free of faults, that its promise is always realized, or that practitioners of mainstream medicine are aware of and use the best possible treatments for their patients. OTA and many other organizations and authors have produced critical analyses of various areas of mainstream research and medical practice, and these are available for the reader. The aim of this report, rather, is to produce an assessment of unconventional treatments, as far as is possible today.

REQUEST FOR THE STUDY

This report responds to a request by the U.S. House of Representatives Committee on Energy and Commerce (a committee with jurisdiction over a wide range of health issues), which asked OTA to examine the subject of unconventional cancer treatments. OTA also received letters signed by 42 individual Members of Congress, asking for an assessment of a particular treatment, Immuno-Augmentative Therapy (IAT). Their request was sparked by the closing of the IAT clinic by the Bahamian government in late 1986. Then-Congressman Guy Molinari of New York, among whose constituents were a number of clinic patients, asked his House and Senate colleagues to cosign letters of request to OTA concerning IAT.. In response to the congressional interest, OTA undertook, as part of this project, a case study to develop a protocol for a clinical trial to study the efficacy and safety of IAT. The results of this effort are reported in chapter 6.

THE TERMINOLOGY OF UNCONVENTIONAL CANCER TREATMENTS

"Unconventional" is just one of many terms, all imperfect descriptors, that were considered, for the purposes of this report, to refer to the wide variety of treatments that fall outside the bounds of mainstream medicine. Other terms used by proponents to describe all or some of these treatments include: alternative, complementary, nontoxic, holistic, natural, and noninvasive. Those used by the sharpest of critics include: unproven, questionable, dubious, quackery, and fraudulent. At the beginning of this study, the term "nontraditional' was used to describe the treatments, but was unacceptable since "traditional' is widely used to refer to various types of native healers and treatments, as in traditional Chinese medicine; nontraditional, therefore, could describe mainstream medicine. During much of the project, the adjective "unorthodox" was used, chosen as a term as free as possible from value judgments about the quality of the treatments being discussed. Eventually, protests from both sides of the debate prompted the change to the term 'unconventional." We intend no implicit message in the use of the word "unconventional;" it was chosen with the hope that debate engendered by this report could center not on that word, but on the issues themselves.

HISTORICAL PERSPECTIVE

Physicians and the organizations they have created have come to dominate health care and biomedical research in the United States during the 20th century. "Scientific medicine" owes much of its rise to major advances in public health: the success of vaccination in preventing infectious diseases; the advent of therapeutic radiation for a wide variety of diseases and for its diagnostic uses in the early part of the century; and the successful treatment of previously life-threatening infections with antibiotics in the period after World War II.

Evaluation methodology developed alongside potential clinical advances, as the need to distinguish the effective from the ineffective took on greater

significance. In addition, the rising toll of chronic diseases-with longer and more unpredictable courses-in the face of dramatically declining death rates from acute diseases heightened the need for reliable methods to gauge the effectiveness of treatments. A formal set of procedures, consistent with the 'scientific method," now governs the clinical evaluation of new medical technology, particularly drugs and biologics. (In contrast, medical and surgical procedures—e.g., surgical operations and diagnostic techniques—are not always subject initially to such rigorous testing.[1]) The formal approach has had particular emphasis in the evaluation of cancer treatments, and over the years has been incorporated into the processes and standards of evidence required by the Federal Government for the approval of new drugs and medical devices, and into the operations of the National Cancer Institute, which funds most cancer research in the United States. The greatest emphasis in cancer treatment, hence in the methods employed in cancer research, has been placed on finding treatments that directly kill cancer cells (cytotoxic agents).

The American Medical Association (AMA) has been the organizational leader of the U.S. medical community during this century. In addition to enhancing the authority of physicians and supporting the structured approach to clinical research, the AMA has attempted to eliminate alleged health fraud, and much of this activity has focused on cancer treatments. From the early 1900s onward, the task of combating activities designated as health fraud was the formal responsibility of one or another organizational unit within the AMA. In addition, Morris Fishbein, editor of the Journal of the American Medical Association (JAMA) from 1924 to 1949, conducted several crusades against particular practitioners of unconventional cancer treatments and, in general, against what he considered quackery.

In recent years, the AMA has reduced its formal activities against certain nonphysician providers and alleged health fraud. While the Division of Archival Services and Public Affairs now answers inquiries about unconventional medicine, the Committee on Quackery and the Department of Investigation were eliminated in 1975. One of the main functions of the Committee on Quackery, formed in 1962, was to oppose recognition of chiropractors as legitimate health care providers. In the mid-1970s, Chester Wilk and three other chiropractors brought suit, charging that the AMA and several other professional societies had engaged in a conspiracy to boycott chiropractors (960). In 1987, after an 11-year lawsuit, the court ruled for the chiropractors and against the AMA (614). Both the Department of Investigation and the Committee on Quackery were eliminated in a 1975 restructuring of AMA.

The American Cancer Society (ACS) has also played a key role in defining the limits of orthodoxy in cancer treatment and in discouraging the use of treatments falling outside their definition. ACS has taken a leading role in efforts against practitioners of unconventional cancer treatments. Their 'Unproven Methods List" is frequently used by doctors in counseling their patients about unconventional treatments, and is used extensively by the insurance industry to determine whether patients should be reimbursed for the costs of treatment (577). It is often referred to as a' 'blacklist' by the proponents of unconventional treatment.

A highly polarized situation exists today. As Lerner puts it:

> *In the "war over cancer therapies" that has been widely publicized in the American media for the past decade, both sides often describe the opposition as a malevolent monolith. Thus the cancer establishment has characterized the alternative and adjunctive cancer therapies as the work of quacks preying on desperate and credulous cancer victims, while the proponents of alternative therapies have depicted established therapies as the 'cut, burn and poison" therapies of a cynical and profit-driven conspiracy. These stereotypes are, from a sociological perspective, familiar to anyone who has studied the phenomenon of propaganda in conflict situations. Each side in the cancer therapies controversy accuses the other of being profit motivated, of preying on desperate cancer patients, of cynically suppressing or ignoring therapies that could be beneficial, and of representing an organized conspiracy to thwart progress in cancer. (528)*

LEGAL ISSUES

The Federal Food, Drug, and Cosmetic Act (FDCA) and other laws regulate the manufacture, sale, and advertising of medical products. In enact-

[1]The 1978 OTA report *Assessing the Efficacy and Safety of Medical Technologies* (863) cites Kerr White's estimate that only 10 to 20 percent of all procedures used in mainstream medical practice have been been shown to be efficacious by controlled trial.

ing these laws, Congress has operated on the premise that the Federal Government has a legitimate interest in protecting the health of its citizens, while at the same time respecting their freedoms. The system that has developed is one that requires reliable evidence of efficacy and safety accepted by the Food and Drug Administration (FDA) before medicines may be offered legally.[2] This status quo is supported by the "consumer protection" point of view. Opposition to this system, called the "freedom of choice' position by some advocates of unconventional cancer treatment, is based on a belief that Americans should be free to decide for themselves which treatments they want to take.

The "consumer protection" point of view is supported by the contention that the average consumer cannot be expected to make informed choices in a complex scientific field. In an early court case under the Food and Drugs Act of 1906, the judge, in his charge to the jury, said:

> *This law was not passed to protect experts especially, not to protect scientific men who know the meaning and value of drugs, but for the purpose of protecting ordinary citizens. (914,916)*

In a case interpreting the 1938 FDCA, Justice Frankfurter stated:

> *The purposes of this* legislation. . touch phases of *the lives and health of people which, in the circumstances of modern industrialism, are largely beyond self-protection. (913)*

The argument for "freedom of choice" in medical care is based on the concept of an individual's right of privacy. It is argued that this right prohibits the government from restraining individuals' rights to obtain treatments of their choosing: "the patient should be permitted to opt for treatment consistent with his views of higher quality of life" (416). A parallel argument is made for the physician's right and responsibility to provide medical care. It reasons that well-informed physicians, following their best judgment and having assessed the risks and benefits of a treatment, should be allowed to provide the care they deem best for their patients (950).

There are, in general, no legal restrictions on a U.S. patient's right to choose a treatment for himself or herself, either in the United States or in foreign countries (though parents choosing treatment for a child may be restricted by legal precedents). However, some treatments are excluded from choice in the United States because they involve the use of unapproved substances that could only be offered illegally here.

Variations on the freedom of choice position have been voiced in recent years. For instance, during the lengthy legal battles over the rights of cancer patients to use laetrile, the argument centered on the right of terminally ill patients to choose a treatment that did not meet the safety and efficacy requirements of the FDA. In the final decision of that case, which initially found for the plaintiffs at the Federal district and appeals court levels, the U.S. Supreme Court found that even terminally ill patients should be protected from potentially unsafe and ineffective medicines (918). The same case indirectly legitimized the autonomy of the FDA, which had been under siege by State legislatures who were independently permitting the use of a federally unapproved treatment within their States, when FDA regulation clearly prohibited State sanctioning.

Laws and regulations designed to protect patients from potentially harmful and ineffective treatments have been criticized by supporters of unconventional treatment for limiting patients' access to treatments of their choice. When State laws have been passed permitting access to specific unconventional cancer treatments that would otherwise be illegal (e.g., laetrile, in the 1970s), they have been criticized by segments of the mainstream medical community for exposing patients to hazardous or ineffective treatments, or for dissuading patients from seeking potential curative treatment.

Relevant laws and regulations address the approval, labeling, advertising, and marketing of pharmaceuticals and medical devices; the certification of various types of medical practitioners; professional sanctions against certified practitioners for inappropriate care of patients; the general exclusion of nncertified individuals from medical practice; and the rules by which publicly funded programs pay for medical care. More generally, criminal and civil statutes, though developed to apply to a wide range of situations, sometimes have

[2]Technically, FDA approval must be obtained before drugs and biologics may be marketed in interstate commerce. This criterion excludes only an exceedingly small proportion of medicines.

applied to disputes involving unconventional cancer treatments.

U.S. laws provide for the regulation of the efficacy, safety, advertising, and sale of medical drugs and devices, under statutory authority of the FDA, the Federal Trade Commission, and the U.S. Postal Service. Professional standards apply to the practice of medicine and are designed to limit the bounds of medicine to practices with known or definable safety and effectiveness, or practices that are generally "accepted' by mainstream medicine, sometimes without formal evidence. Though the threat of professional sanctions exists, physicians appear to have considerable latitude in treating their patients; there are relatively few medical conditions for which the choices of physicians are entirely constrained.

In addition, the enforcement of laws and professional norms is incomplete, so that, in practice, even set bounds are readily exceeded without legal or professional consequences to the physician. The potential for legal action exists against those overstepping the bounds of law, but relatively few actions are actually taken by the Government or by disciplinary bodies. A member of the advisory panel for this study reported to OTA that, based on an informal survey he conducted, it appears that in the last three years an increasing number of disciplinary actions against unconventional practitioners may have taken place (219). In addition, at least some physicians with an interest in using unconventional treatments along with mainstream treatments have informed OTA that they are reluctant to do so because of the fear of legal action or professional sanctions (82,218).

This report describes the legal standing of unconventional treatments and their practitioners and the legal arguments on both sides of the issue. Laws and regulations affecting unconventional cancer treatments are discussed in chapter 10. Those that affect practitioners are discussed in chapter 11. It was not within the purview of the report to suggest an overhaul of the basic regulatory framework for drugs, and options that would accomplish that change are not included. However, the information in the report might be useful in considering a suggestion made in a joint letter to OTA by several members of the project advisory panel, should the Congress wish to consider changes. The panel members believe that it would be useful:

To find appropriate mechanisms in the Congress for thoughtful review of the fundamental issues raised by the "freedom of choice" versus "consumer protection" quandary, and to determine whether there are not better laws and regulations that would enhance both consumer protection and freedom of choice in the interests of Americans with cancer. (8)

INTERNATIONAL PERSPECTIVE ON THE AVAILABILITY OF UNCONVENTIONAL CANCER TREATMENTS IN THE UNITED STATES

The FDCA codifies standards of safety and efficacy for new medical drugs and medical devices, but does not set standards for the practice of medicine; the medical profession sets its own standards for the conduct of physicians. A wide variety of unconventional cancer treatments are available in the United States despite the limits implied by these laws and professional standards. A book published in 1988, Third *Opinion (289),* ***lists 60 clinics and physicians in the United States offering alternatives to mainstream medicine.***

Advocates of unconventional cancer treatments often contrast the situation in the United States to the relative openness of a number of European countries-e.g., Switzerland, Germany, England, the Netherlands-to unconventional medicine. No thorough international comparison of the availability and legal status of unconventional cancer treatments has been done, and OTA did not undertake such a comparison. However, it is clear that many treatments not available legally in the United States are offered openly and legally in those countries. In those countries, it appears that, particularly for treatments that are supportive and adjunctive to mainstream treatment, they coexist more harmoniously with the mainstream community than is the case in the United States. For example, the Bristol Cancer Help Centre, in England, which offers a range of supportive psychological and nutritional approaches, has many cancer patients who were referred there by their physicians. Such programs exist in the United States, the Commonweal Cancer Help Program, for instance; the issue of differential treatment internationally is not simply one of legality, but of acceptance.

Some unconventional treatments about which OTA has specific information are not in fact treated equally to mainstream medicine in other countries. In the case of IAT, for instance, though it is available at a clinic in West Germany, it is not licensed by that Government. According to an official of the German Government (422), the "effectiveness of the method described [in the patient brochure] is not proven by the statements advanced. Whether the treatment can lead to risks for patients is, from the submitted information, not clear, but cannot in any way be excluded" [emphasis in original]. The costs of treatment with IAT are not covered by social insurance carriers for German citizens. In other countries as well, unconventional treatments are not necessarily paid for by publicly funded health plans (e.g., the Netherlands (222)). In a joint letter to OTA, members of the advisory panel for this study commented on the "broad availability of insurance coverage in other countries, such as Germany, for many unconventional cancer therapies. '

Defenders of the U.S. drug approval system point to the many instances in other countries, Great Britain, for example, in which drugs never approved in the United States have been approved, later to be banned because of serious side effects not detected during pre-approval clinical studies (966). It is likely that more unsafe as well as ineffective products are approved in countries other than the United States. No comparative analysis of international drug laws as they relate to unconventional medicine exists so it is not possible to draw conclusions about the relative merits and deficiencies of each approach.

CURRENT MAINSTREAM TREATMENTS FOR CANCER

Surgery, radiation therapy, chemotherapy (drug therapy), hormonal therapy, and immunotherapy are the main tools of conventional cancer treatment. Surgery is the oldest and still most effective mainstream treatment for solid tumors, and is curative in many cases of localized cancer in which all or nearly all cancerous tissue can be removed. When used with chemotherapy, radiation, or both, surgery's aim is to remove as much tumor as possible without disabling the patient, so that the other treatments have a greater chance of successfully eliminating the remaining tumor cells. In advanced stages of cancer, surgery is sometimes used for palliative purposes, to alleviate the physical interference of a cancer with other organs.

Advances in oncologic surgery include a move toward less radical operations for some cancers, particularly early stage breast cancer. The shift is based on the results of large randomized clinical trials of various degrees of surgical removal (from removing the least amount of tissue, ''lurnpectomy," to the most, radical mastectomy), which demonstrated that, combined with appropriate adjunctive treatment, surgery that is less radical results in survival equivalent to that of more radical surgery. Another trend has been toward more aggressive surgical removal of metastatic tumors.

Chemotherapy and radiation therapy are used as primary treatments for some leukemias and lymphomas, and are used in addition to ("adjuvant" to) surgery for solid tumors that have advanced beyond their original location, including both regional and distant (metastatic) spread. Out of the thousands that have been tested, a relatively small number of drugs (about 30) are approved for use today. The regimens considered "state of the art" vary according to the site of the cancer, in some cases the type of cells that make up the tumor, the stage of the cancer, and, to some extent, characteristics of the patient.

General rules for mainstream cancer chemotherapy are that the highest tolerated doses be used, and that multiple drugs be used in combination. The use of high doses, the systemic administration, and the toxic properties of many anticancer drugs account for the often severe side effects of cancer treatment. The rules are based on the observation that some cancer cells are resistant to the effects of some drugs. One of the most widespread mechanisms of naturally occurring drug resistance is a molecular "pump" which works to transport chemotherapeutic drugs out of the cancer cell before any damage takes place. A number of other mechanisms are known, though all drug resistance is not explained with current knowledge (252). If clones of resistant cells proliferate, there is little hope for control with existing chemotherapy. The emergence of resistant clones and regrowth of drug-resistant cancers is a particular problem after treatment with lower than optimal doses of chemotherapy.

Efforts to improve the success of chemotherapy include developing means of more specifically targeting the drug to the tumor, and devising ways of increasing the doses. An example of the former is

linking cell-killing agents to monoclinal antibodies that are attracted to specific proteins on the surface of cancer cells. When the 'conjugated' molecule is administered, it will not find appropriate sites on most normal cells to which it can attach, but will link to cancer cells. Photodynamic therapy (PDT) is another approach still under development to provide localized cancer treatment, though its use is still quite limited. PDT capitalizes on the greater attraction of "hematoporphyrin" molecules (the "sensitizer' to tumor tissue than to normal tissue, though the basis of the attraction is not well understood. Some time after the sensitizer is administered, the area of the tumor is illuminated with light of a particular wavelength, either from the surface or from inserted fiber optics. The light provides energy for a chemical reaction that results in the release of oxygen, which kills cancer cells by damaging them physically.

Hormonal treatment has been successful for types of cancer that are "hormone dependent," notably breast and prostate cancers. The theory behind hormonal, or endocrine, therapy, is that hormones produced internally are "blocked" by drugs. These drugs bind to receptors on the surface of tumor cells where the hormones would normally bind, but they do not cause the cell to grow or replicate. These drugs are generally taken for long periods of time following surgery to prevent metastatic disease.

Radiation therapy is used most often as an adjunct to surgery, and maybe used before or after surgery in different situations. It is also used as a palliative measure, to reduce the pain of bone metastasis and to shrink tumors in other parts of the body. Radiation may be applied at or near the site of the tumor as an implant (by insertion of a radioactive isotope) or it may be delivered to the site of the tumor by a high-energy x-ray generator (teletherapy). (Whole-body irradiation is used to intentionally destroy the bone marrow of patients being prepared for bone marrow transplantation.) It is thought that the main effect of ionizing radiation on cells is to interfere with the capacity of the DNA molecule in the nucleus to reproduce, but cells may be harmed in other ways as well. In general, therefore, it is at the time the cells are dividing that they die. Since ionizing radiation also affects normal cells, the dose must be modulated to achieve the greatest antitumor effect while attempting to minimize effects on normal tissue, to optimize the "therapeutic index. "

The use of radiation therapy began early in the 20th century, preceding chemotherapy, and preceding the wide-scale use of randomized clinical trials to determine the effectiveness of medical treatments. It is only in recent years, therefore, that radiation therapy has been subjected to rigorous evaluation. It is likely that radiation has been used routinely beyond its effectiveness for many types of cancer; valid evidence for these practices still is being gathered. Advances in radiation therapy have centered on more precise delivery systems and on attempts to pair radiation with specific chemotherapeutic agents to enhance their effectiveness.

"Biologic therapy," the most recent approach in conventional cancer treatment, refers to "cancer treatment that produces antitumor effects primarily through the action of natural host defense mechanisms or by the administration of natural mammalian substances' (763). Though biologic treatments for cancer are relatively new, the field of biologic therapy, also called "biotherapy," developed from observations and experimentation in the late 19th century, which suggested that an immune response could effect tumor regressions (215). Biotherapy is based on the principle that tumor cells are immunologically "different" from normal cells, and that the immune system, which has developed to protect against "nonself,' can be manipulated to destroy cancer cells.

Mainstream biologic therapy includes a number of approaches. One line of development has been to attempt to induce reaction in the patient's own immune system, either with nonspecific stimulators (e.g., Bacillus Calmette-Guerin; BCG) or, more currently, with stimulators related to the tumor itself. The latter includes efforts to develop "tumor vaccines" that would cause the body's immune system to activate against tumor cells. Another approach is to inject the patient directly with immune system products and cells (e.g. "lymphokine-activated killer cells' '). "Cytokines" (soluble proteins produced by certain immune system cells), particularly the interleukins, have been the focus of considerable attention in the last few years. Another group of cytokines, the interferon, was studied intensively throughout the 1970s and 1980s.

Many of the biological treatments that have been tried have produced some encouraging effects in cancer patients, but, as of yet, few are of lasting benefit to patients. Research in biological therapy is

geared toward increasing understanding of immune function and on developing effective ways to apply these tools in conjunction with other forms of cancer treatment.

The trend toward increased participation by patients in decisions about their medical treatment has affected mainstream medicine. Whereas in the past few people would have questioned the recommendation of a physician, questioning has become common, perhaps even the norm. In addition, public discussion about health and disease, including all aspects of cancer, has risen, and the level of detailed coverage of cancer by the press has grown continuously. Patients and their families openly discuss the disease. During the 1980s, patient support groups, many independent of organized medicine, have taken hold, and patients have much greater opportunities to exchange information about their treatments.

The participation of patients in decisionmaking about their treatment and their more active questioning of medical authority have also raised awareness of the importance of the quality of cancer patients' lives. A panel evaluating the measurement of progress against cancer (896) strongly emphasized the various dimensions embodied in "quality of life" as being aspects of the impact of cancer on which systematic data should be collected on a nationwide basis. Such dimensions include: physical side effects (of treatment) such as nausea, general health conditions, and pain; functional status including self-care (eating, dressing, and bathing), mobility, and physical activities such as walking and doing household chores; psychological morbidity including emotional distress, anxiety, and depression; and social interaction including everyday interpersonal contacts, social support, and the work role.

CONTROVERSIES IN MAINSTREAM CANCER TREATMENT

During the past few years, the rates of success of conventional cancer treatment have increasingly been examined, debated, and subjected to criticism by both scientists and the general public. Attention has focused on the lack of substantial progress in successfully treating the most common and life-threatening types of cancer. While the last few decades have seen undisputed success in treating a number of cancers-particularly those affecting children and young adults-the gains in survival for most solid tumors (lung and colon cancer, in particular) are small or nil. The long-term survival advantage of some established treatments, particularly the treatment of early stage breast cancer, has been demonstrated definitively only recently (268). Long-term effects of some recent treatments, for example anew chemotherapy regimen for advanced colon cancer that has shown promise in early randomized clinical trials, are not yet known.

Individuals in the cancer research community and in government have begun to examine the results of the "War on Cancer," begun officially in 1971, and have noted a lack of significant progress in treating most cancers. The National Cancer Institute (NCI) has been criticized for misleading the public about what the results have actually been. One journal article, in particular, became a centerpiece of the debate. "Progress Against Cancer?" by John Bailar and Elaine Smith, which appeared in the New *England Journal of Medicine* ***in May 1986 (65), took abroad view of the emphases in cancer research and the changes in various measures of the disease since 1950, and noted that the age-adjusted mortality rate,[3] which was chosen as a measure of overall progress, has risen since 1950. They concluded that treatment for most cancers hasn't gotten much better, and that the greatest promise for cancer control lies in research on prevention. Bailar commented further on his position in a later article (63), in which he stated: "Modern medicine already has much to offer to virtually every cancer patient, for palliation if not always for cure; the problem is the lack of any substantial recent*** *improvement* ***[emphasis in original] in treating the most common forms of cancer. '***

The article by Bailar and Smith stirred up interest and controversy, which was furthered by a report by the General Accounting Office (GAO, a congres-

3A mortality rate measures the proportion of the population dying during a given time period. An age-adjusted rate removes the effect of changes in population size and age distribution within the population, allowing direct comparison of the rate over time. In the United States, this allows for population growth, as well as growth in the percentage of people in older age groups.

[4]Bailar went on *in that article to say:* "There is no comfort here for the 'medical counterculture'; nonstandard (or 'unorthodox') treatments are likely to be dangerous as well as utterly ineffective."

sional agency) that looked at NCI'S reporting of cancer survival statistics. GAO examined changes in survival since 1950 for 12 different kinds of cancer and compared its independent findings with those reported by NCI. NCI reported gains for all 12 types. In each case, GAO found a more modest improvement than did NCI, or no gain at all. These results, released in early 1987, again raised controversy about the rate at which progress in treating cancer is being made, and further opened the debate about cancer treatment to public scrutiny. The article by Bailar and Smith and the GAO report have been used by supporters of unconventional treatments to challenge the dominance of the NCI, ACS, and mainstream medicine in general (see, e.g. 189).

The widespread use of chemotherapy among classes of patients unlikely to benefit, or for which benefits have not yet been demonstrated, also has drawn criticism from respected researchers (147). The cancer research community itself has been reexamining the value of long-accepted chemotherapy for certain types of cancer. An example is adjuvant treatment of cancers of the colon and rectum, the most common types of cancer in the United States. Debate was focused by a review of all the randomized clinical trials of radiotherapy and standard chemotherapy for these cancers, published in the Journal of the American Medical Association in 1988 (144). The review suggested that these treatments might offer little survival advantage, or at least less than had been assumed, beyond the benefits of surgery, which is the primary treatment. A debate in the medical literature ensued (see, e.g. 108,204) with opinions strongly held for and against the value of adjuvant treatment, based on differing interpretations of the same data. (This debate preceded the dissemination of the results of advanced colon cancer treatment with a new combination of agents, which has shown a survival advantage.)

Another debate concerns the use of adjuvant chemotherapy for women who have undergone surgery. for early stage breast cancer. Early results from clinical trials prompted the NCI to issue a "Clinical Alert' (895), with the strong message that women with early (stage 2) breast cancer without evidence of cancer in the lymph nodes can benefit from adjuvant chemotherapy. The Clinical Alert elicited strong criticism from prominent members of the medical community, who objected mainly on grounds that the data available from the trials were only preliminary and that they were insufficient to support recommending widespread treatment with toxic chemotherapy (391,572).

One result of the debate over progress in cancer was a request by the Senate Appropriations Committee to NCI in 1988 to establish a panel of technical experts and nonexpert public representatives from outside NCI to "recommend what measures or series of measures are most appropriate to assess progress in cancer" (874). The panel reviewed measures of progress currently in use and suggested additional approaches (896).

TREATMENTS DISCUSSED IN THIS REPORT

The phrase "unconventional cancer treatments" encompasses a tremendously heterogeneous group of practices. These treatments vary in content, probably in safety and effectiveness, and in the types of practitioners delivering them. They are defined in this report not by what they are, but by what they are not: they are not part of mainstream, conventional medicine in the United States. Because of this variety, the treatments described do not easily lend themselves to simple, general characterizations. Statements or judgments about one treatment cannot be assumed to apply to others; this applies equally to positive and negative aspects.

This report is about the common cancer treatments found by U.S. cancer patients outside of mainstream medicine; in using these treatments, patients may be rejecting conventional medicine, they may be seeking approaches to supplement conventional medicine, or they may believe that conventional medicine has given up on them. Though no census of patients receiving unconventional treatment exists, the literature and expert opinion strongly suggest that Americans are most likely to seek a wide variety of unconventional treatments in the United States, Mexico, or the Caribbean. A few seek particular unconventional treatments in Europe. A large number of unconventional treatments are available in the United States, some practiced in violation of the law and some within the bounds of the law.

Some treatments that might be considered unconventional are excluded from discussion in this report. One is the unconventional use of conventional cancer treatment, such as low-dose, high-frequency regimens of chemotherapy, or high-dose pulses of

chemotherapy. Although chemotherapeutic regimens are being used in unconventional ways, they are, nevertheless, approved drugs with known efficacy by some route of administration.[5] *Another type of treatment not included in this discussion is experimental treatment developed within conventional medical research channels, but applied to patients outside of the clinical trial system before they have been approved for use. The most prominent examples of this are the biological response modifiers (such as interleukin-2 and LAK cells) that were (until 1989) offered by Biotherapeutics, Inc. (Franklin, Tennessee) on a commercial basis to patients who were not eligible for or who chose not to participate in clinical trials involving these substances.*

This report concentrates on unconventional treatments that are well known or that have been used by large numbers of patients. We do not attempt to cover the many individual treatments of various kinds that are offered on a small scale, perhaps to neighbors or friends. It is impossible even to approximate the number of such cases. More often than not, these types of treatment come to public attention only through the legal system, when patients or their survivors bring suit to try to recover money spent on allegedly ineffective treatments or to try to stop the practitioner from continuing to fraudulently treat patients (see, e.g., a recent case in Arizona) (398). The cases that do surface in this way may represent only the worst end of the spectrum, but there is no way to confirm this.

This report also does not attempt an account of unconventional treatments that once held the spotlight but have fallen out of favor. A 1949 report of the American Medical Association Council on Pharmacy and Chemistry, for instance, lists many unconventional cancer treatments largely unknown today-' "collodaurum," "HettCancer Serum," "AF-2,' and the 'orgone accumulator" (39). Some other treatments of the past-the Rife Ray Machine, Krebiozen-still have their supporters, but, by and large, they are no longer in widespread use and are not reviewed in this report.

Perhaps the most significant area not included consists of spiritual approaches, among the oldest human responses to illness. How patients express their beliefs and what they do under such circumstances can take many different forms (419,529). Religious figures such as ministers, priests, and rabbis are often called on to counsel patients and their families. Some are also involved in various forms of religious healing, e.g., faith healing, laying on of hands, and prayer. People from all over the world have traveled to the famous religious shrine at Lourdes, France, to pray for miraculous cures. An estimated four million people visit Lourdes each year, 65,000 of whom are ill. The Lourdes medical board has examined thousands of cases claiming cures, and 64 of these have been designated by the Catholic Church as miraculous cures (264).

Several of the unconventional treatments discussed in other sections of this report also include a spiritual or religious component. In macrobiotics, for instance, the dietary guidelines are one aspect of a much larger philosophical and spiritual system. Similarly, Anthroposophic medicine, which includes the use of the herbal preparation Iscador for cancer patients, is based on a complex religious philosophy and "spiritual science" developed by Rudolph Steiner in the late 19th and early 20th centuries. Other unconventional treatments that were designed specifically for cancer patients include a spiritual component. Spiritual aspects of the original Kelley regimen, for example, reflected the developer's strong religious beliefs. A physician who founded the first clinic in Tijuana offering laetrile to cancer patients, Ernesto Contreras, includes a strong spiritual orientation in his regimen and often leads services for patients at a chapel he built at his clinic.

Patients may also seek care from traditional healers (outside their own culture), e.g., Native American healers, curanderos, shamans, and others, who use a strong spiritual component in their approach to treatment. Although the extent of use of traditional healing methods by U.S. cancer patients is undocumented, the popular literature suggests that some approaches have become relatively common in recent years. The 'New Age' movement beginning in the 1960's and 1970's in the United States has popularized a number of mystical practices, such as crystal healing, channeling, and 'neo-shamanism,' as well as some traditional healing practices involving curanderos, herbalists, and others (421).

[5]This is distinguished from the use of a substance for cancer treatment that is approved only for indications not related to cancer, such as the use in unconventional cancer treatment of dimethyl sulfoxide, a drug currently approved only for the treatment of interstitial cystitis. Uses such as these are within the scope of this report.

While most spiritual approaches treat cancer as any other disease or misfortune, some techniques with spiritual or mystical components are often associated specifically with cancer. "Psychic surgery" refers to a procedure involving removal of spirits or physical manifestations of spiritual pathology from a patient. Some Americans travel to the Phillipines for "psychic surgery," where it is practiced in its original context of religious and traditional healing (419,530). Psychic surgeons from the Phillipines have also come to the United States, holding treatment sessions as they travel around the country. They have often been pursued by legal authorities and some have been convicted of practicing medicine without a license. Psychic surgery is considered by many in the unconventional community to be a "fringe' treatment.

Categories of Unconventional Cancer Treatment

The treatments described in this report are grouped, for convenience, into four general categories: psychological and behavioral, nutritional, herbal, and pharmacologic and biologic. These categories are not the only ones that could be devised, and the groupings do not connote commonality among their elements beyond the basic nature of the treatment. Since many of the treatments include a variety of components, however, assignment to certain categories was not straightforward and could have been done differently in a number of cases. In general, assignment to the categories was based on the nature of the central or unique element of each approach.

Chapter 2 of this report discusses behavioral and psychological approaches to cancer treatment. Many forms of psychological and behavioral intervention are used adjunctively to relieve pain and distress associated with cancer and its treatment, and generally, to improve a patient's psychologic outlook. Some individuals have claimed that psychological approaches can cause tumor regression and prolong survival. The potential contribution of psychosocial interventions to extending life has recently begun to be studied by mainstream researchers, with encouraging results. The efficacy of psychological and behavioral approaches in improving the course of cancer is still uncertain, however. The chapter describes three of the most popular psychological interventions for which claims of tumor regression or life extension have been made: mental imagery, a method involving the creation and interpretation of mental images that was popularized by O. Carl Simonton, M.D., and Stephanie M. Simonton-Atchley; intensive meditation as practiced by the late Australian psychiatrist Ainslie Meares, M.D.; and a unique form of psychotherapy developed by Lawrence LeShan, Ph.D. While these methods are the ones cancer patients are likely to find out about, they have been widely adopted and modified by both mainstream and unconventional practitioners. Applications of psychological and behavioral approaches, particularly when used in addition to mainstream treatment, are considered by some as "middle ground" treatments.

Chapter 3 discusses treatments whose primary component is dietary. Three widely known regimens are included. Several other treatments described in this report, especially in the pharmacologic category, also include dietary components, but in these cases the dietary element is secondary to other components or is one of several other approaches used. The first discussed in chapter 3 is the Gerson regimen, consisting of a low-salt, high-potassium, vegetarian diet, various pharmacologic agents, and coffee enemas. It was developed in the 1940's and 1950's by the late Max Gerson, M.D., and is now offered at a clinic in Tijuana, Mexico. The second nutritional approach is the Kelley regimen, originally developed by William D. Kelley, D.D.S. The Kelley regimen as currently practiced by Nicholas Gonzalez, M.D., involves a complex nutritional program based on dietary guidelines, vitamin and enzyme supplements, and metabolic typing. Another treatment discussed is the macrobiotic diet, consisting largely of cooked vegetables and whole grains, which proponents recommend as part of an overall macrobiotic philosophy and belief system incorporating many aspects of daily living. The regimens presented here are examples of a wider group of approaches using nutritional components, many of which are poorly documented and are lesser known.

A dietary program, which is actually part of a multifaceted approach that includes conventional cancer treatment, stress reduction, exercise, and psychological support, developed by a practicing U.S. physician, Keith Block, M.D., is discussed as an example of a "middle ground" approach. In his practice, the dietary needs of cancer patients are assessed using a system that attempts to bring together findings from mainstream nutritional and

cancer research with a modified macrobiotic-type diet (without the ideologic underpinnings of macrobiotics). The results of this approach, however, have not yet been assessed in any formal way. Block may be representative of a type of physician who incorporates some dietary advice, often leaning toward a diet with little animal protein, with low fat and high fiber, and who may use psychological and behavior components as well in the treatment of cancer patients, though Block's program is probably more formal than most. There is no documentation of the number of physicians in this category or the content of their nutritional advice, since little has been written about it. However, according to some members of the advisory panel for this study:

> It is our collective professional judgment that nutritional interventions are going to "follow" psychosocial interventions up the ladder into clinical respectability as adjunctive and complementary approaches to the treatment of cancer. (8)

Chapter 4 discusses five of the best known herbal substances used in unconventional cancer treatments. These include proprietary mixtures of herbal products, such as in the Hoxsey treatment, developed by the late Harry Hoxsey and currently offered in Tijuana; Iscador, made from a species of European mistletoe, used mainly in the context of Anthroposophic medicine in Europe; and Essiac, an herbal tea developed by the late Rene Caisse, R.N., and currently offered in Canada. Also discussed are single-agent treatments, such as chaparral tea, prepared from the leaflets and twigs of-the creosote bush, a plant indigenous to the desert areas of the southwestern United States, and Pau d'Arco, a substance derived from the inner bark of trees native to Argentina and Brazil and sold in health food stores in the form of capsules, tea bags, or loose powder.

Many other herbal substances are sold in health food stores and are advocated for general health purposes in the unconventional literature, but few others for which information is available appear to be advocated specifically for cancer treatment (exceptions include, e.g., Jason Winters Herbal tea, which is specifically for cancer treatment).

Chapter 5 discusses a large and diverse group of unconventional cancer treatments that have as their central component a pharmacologic or biologic substance, such as biochemical agents, vaccines, blood products, and synthetic chemicals. One of the treatments discussed is the regimen developed by the late Virginia Livingston, M.D., and offered at her clinic in San Diego. The main component of the regimen is a vaccine designed to treat and prevent infection with the microbe that Livingston believed to be a cause of cancer. The treatment regimen also includes a variety of components intended to bolster patients' immune responses in general and to counteract effects of microbial infection, including antibiotics, vitamin and mineral supplements, and a special diet.

Another treatment described is one offered by Stanislaw Burzynski, M.D., Ph.D., at his clinic in Houston. Burzynski uses what he calls "Antineoplastons,' substances described as peptides or amino acid derivatives isolated from urine or synthesized in the laboratory. His current regimen for cancer patients includes oral and intravenous use of approximately 10 types of Antineoplaston, all of which are manufactured at the Burzynski Research Institute in Texas.

Another pharmacologic treatment is described by its developer, Emanuel Revici, M. D., as "biologically guided chemotherapy" and reported to consist of a variety of minerals, lipids, and lipid-based substances. Revici practices his regimen in New York.

"Eumetabolic" treatment offered by Hans Nieper, M.D., in Hannover, West Germany, is also described. Nieper prescribes a combination of conventional and unconventional agents (including pharmaceutical drugs, vitamins, minerals, and animal and plant extracts), and recommends that patients follow a special diet and avoid particular agents, foods, and physical locations ("geopathogenic zones") that he believes are damaging. Nieper reportedly treats a significant number of U.S. patients.

Chapter 5 also describes a number of other pharmacologic and biologic agents that are used as unconventional cancer treatments, some singly and some in combination. Examples include laetrile, a substance widely popular in the 1970's and currently offered in several clinics in Mexico; vitamin C, whose most prominent advocate for use in cancer treatment is the biochemist Linus Pauling, Ph.D.; dimethyl sulfoxide (DMSO), an industrial solvent often used in combination with laetrile and vitamin C; cellular treatment, processed tissue obtained from animal embryos or fetuses given orally or by injection; and various substances containing oxy-

gen, including hydrogen peroxide and ozone taken orally, rectally, or via blood infusion. Hydrazine sulfate, a substance that, from 1975 to 1982, was on the American Cancer Society's Unproven Methods List, was taken off when clinical trials under an investigational new drug exemption (IND) were started. The trials were controversial, however, and it is still considered in the context of unconventional cancer treatments. Its supporters persisted, however, and recent studies in major research institutions have suggested strongly that this substance may help to improve the nutritional status and prolong the lives of cancer patients by moderating the cachexia (the wasting of the body) that often accompanies late stage cancer. More definitive clinical trials are planned. Supporters of unconventional treatments often point to hydrazine sulfate as a treatment that was unfairly branded by the mainstream but which actually is effective.

Some of these pharmacologic and biologic treatments are offered only at single sites under the direction of their developer and chief proponent. Others are more widely available, are not necessarily associated with particular proponents, and may be used in combination with a variety of other unconventional treatments.

"Immuno-augmentative therapy" (IAT), offered by Lawrence Burton, Ph.D., at his clinics in the Grand Bahamas, West Germany, and Mexico, is the subject of chapter 6. IAT consists of daily injections of dilute serum fractions made from pooled blood samples. As a case study for this assessment, OTA attempted to develop a protocol for studying the efficacy and safety of IAT, in conjunction with Burton, and this attempt is described in the chapter, as is the treatment itself. The protocol attempt ended in a failure to arrive at a plan for study that both Burton and OTA believed would constitute a fair and valid test of IAT.

Information Included About Treatments

OTA drew from a variety of sources, including peer-reviewed literature, non-peer-reviewed or unpublished literature, patient brochures from individual practices or clinics, and personal communication with practitioners and their associates. The descriptions include, where possible, the approach taken in each treatment, how each is used to treat cancer, the proponents' claims for mode of action and intended outcome, potential adverse effects, and attempts at evaluating each treatment. The uneven coverage of treatments results mainly from the paucity of information about some treatments.

In many cases, little or no specific information was available on adverse effects, though the absence of information cannot be taken by itself as an indication that the treatments are safe. According to one observer (21 8), one reason that little information has been generated about adverse effects of unconventional treatments is the implicit threat of personal legal actions for admitting an adverse effect. While mainstream physicians face little sanctioning for reporting adverse effects of mainstream treatments, an unconventional practitioner might find himself or herself the object of a disciplinary board investigation if he or she were to freely report adverse effects from giving an unconventional treatment. No efforts have been made by licensing boards or other responsible bodies to safeguard against such self-incrimination. For this and other reasons, in the case of each treatment covered in this report, instilcient information exists to support an adequate evaluation of safety and efficacy, though, as mentioned earlier, common sense suggests that some treatments-e.g., psychological, behavioral, and some nutritional approaches—are likely to be inherently safe.

"Adverse effects" are defined broadly in this report to refer to at least five types of harm that may apply (to both unconventional and conventional treatments). These include hazards posed directly from the treatment itself (intrinsic harm); harm resulting from a patient's improper use of the treatment; harm caused by contaminated or otherwise substandard products resulting from poor manufacturing practices (quality control, design of equipment, etc.); harmful interactions or conflicts with other treatments (conventional or unconventional); and deterioration in a patient's condition caused by forgoing or seriously delaying other treatment that could have been effective. While all these types of adverse effects are possible, it is important to note that on the basis of current information, their significance and magnitude for any given unconventional treatment is unknown.

The standards we used for judging the quality of evidence for safety and efficacy are the same standards OTA has developed and applied in a wide range of studies. All past and current OTA studies, except this one, have dealt with mainstream medical practice and research. Many have been critical of the quality of studies and the inadequate basis they form

for making health policy decisions. These include studies of well-child care (871), glaucoma screening (873), computed tomography (CT) scanning (865), and alcoholism treatment (868), to name just a few. A number of earlier OTA studies have dealt specifically with the methods of technology assessment, including clinical research. The reader is referred to Assessing the Efficacy and Safety of Medical Technologies (863), The Implications of Cost-EffectivenessAnalysis of Medical Technology (864), Strategies for Medical Technology Assessment (867), ***and*** *The Impact of Randomized Clinical Trials on Health Policy and Medical Practice (869).*

The ***standards that have developed are based on the experience of clinical trials over the last 30 years or so, largely during which time the methodology has been developed. What has emerged is an understanding of which type of study is likely to produce valid evidence and which is prone to produce answers that are later found, in better designed studies, not to be corroborated. The pros and cons of various study designs are discussed in chapter 12.***

PRACTITIONERS OF UNCONVENTIONAL CANCER TREATMENTS

Practitioners of unconventional cancer treatments range from charismatic figures with no medical training to highly trained physicians or other health professionals who have departed entirely from mainstream practice. Another important group, though of unknown size and largely undocumented practice, are the "middle ground' physicians. Members of the advisory panel for this study offered the following opinion:

> *Most practitioners of unconventional cancer therapies. . are interested in and attracted primarily to this "middle ground." They seek to supplement judicious use of conventional therapies with spiritual, psychological, and nutritional approaches that they hope will improve quality of life and possibly contribute to life extension. (8)*

These practitioners do not forma cohesive group and have been relatively silent in the public debate about unconventional cancer treatments.

There are also practitioners who are not licensed health professionals who promote specific unconventional cancer treatments, but it is impossible even to estimate the number of such individuals in the United States. Some of these practitioners treat friends and neighbors, while some operate more widely, advertising in alternative publications and promoting themselves nationally. Since these individuals may be in contravention of the law by practicing medicine without a license, some are understandably quiet about their activities. After bad experiences, cancer patients or their families occasionally report these unlicensed practitioners, who then may be subject to civil and criminal charges.

A more readily identifiable group of unlicensed practitioners who often give advice about unconventional cancer treatments are some health food store employees. These individuals generally are not formally trained health professionals and are not permitted under law to dispense medical advice or prescribe treatments. A field study carried out for this assessment in three urban areas (420), as well as earlier work (839), suggest that many health food store personnel will, in fact, give medical referrals to unconventional practitioners, will in some cases discourage people from seeking conventional medical care, and will in other cases recommend specific products as treatment.

Historically, there have always been a number of well-known practitioners active at a given time. The practices of some, e.g., Max Gerson and Harry Hoxsey, are continued by associates or relatives after the developer dies. Those who become well known have generally been strong personalities, charismatic, who evoke great loyalty on the part of their patients.

Physicians in the United States are subject to civil and criminal laws related to the practice of medicine, as well as State licensing requirements and professional standards which, if violated, may lead to sanctions limiting the physicians' ability to practice. Licensed physicians who practice unconventional medicine are subject to the same laws and standards, and have, occasionally, been charged with civil or criminal offenses, had their medical licenses revoked, or been subject to lesser professional sanctions. Some have also had privileges for reimbursement by the Federal Medicare program revoked.

THE INFORMATION NETWORK FOR UNCONVENTIONAL CANCER TREATMENTS

The mainstream medical literature contains very few substantive articles for physicians and patients who want to find out about unconventional cancer treatments. Very few scientific studies of these approaches have been done (529). Most reports that make their way into medical journals concern adverse effects of particular treatments or are generally negative.

The unconventional community publishes its own magazines and newsletters (e.g., Health Freedom News, East West: The Journal of Natural Health and Living, Cancer Victors Journal, The Townsend Letter for Doctors) *with articles and advertisements for a wide range of unconventional medical treatments, including those for cancer. They commonly include articles critical of mainstream medicine and the government agencies involved in drug policy and health care, in particular the FDA.*

"Alternative" papers and magazines, and sometimes the popular press, often report on unconventional treatments in an uncritical way, relying on individual case histories or the unsupported claims of proponents. Many of these publications also convey a strong anti-mainstream medicine viewpoint. Particular treatments occasionally are publicized through national magazines or television shows. Penthouse, *for instance, has run a series of articles on alternative medicine over the past several years, and particular cancer treatments and practitioners have been featured (549,683,684). Some popular television shows, such as 60* Minutes *and 20/20 and talk shows such as* The Sally Jesse Raphael Show *and* The Morton Downey, Jr. Show *also have featured controversial figures in unconventional medicine, and these appearances have reportedly had enormous impact on the number of patients contacting their clinics (365).*

Patients may decide to look into unconventional treatments after seeing a television show or reading an article on the subject, but most people are aware, even without a specific reminder, that such treatments exist. According to the few studies that have been done, most patients initially hear about particular treatments by word of mouth, from friends, relatives, or clergy. A large enough number of people have used these treatments that an easily accessible body of descriptive and anecdotal information about them exists. Health food stores are often part of the discovery process, as well. Alternative newspapers and magazines, books and pamphlets, and the health food store personnel themselves are influential sources of information. Written material is available about specific treatments and about organizations that patients can contact for general information on unconventional cancer treatments.

From the cancer patient's point of view, the decision to use an unconventional treatment maybe based on where treatments are offered and on the claims that are made for them. Most major clinics in the United States, Mexico, and the Caribbean produce brochures for prospective patients, and also give information by telephone. The brochures vary from those using scientific language and claiming various degrees of clinical success to those akin to resort brochures. A patient's decision to take a particular treatment may be influenced by many factors, but in most cases is not made with the help of a physician.

Some patients become frustrated when they discover there is so little concrete information about the effectiveness and safety of specific unconventional treatments. Many will have been told, perhaps by a clinic itself, perhaps by other patients or advocates, that the treatment will improve their quality of life and will cause their cancer to regress and possibly disappear. They may have been told by prominent national groups (e.g., ACS, FDA) that, at best, the treatment is untested and therefore unproven, or worse, that it also has dangerous side effects. Based on the work done for this assessment, a common situation is that effectiveness is unknown and relevant information on adverse effects is nonexistent.

Patients often decide to go ahead with unconventional treatment because no reliable information confirms that the treatment doesn't *work or that it would likely be harmful. They may feel they have nothing to lose by trying it.*

During the course of this project, OTA was contacted by dozens of patients or their friends or relatives who did want valid information for their decisions about unconventional treatments, and were frustrated to find so little.

PATIENTS WHO USE UNCONVENTIONAL CANCER TREATMENTS

An image *persists, and is propagated by at least some mainstream medical literature, that patients taking unconventional treatments are gullible and unsuspecting, or desperate, alienated miracle seekers (see, e.g., (105,223)). Little systematic inquiry has been undertaken on which to base generalizations about these patients, but what has been done suggests that such stereotypes do not apply to many patients who use unconventional cancer treatments. Most of the systematic information that is available has come from patients who have gone to established unconventional treatment clinics, rather than from those treated by independent practitioners. Of the former group, many are highly motivated, college educated, and middle to upper class. Most have had little or no previous contact with unconventional treatments (177).*

The slim evidence that exists suggests that most patients have had at least some conventional treatment before deciding to try an unconventional course, and many have had full courses of mainstream treatment. In some cases, however, people reject what could be curative conventional treatment in favor of the unconventional, either for themselves or for their children. Some cases have come to light when parents have made that decision for a minor child and legal proceedings against the parents have ensued. A highly publicized case in the late 1970's of this type involved a child with potentially curable leukemia, whose parents decided to forgo chemotherapy for laetrile (see ch. 10 for a discussion of this case). Some unconventional practitioners have been charged criminally with discouraging people, who later died of progressive cancer, from seeking possibly curative treatment, or for failing to encourage them to seek such treatment (see ch. 11).

Once begun on an unconventional course, many patients also continue to see mainstream medical practitioners, but many do not; one reason for this is that many mainstream physicians generally disapprove of unconventional treatments. In addition, some prominent unconventional practitioners discourage patients from returning to their doctors at home, and some insist that they not take any other treatment. In some cases, patients hide their unconventional treatment from mainstream physicians, and hide mainstream treatment from unconventional practitioners. Followup on patients and, therefore, documentation of the course of their treatment and disease, are generally unreliable. In one of the few direct studies of patients who were using unconventional treatments, Cassileth and colleagues found that most, about 85 percent, had used both conventional and unconventional treatments during their illness. Fifteen percent had sought only unconventional treatment after diagnosis (177).

Whenever the characteristics of patients using unconventional treatments are discussed, the same few studies and surveys are mentioned: These usually include the study by Barrie Cassileth and colleagues (referred to above) of about 600 patients, half of whom were in treatment at a University-based cancer center and half of whom were patients at an established alternative clinic (177); and a 1986 Lou Harris survey for the FDA of a general population sample concerning their use of unconventional medical care of all kinds (566). Overall, too little information exists to characterize reliably the circumstances under which patients use unconventional cancer treatments. This is an area in which it is possible to gather information, however, and there are researchers interested in doing so. But according to some interested researchers, little money is available for this type of social science research (175).

COSTS AND INSURANCE COVERAGE OF UNCONVENTIONAL CANCER TREATMENTS

Since *most health insurance policies-public and Private-do not cover charges for unconventional cancer treatments, patients generally pay for them directly. OTA gathered information on costs of unconventional cancer treatment at 44 clinics or other sites in the United States, Canada, Mexico, and the Bahamas, and on the practices of several major third-party payers regarding such treatments. It was found that the costs of treatment vary widely, from a few hundred to several hundred thousand dollars per patient; however, most major clinics currently charge between $5,000 and $40,000 for an "average" course of treatment. Some clinics charge a set fee for an entire course of treatment, while others charge by individual components, making it difficult*

or impossible for patients to estimate in advance what treatment will cost.

Insurance coverage under the Federal Medicare program (for people 65 and over) is limited to care that is "reasonable and necessary,' which for drugs generally refers to those that are FDA approved, and in some cases to drugs designated by NCI as "Group C" (Group C drugs have been found to have some therapeutic value in clinical trials, but have not yet been approved by FDA). Most Blue Cross/Blue Shield and private insurance plans have similar restrictions. Most health insurance contracts contain general language that excludes coverage of unconventional treatments, and some specify particular treatments by name. Examples in some plans are exclusions of coverage for laetrile, IAT, and cell therapy. Nevertheless, a number of clinics offering unconventional cancer treatments state or imply in their brochures that the treatments costs are covered under various insurance plans, perhaps creating an expectation that patients may be reimbursed. The IAT brochure, for example, states, "More and more insurance companies are readily accepting IAT claims for full or partial reimbursement' (429). Clinics may also advise or assist patients in filling out insurance claim forms; other clinics may be affiliated with a contractor who will submit reimbursement forms to insurers on a patient's behalf. In some cases, the claims are paid, but rarely if the claim explicitly states that it is for an unconventional treatment. A number of insurance fraud cases have involved unconventional cancer treatments.

Advocates of unconventional cancer treatments consider the lack of insurance coverage a major problem. In a joint letter to OTA, some members of the advisory panel for this study expressed their opinion on the need for a critical review of whether the U.S. health insurance system "is in fact acting in the public interest in seeking categorically to deny reimbursement for all forms of unconventional cancer therapies" (8). Refusal of reimbursement, they assert, extends to "psychosocial interventions for control of pain, nausea, and enhanced quality of life at leading teaching institutions." They also commented that " 'Fraudulent' claims are the social consequence of a reimbursement system that restricts itself to the narrowly construed cytotoxic and biomedical treatment of cancer. '

EVALUATING UNCONVENTIONAL CANCER TREATMENTS

In chapters 2 through 6 of this report, information is provided about a variety of unconventional cancer treatments. As mentioned above, and to the extent possible, the composition of treatments and the ways in which they are used are described, the rationales and theories provided by their supporters discussed, and the available evidence concerning their effects on cancer patients presented and critiqued. In these treatment "portraits," there are pieces of information, ideas, various fragments that some might find provocative, or suggestive of a worthwhile approach, and other pieces suggesting that a treatment is groundless.

No doubt this report will be used selectively by individuals wishing to portray various points of view, in support of or in opposition to particular treatments. The reason this is possible is that, almost uniformly, the treatments have not been evaluated using methods appropriate for actually determining whether they are effective. Regrettably, there is no guidance for new patients wanting to know whether these treatments are likely to help them. Digging through descriptive information, theoretical discussions, laboratory tests, or individual case histories of exceptional patients does not adequately answer the question of whether the treatment works-whether it prolongs or otherwise improves life, or effects a cure. The background information is useful, vital in some cases, to get to the point of evaluation. Regardless of the nature of the treatment, however, or of its intended effects, it is as true for unconventional as it is for mainstream treatments that in the final analysis, except for those extraordinarily rare treatments whose effects are dramatic, gathering empirical data from clinical trials in cancer patients using valid, rigorous methods is the only means currently available for determining whether a treatment is likely to be of value to cancer patients in general or to a class of patients. For none of the treatments reviewed in this report did the evidence support a finding of obvious, dramatic benefit that would obviate the need for formal evaluation to determine effectiveness, despite claims to that effect for a number of treatments.

Pursuit of evaluation by practitioners and supporters varies considerably among the wide range of treatments covered in this report. As portrayed by members of the project Advisory Panel, proponents of the "middle ground" (mainly psychological, behavioral, and dietary approaches used along with mainstream treatment) may be most interested in testing and refining their treatments, but they apparently find the current system for doing so unsupportive (8). An additional hurdle is posed by the different orientations toward evaluation in the social sciences, from which a number of psychological and behavioral approaches have come, as opposed to that in medicine. The former rely more heavily on inferences from uncontrolled, nonexperimental observation, whereas the evaluation of medical technologies relies heavily on experimental designs, particularly randomized clinical trials. At least some psychological practitioners and researchers (7) have expressed an explicit belief that such experimental methods are not necessary or appropriate to determine the effects of psychological and behavioral approaches.

From a methodological point of view, for treatments consisting of pharmacologic or biologic agents that are intended to extend survival time, with or without affecting the tumor directly, appropriate evaluation methods would be the same as those that have been developed and validated for mainstream pharmacologic and biologic treatments. Should new, validated methods become available--e.g., approaches currently being investigated under the rubric of "outcomes research" or "medical treatment effectiveness research" (88O)-these, naturally, could apply to unconventional as well as conventional treatments. In the case of outcomes or effectiveness research, however, it will probably be some years before enough is learned about these techniques to gauge their long-term usefulness.

For many-faceted approaches e.g., combinations of dietary, psychological, and behavioral aspects-which have as major goals improved quality of life, some adaptation of methods maybe necessary, perhaps borrowing from social science research, where appropriate. But in the final analysis, the concepts basic to the unbiased evaluation of medical interventions and the reliance on randomized clinical trials will still apply. Practical problems, not methodologic ones, however, are likely to be the most significant obstacles to evaluating unconventional cancer treatments.

Chapter 12 of this report discusses past approaches to evaluating unconventional treatments, along with some ideas that might be adopted to further evaluation efforts. The term "evaluation" is used broadly here to describe the systematic gathering of evidence related to the effectiveness and safety of treatments, including information provided by supporters of unconventional treatments and individuals unaffiliated with specific treatments.

Review of Evidence for an Unconventional Treatment: An Example

For the most part, evidence put forward by individuals identified strongly with particular treatments has been of a type not acceptable to the mainstream medical community. A common format is a series of individual case histories, described in narrative. The endpoints are more often than not "longer than expected" survival times, sometimes with claims of tumor regression. In mainstream research, case reports of unexpected outcomes have been useful and do have a place, but they almost never can provide definte evidence of a treatment's effectiveness.

An example, well known among supporters of unconventional treatments, of evidence put forth systematically by a proponent is a series of case reports of 50 patients treated by Kelley with his nutritional program, and described by Gonzalez, a physician, in his unpublished book about Kelley, One Man Alone: An Investigation of Nutrition, Cancer, and William Donald Kelley *(353). (Gonzalez himself practices a variation of the Kelley program.) This series has been singled out by unconventional treatment proponents as one of the best of its kind, which has been ignored by mainstream medicine (529,596). OTA carried out a review of Gonzalez' material by six members of the advisory panel for this project, three physicians generally supportive of unconventional treatments (though none associated directly with the Kelley program) and three mainstream oncologists. Each case was assigned randomly to one unconventional and one mainstream physician.*

Fifteen cases were judged by the unconventional reviewer as definitely showing a positive effect of the Kelley program; the mainstream reviewer of each case found 13 of these unconvincing and 2 unusual. Nine cases were judged unusual or suggestive by the unconventional reviewer; the mainstream reviewer found these cases unconvincing. Fourteen

cases were judged by the unconventional reviewer to have been helped by a combination of mainstream plus Kelley treatment; the mainstream reviewer found 12 of these cases unconvincing and 2 unusual. Twelve cases were considered unconvincing to both the unconventional and mainstream reviewers.[6]

The mainstream reviewers had similar general comments about the cases. A general theme was that, based on the material presented, it was not possible to relate results to particular treatments. Nearly all patients had mainstream treatment, which, along with the natural variability of the disease, might have been sufficient to account for the observed outcome. One reviewer commented:

> *Those of us who have worked over the years with cancer patients have come to respect the vagaries of human biology wherein there are cancer patients who for unclear reasons fare better than we would have expected. (544)*

Another common criticism was that comparing an individual patient's survival with average group statistics is misleading and an invalid use of data.

General comments of the unconventional reviewers were significantly different and, in general, positive about the Kelley treatment. One reviewer wrote:

> *... I would judge that the patients under my review appear probably, but not certainly, to have presented for the most part an unusual course, that the outcome exceeded normal management and that the effect of the Kelley treatment contributed significantly, although not necessarily exclusively, to the outcome. (218)*

What this review demonstrates most clearly is that some of Gonzalez' cases may be convincing to physicians already supportive of unconventional treatment but that they were not convincing to the mainstream physicians who participated in the OTA review, and, because of the reasons given, probably would not be to most other mainstream physicians. Key issues appear to be lack of adequate documentation of the course of disease and reliance on unusually long survival rather than documented tumor regression in most cases.

Clinical Trials of Unconventional Cancer Treatments

Relatively recently, studies by independent researchers have contributed to the evaluation of unconventional treatments. Studies of particular note include two randomized trials, one of hydrazine sulfate by researchers at the University of California at Los Angeles (186), and the other of a psychological intervention, carried out by a psychiatrist-researcher at Stanford University (824). Both studies were methodologically sound, published in peer-reviewed journals, and, in both, the interventions were associated with increased longevity and with improvements in some more subjective measures. Further studies of these interventions have been planned as a result of these initial studies.

Formal attempts at evaluating unconventional cancer treatments have been made by the Federal Government in various ways. The best known axe clinical trials of laetrile and vitamin C that were carried out by researchers at the Mayo Clinic under contract to NCI. In both instances, the Government was responding to the expanding popularity of these compounds with the public. In the case of laetrile, although it was not approved by FDA, by 1982 its use had been legalized by more than half the States and it could be used legally in the rest of the country as a result of a court order. The published laboratory studies of laetrile's activity did not suggest that it would be active against cancer, however, and no adequate study of cancer patients had been done. Interest in the use of vitamin C, a widely available product, grew as a result of studies of cancer patients reported by Ewan Cameron in the early 1970s, later in collaboration with Linus Pauling, and because of evidence from in vitro and animal studies suggesting beneficial effects of vitamin C. The laetrile experience is discussed here.

During its period of greatest popularity, laetrile was promoted mainly as an agent that acts directly against tumor cells, and it was treated as such when the Government decided to evaluate it. The first step taken was to look for evidence that laetrile caused tumors to regress. To do this, about 450,000 physicians and other health professionals were solicited for reports of patients with documented antiitumor responses to laetrile. In the end, 67 cases had sufficient information to be evaluated independ-

[6]Termed "unconventional reviewers" and "mainstream reviewers" for purposes of this discussion.

ently. Out of these "best cases," a blinded review resulted in establishing two complete and four partial remissions (274).

NCI decided to proceed with a prospective study of laetrile, carried out by researchers at the Mayo Clinic. They began with a typical "phase I" study to determine toxicity and dose (620). Those results were used in designing the phase II study of antitumor activity in 178 patients with a variety of cancer types (623). Among the 175 patients evaluable at the end of the study, one had a partial remission. No further clinical trials were deemed necessary, as the drug was considered ineffective.

A host of criticisms was heard from laetrile proponents. In the confrontational atmosphere that exists around unconventional cancer treatments, it appears impossible to resolve these questions conclusively, but this study appears to have been a fair test of the main claim for laetrile, that it was an antitumor agent.

Possibilities for Improved Evaluation of Unconventional Treatments

The basic principles of scientific evaluation are firm, but the process of reaching the point of formal evaluation and the practical problems of acquiring useful evidence about the efficacy and safety of unconventional treatments may be different in some ways from those encountered in mainstream treatments.

Multifaceted treatments, such as the Gerson treatment and macrobiotics, which would be difficult if not impossible to reproduce in a medical center for the purpose of evaluation, pose additional practical problems, and suggest the need for studies to occur in their own settings. It has been suggested that this might be possible with the participation of "dispassionate researchers, on site" (88), who would evaluate patients for objective evidence of effectiveness before and after treatment. It would not be possible to measure improved survival in this way (without an appropriate comparison group), but it might be possible to determine whether the treatment had antitumor effects. Descriptive information about quality of life could be gathered, but again, without an appropriate comparison, it would be difficult if not impossible to attribute benefits to the treatment.

Such studies would represent a new direction; OTA could identify no examples of methodologically sound clinical trials, assisted by dispassionate observers, of unconventional treatments carried out in their unconventional settings.

In principle, clinical trials are simple, but they can be extremely difficult to organize, even working entirely within the system. The added complications of working with an unconventional treatment render such trials a true challenge. OTA's experience during this assessment in developing a clinical trial protocol for IAT illuminated some key points. One of the most significant is that, except in rare cases, evaluation should be initiated by and the responsibility of the practitioners using or otherwise positively interested in the treatment, though they need not be (and preferably are not) associated exclusively with the treatment. (The Federal Government has initiated evaluations only when treatments [e.g., laetrile and vitamin C] have become very popular and potentially affected large numbers of patients.) Whoever undertakes these studies, it is important to involve developers or other key practitioners of the treatment in developing a plan for the study, and in reporting and publishing its results. To ensure credibility and the availability of technical expertise, the trial should, if possible, be carried out in an accredited medical institution in the United States, with the consent of the appropriate Institutional Review Boards. Finally, it is of the greatest importance that in any study the safety of patients is ensured. This may be best accomplished by carrying out studies in accordance with FDA regulations governing new and unapproved drugs and devices (when applicable).

A "Best Case Series" Approach

New treatments for cancer coming from mainstream research typically progress through a sequence of preclinical and clinical studies before they are offered to cancer patients outside an experimental setting. Clinical trials generally continue even after anticancer agents are approved, building on the pre-approval research. Unconventional treatments currently in use have bypassed this system before being used to treat cancer patients. While OTA has not taken a position condoning or condemning the use of treatments unproven through generally accepted means, the fact that this is the case with unconventional treatments cannot be ignored.

In the course of this study, OTA explored the potential for using the experience of the self-selected patients who have undergone unconventional treatments to inform the evaluation process. It is possible that this experience, presented systematically, might be useful in generating interest in a treatment, and possibly in designing a clinical trial. However, no valid mechanism exists to use this retrospective patient experience to actually determine the efficacy and safety of these treatments. Except in rare circumstances, because of the heterogeneity of cancer patients' clinical courses, it is virtually impossible to predict what would have happened to a particular patient if he or she had had no treatment or a different treatment. Groups of patients who have chosen to take a particular treatment cannot be compared retrospectively with other groups of patients, even those with similar disease, to determine the effects of the treatment. The factors that set apart patients who take unconventional treatments from other cancer patients may be related to prognosis (these may be both physical and psychological factors), and the means do not exist currently to confidently 'adjust' for these factors in analyses. Examples of retrospective evaluations that have turned out to be wrong are well documented (see, e.g., (146)) as are problems with attempting to evaluate the efficacy of treatment from registries of cancer patients (145), though the problems are not necessarily widely appreciated.

Nonetheless, the clinical experience of practitioners with unconventional cancer treatments may be useful for: 1) providing preliminary evidence that can be used to support undertaking formal evaluation; and 2) helping design a formal evaluation, by identifying tumor types that might be responsive, by specifying dosages, and by suggesting potential adverse effects for which monitoring might be necessary. One way to summarize and communicate the clinical experience for these purposes is to conduct a formal retrospective review of "best cases,' which would include full diagnostic, treatment, and outcome information for a group of patients treated previously and followed up. This is particularly well suited to treatments intended to cause tumor regression. The objective would be to provide clear evidence of tumor regression after the unconventional treatment which could not logically be ascribed to either other treatment or the natural history of the disease itself. The responsibility for best case reviews would rest with the practitioners offering unconventional treatments, ideally with technical advice from appropriate experts. This approach, still untested, would place the burden of initiating the evaluation process on the practitioner. No matter how well done, however, a best case review cannot take the place of prospective clinical trials, and no firm statements about effectiveness could be made on the basis of a best case review. It is possible that, like the review of laetrile cases,[7] relatively little will be learned from best case reviews, despite significant effort. This will depend, to some extent, on the availability of sufficiently detailed medical records, from both unconventional and mainstream treatment. The latter, particularly, may not be accessible to unconventional practitioners.

What might happen after a successful best case review is still an open question. In general, 'the aim would be to apply widely accepted research methods-preclinical, clinical, or both, depending on the intervention-to begin formal evaluation.

Improvements in survival, "disease-free survival" (surviving without signs of cancer), and quality of life are the desired outcomes of cancer treatment. As it turns out, treatments that thus far are known to improve survival have a direct effect on tumor cells, causing regression of tumor masses, so tumor size is also of interest as an indicator of antitumor activity. In some cases, tumor shrinkage, even if not complete, can relieve physical problems caused by the position and size of a tumor, increasing survival time and improving quality of life. However, because many chemotherapy regimens also have significant toxicity, the ability to shrink tumors does not necessarily correlate with improved survival (see, e.g., (91)).

Getting reliable evidence about antitumor effects, improvements in survival and disease-free survival, and quality of life requires formal clinical trials in almost all cases. Exceptions would be treatments that axe dramatically effective, that produce long-term remissions in a sizable percentage of patients with advanced cancer. Unfortunately, such treatments are rare. The challenge is to find ways in which unconventional cancer treatments can be

[7]The laetrile review, however, was different from what is proposed here in that the Government conducted it.

evaluated adequately, and in which less dramatic but still worthwhile benefits could be detected.

If an unconventional treatment appears "promising" (e.g., on the basis of a best case review), there might be sufficient impetus for pursuing formal evaluation. There may, in addition, be other reasons for conducting an evaluation of an unconventional treatment. Such studies could be very important in terms of public health, though they might well not lead to advances in cancer treatment. A treatment's popularity might influence the decision. It might be considered important, for public health reasons, to evaluate treatments used by large numbers of people, e.g., treatments offered by the long-established clinics or particular treatments that gain widespread acceptance without proper clinical trials (e.g., laetrile). This is not to suggest that negative evidence will always dissuade cancer patients or that mere popularity should be taken as a sign of effectiveness. Indeed, it is clear from past experience in both conventional and unconventional medicine that the two are not necessarily synonymous. Another factor that, in the real world, might stimulate consideration of an evaluation is political interest. This was the case in OTA's undertaking protocol development for a clinical trial of IAT.

Technical and Financial Support for Evaluations

The Federal Government, through the NCI, is the country's largest sponsor of cancer clinical trials. Others sources of funding do exist. The most obvious case is funding of research by pharmaceutical companies. Another recent model is the funding and running of clinical trials by AIDS activists. Their first, successful venture was a clinical trial of aerosolized pentamidine, a drug that inhibits the development of pneumocystis pneumonia in HIV-positive individuals. While this model is new, it is available to supporters of unconventional cancer treatments, and it bypasses the NCI peer review process. But funding by the Federal Government should be a real possibility, particularly for treatments that could, if they should prove effective, be made widely available to cancer patients.

While no formal barriers block requests from practitioners of unconventional cancer treatments for Government support of research, these practitioners, in general, will be unsuccessful in competing for research dollars without technical assistance. The informal barriers are formidable.

The most serious problem in attempting to assure that evaluations of unconventional treatments are scientifically credible is that many or most practitioners of unconventional cancer treatments are not familiar with mainstream clinical research methods, nor do they have easy access to experts who are. What is needed, and would be particularly helpful at the stage of preparing best case series or conducting small studies within unconventional settings, is technical assistance to make sure that the standards of evidence are understood, and for helping the practitioner prepare a work plan for the project. It is in the public interest for the Federal Government, NCI in this case, to be involved in providing some technical assistance, and easing access to NCI review of formal best case series. NCI can help assure the quality of any such best case reviews that are submitted, and, if the results are promising, assist in developing a plan for further evaluation.

Funding by the Federal Government carries with it conditions on research that some parts of the unconventional community may find problematic. These include a general prohibition against funding clinical trials outside the United States, the requirement that clinical trials be carried out in compliance with FDA regulations, the particular requirements for informed consent of patients participating in clinical trials, and the general concerns for complete disclosure and reporting.

OPTIONS

Options To Broaden the Base of Information on the Use of Unconventional Cancer Treatments in the United States

1a. Studies on the Characteristics and Motivations of Cancer Patients Who Use Unconventional Treatments-Relatively little is known about the types of patients who use unconventional treatments, and their motivations for doing so. The few studies that have been done do not support the stereotype of the desperate, ignorant miracle seeker. Research could be carried out to gather this information through broadly based surveys of patients in the United States. As with all research of this type, the anonymity of the patients surveyed should be guaranteed. It might be useful to consider studies specifically in "SEER" (Surveillance, Epidemiology, and End Results) areas, in which incidence data are routinely collected. Such information would be

useful for determiningg the types of information the public desires and developing the best means of targeting that information.

lb. Utilization Studies--Studies could be done to determine the types of unconventional cancer treatment used in the United States and the extent of use. This information, together with the information from studies of patients (option 1), could be used to determine the appropriate priority to be given evaluations of unconventional cancer treatments.

Gathering and Making Available Information on Unconventional Cancer Treatments and Practitioners

2. Studies on Information Dissemination by Federal Agencies-The National Cancer Institute could have its Cancer Information Service (and Cancer Communications Office) evaluated for the adequacy and quality of information it supplies about widely used unconventional cancer treatments in relation to the information requirements of its users.

Improving Information on the Efficacy and Safety of Treatments Used by U.S. Citizens

3. Mandated Responsibility of NCI To Pursue Information About and Facilitate Examination of Widely Used Unconventional Cancer Treatments for Therapeutic Potential—NCI does not now formally seek out information on a wide range of unconventional treatments. Most of their activities in the past have been in reaction to reported problems or as a result of congressional pressure. Activities might take place in various sections of NCI (e.g., the Natural Products Branch would be the logical place for herbal treatments to be examined). Particularly with a new set of in vitro screening tests coming into use by NCI, consideration could be given to screening appropriate components of unconventional treatments. (Many herbal compounds have been screened in the past, with a mixture of positive and negative test results.)

4. Facilitating "Best Case Series" of Unconventionally Treated Patients

4a. NCI could develop and circulate widely specifications for a simple process for assembling "best case" series in a form that might be acceptable for publication in the peer-reviewed literature. NCI might consider providing for a meeting with the preparer after the review has been completed, to discuss the review, for the purpose of minimizing avoidable ambiguities or misunderstandings.

4b. NCI could provide funding to recruit and support a small group of consultant experts in evaluation methodology to advise unconventional practitioners or their advocates who wish to plan and carry out evaluations. These could range from advising on plans for "best case" series to planning randomized trials, when appropriate. These consultants could also assist with filing IND applications, should evaluation reach that stage.

One possible mechanism for carrying out this option would be to contract, on a competitive basis, with a university or other appropriate organization to assemble and direct the consultant group. Consultants would most likely be academics or researchers who would devote a limited amount of time per year to this activity, but to whom unconventional practitioners could have easy access. Initially, this group could be given the task of drawing up specifications for best case reviews.

5. Providing Funds for Meritorious Evaluations of Unconventional Cancer Treatments-In a time-limited demonstration project, the Federal Government, either through NCI or through another office, could provide funds for evaluating unconventional cancer treatments. A review committee could be established to review proposals for evaluations, which would have to meet appropriate methodologic standards. The committee should include both mainstream scientists/physicians and scientists/physicians identified with unconventional treatments. Four years might be an appropriate time period for the demonstration, divided into the two phases described below. If implemented, the program should be evaluated after three or four years to determine whether the mechanism has stimulated worthwhile evaluative efforts, and whether it should be continued. The amount of funds that would be used for such a demonstration depends on balancing two conflicting factors: funds would need to be large enough to provide for a fair test of the program, but the Government needs to limit the amount to reasonable levels until the value of such an effort

is demonstrated. During the first phase, research proposals would be solicited and reviewed. The review committee would be funded in this phase, but no actual research funds would be allocated. Estimates of annual funding requirements for phase two would be based on the quantity and quality of proposals received during the first phase.

6. *Reporting System for Remissions With Unconventional Treatments or Without Treatment—The Federal Government could maintain a registry for reports of documented tumor regressions that follow unconventional treatment in circumstances where the regression cannot plausibly be ascribed to the effects of previous or concurrent conventional treatments, and for regressions occurring in the absence of any treatment. Criteria for documentation of cases would be specified. This would be of value not only to gather information about potentially useful unconventional treatments, but also to further knowledge about spontaneous remissions.*
7. *Reporting System for Adverse Effects of Unconventional Treatment—The Federal Government could maintain a registry for reports of documented adverse effects of unconventional cancer treatments (and of unconventional treatments in other major disease). Currently, physicians are required to report adverse reactions to prescription drugs, but no such requirement exists for unapproved substances. Criteria for acceptable cases would be specified.*

Making Available Information on Legal Sanctions Against Practitioners and Health Fraud Related to Unconventional Cancer Treatments

8. *Information About Prosecutions for Practicing Medicine Without a License--Little information is currently available to the public on practitioners of unconventional cancer treatments who have been convicted for practicing medicine without a license. This information might be useful to patients seeking background information on available treatments and on the practitioners. States' Attorneys General offices might assemble this information and make it more readily accessible to the public. A Federal effort could link information from the States.*

Chapter 2

Behavioral and Psychological Approaches

CONTENTS

Chapter 2

Behavioral and Psychological Approaches

INTRODUCTION

Over the past two decades, the role that personal characteristics and behaviors might play in recovery from serious illness has become a widely discussed topic, both in the scientific and popular literature. In self-help books geared toward cancer patients, for example, certain attitudes and characteristics, such as having a "cancer-prone personality," are commonly linked with hastening the course of illness or allowing it to develop in the first place. Other characteristics, such as a strong "will to live" and a good "coping style," are often credited with preventing illness, reversing the course of existing disease, or prolonging life. Newspaper and magazine accounts of spontaneous remissions and of individuals who outlived their physicians' predictions lend widespread support to these ideas. Recently, reports of spontaneous remissions from cancer have begun to be collected in an annotated bibliography intended for researchers studying psychosocial factors and interventions in cancer treatment (688).

Several popular books on the role of emotions and behavior in recovery from serious illness have helped bring this subject into the foreground of cancer treatment. Some of the best known examples include Norman Cousins' Anatomy of an Illness *and* Head First, *Bernie Siegel's Love,* Medicine and Miracles *and* Peace, Love and Healing, *and the Simontons'* Getting Well Again. *From various points of view, these books encourage patients to combat feelings of hopelessness, passivity, and depression that may accompany life-threatening illness and to develop positive outlooks and effective coping strategies. Along with a number of other available books on the subject, these books support the view that patients' efforts to promote physical, emotional, psychological, and spiritual well-being, or "healing," can enhance the environment for medical care, improve psychological and physical adjustment to the disease, and in some cases tip the balance toward recovery. Guided imagery, meditation, psychological counseling, support groups, and other approaches are often used to help patients achieve these goals.*

Increasingly, psychological and behavioral methods are becoming a regular part of cancer treatment, whether included explicitly as part of conventional regimens or sought out independently. For the most part, the aim of these methods is to enhance quality of life. In some cases, however, claims of tumor regression or prolonged survival are made, based largely on case reports and uncontrolled studies. Although initial attempts at controlled studies evaluating psychosocial interventions have recently been made, the efficacy of psychological and behavioral approaches in improving the course of cancer is still uncertain.

This chapter focuses on the use of psychological and behavioral methods for modifying the disease process itself-in other words, as unconventional cancer treatment. *Conventional uses of psychological interventions in enhancing quality of life are summarized first, followed by a brief discussion of current research on relationships among emotions, immunity, and cancer. The next section of this chapter describes three of the most popular psychological interventions for which claims of tumor regression or life extension have been made. The final section summarizes the available information from studies attempting to evaluate the efficacy of various psychological and behavioral interventions in altering the course of cancer.*

PSYCHOSOCIAL SUPPORT FOR CANCER PATIENTS

In the past decade, demand by cancer patients and survivors for psychosocial support services has grown. Community organizations, patients, treatment centers, and professional societies have worked together to develop support services for an estimated 5 million U.S. cancer patients and survivors (406). A variety of psychological and behavioral interventions are being used to address physical and psychosocial needs of cancer patients and long-term survivors. Some of these interventions are incorporated into conventional treatment programs, while others are offered outside of medical settings, e.g., as part of cancer support group activities. For the most part, these interventions are designed to help patients reduce pain, control nausea and vomiting associated with chemotherapy, and cope with

other physical or mental disorders that the disease and its treatment may bring about (523,742). Examples of interventions used to reduce distress associated with cancer and chemotherapy include hypnosis, progressive muscle relaxation training with guided imagery, and systematic desensitization (102,169,823,844).

Increasingly, psychological approaches are also being used to address broader emotional and social issues among cancer patients and their families. Patients may seek help in changing their lifestyles, in reducing stress, in reexaminingg their relationships with others, or in planning for the future (807).

There is a wide variety of hospital-based and independent support groups and peer support programs for patients and their families.[1] These groups differ in scope, components, and approach. Some are sponsored by the American Cancer Society (ACS), including CanSurmount, Reach for Recovery, and Candlelighters Childhood Cancer Foundation. Patients calling ACS's Cancer Response System telephone number can be referred to local ACS support groups, hospital-based groups, or affiliated groups. A number of others are associated with the National Coalition for Cancer Survivorship, an Albuquerque-based organization that encourages the development of local support groups, provides information for patients and researchers, and assists patients with problems in job discrimination, insurance coverage, and doctor-patient communication (825).

The psychosocial support offered by the groups described below is based on the idea that cancer patients can improve the quality of their lives and perhaps contribute to their treatment and recovery by becoming actively involved in the fight against their cancer. Unlike self-help groups that also act as advocates of either mainstream or unconventional cancer treatments, these groups are relatively autonomous (528). They are not affiliated with facilities or organizations that provide medical care or advocate particular types of cancer treatment. They all, however, see their programs as complementary to ongoing medical care.

While there is a growing population of cancer patients who wish to become actively involved in the fight against their illness through these sorts of programs, it is estimated that only about one in ten patients follow this route (528). It is possible that more cancer patients will choose to pursue these approaches if they become more widely known and readily accessible (e.g., through oncologists or hospitals) (528).

One of the best known programs offering psychosocial support is the Wellness Community, which was founded by Harold Benjamin in 1982 in Santa Monica, California and is expanding, through patient demand, to other parts of the country.[2] The Wellness Community's program, which is free to participants, is intended to encourage cancer patients and their families to participate actively in the fight for recovery, thereby improving the quality of their lives and possibly enhancing their chances of long-term survival (612). Since its beginning, it has attracted more than 8,000 cancer patients and family members (954).

The Wellness Community explicitly states that its approach to patient care is in support of, not a substitute for, mainstream medical care. Many cancer patients are reportedly referred to the program by their oncologists. Oncologists also serve on the centers' Professional Advisory Boards, which have direct input to the staff of State-licensed psychotherapists at each center. The size of the staff at each facility varies according to the community; as of 1987, the program in Santa Monica was staffed by seven psychotherapists and seven psychotherapy interns (612).

The central elements of the Wellness Community are the mutual aid groups that focus on cancer patients' feelings and that teach self-help techniques with the idea that "positive emotions and positive mental activities may improve the possibility of recovery from cancer" (954). Other group activities include lectures for patients (on topics ranging from self-esteem to nutrition), potluck dinners, charade nights, joke festivals, picnics, and other group activities designed "to bring smiles and laughter into the lives of cancer patients" (612). In addition,

[1]Examples include Cancer Care, Cancer Guidance Institute, Cancer Lifeline, Center for Attitudinal Healing Phone Pal/Pen Pal Program, Cancer Hopefuls United for Mutual Support, the International Association of Laryngectomies, Make Today Count, Ronald McDonald House, and the United Ostomy Association.

[2]As of early 1990, programs were in operation in Redondo Beach, CA, San Diego, CA, and Knoxville, TN in addition to Santa Monica. Several other centers were planned or were in various stages of development at that time (74).

members may also have one-on-one sessions with the staff psychotherapists.

Another widely known support group is the Exceptional Cancer Patients (ECaP) program founded in 1978 by Bernie Siegel, M.D. in New Haven, Connecticut. The program is said to be based on "carefrontation,' described as "a loving, safe, therapeutic confrontation, which facilitates personal change and healing" (804). Siegel's program includes individual and group support that makes use of patients' dreams, drawings, and images in an effort to "make everyone aware of his or her own healing potential" (804) and to become an "exceptional cancer patient,' which Siegel defines as one who gets well unexpectedly. Patients are charged for an initial, intensive, intake session,[3] and for group and individual sessions thereafter.

ECaP states that its psychotherapy is in addition to, not in place of, mainstream medical care, and that no medical advice is offered to participants (293). ECaP also seines as an information resource; according to its patient literature, more than 750 people from all over the country write or call ECaP each week seeking information (803). It can supply books, audio- and videotapes, and reading lists. ECaP also keeps track of other centers that offer similar services and may refer callers to facilities in their vicinity. In an effort to further expand the availability of its services, about once a month ECaP offers intensive, 2-day training sessions for people interested in setting up similar groups (which can be called ECaP-like groups, as there is only one ECaP center). As of early 1990, approximately 160 people had received this training (293).

Another model support program is the Commonweal Cancer Help Program, which was started in 1985 in Bolinas, California. Michael Lerner, Ph. D., Commonweal's President, and Rachel Naomi Remen, M.D., medical director, organize groups of 8 to 12 patients for intense, week-long sessions aimed at helping patients cope with stress and resolve fears and anxieties (particularly about pain, illness, and death), and improve the quality of their lives. The main purpose of the sessions is to help cancer patients "discover those inner and outer conditions under which they may best maximize their health and wellbeing" (744).

Commonweal retreats are held in a rustic oceanside center about an hour drive north of San Francisco. The retreat staff includes the director, a co-director who is a psychologist trained in cancer work, a yoga teacher, a vegetarian cook and art teacher, and a massage staff. The program includes a cognitive or informational component and a multifaceted lifestyle component. Commonweal offers participants access to its library of books and articles from the medical and popular literature dealing with cancer treatment and research. The remainder of its program offers patients a daily regimen designed to release stress and encourage personal expression of feelings. The program includes small group sessions, lectures, massage, yoga, training in relaxation and stress reduction techniques, meditation, imagery, walks in nature, journal and dream work, reflection, and other forms of artistic expression and personal exploration. Commonweal's directors believe that these activities-exercise, healthful diet, deep relaxation, opportunity for personal expression, access to information and caring support-release fear and stress and enable patients to identify lifestyle and healing path that is best for them (532,744).

The majority of the participants in the program have been women, and the relatively low cost of the retreat has allowed people from varying backgrounds to attend. Generally, participants have heard about the program through physicians, other health care providers, or previous participants. People interested in the program are screened by the coordinator to ensure that they understand the nature of the program, can work well with a small group, and ace able to take care of themselves. Participants must also be under the care of a physician and understand fully that the program is not itself a complete treatment (532).

PSYCHONEUROIMMUNOLOGY

It is often suggested in the popular literature that various types of behavioral intervention designed to reduce stress or to promote positive mental images act by enhancing the immune system. Since the immune system is the body's primary defense against many diseases, its enhancement is commonly linked with reducing the susceptibility to cancer or with enhancing the ability to fight cancer.

[3]All services are available on a sliding scale if a cancer patient cannot afford their cost.

Unfortunately, the actual relationships among emotions, immunity, and disease are still poorly understood, despite a large body of literature on the subject spanning several decades. Within the last 10 years, however, new evidence has emerged concerning the biological basis of interrelationships among personality, emotion, behavior, immune alterations, neuroendocrinology, and the onset and progression of disease. The relatively new interdisciplinary field of psychoneuroimmunology (PNI) encompasses these diverse areas of research (1 1,358,461).

One of the catalysts for the recent interest in PNI research was the discovery by Ader and colleagues that immune functions in experimental animals could be altered by behavioral changes (13). That observation provided evidence that the immune system did not function completely autonomously, as was previously thought, but that other biological processes, e.g., necrologic and endocrine factors, could directly modulate immune function. Recent PNI research has revealed a number of biochemical and neurological connections between the immune system and the central nervous system. Their clinical significance, however, is still unclear (14,230,358,817).

For many years, certain types of cancer have been thought to be influenced by immune processes, although the nature and extent of these influences are still only partially understood. Experimental animal data suggest that tumors induced by viruses or ultraviolet radiation appear to elicit immune responses (via antigen-specific T-lymphocytes) that act against those particular tumor cells. However, the majority of cancers of internal organs (not induced by viruses or ultraviolet radiation) are apparently not affected by T-cell-mediated immunity (488), although they could be susceptible to other immune processes in ways that are also poorly understood. Burnet's widely known immune surveillance theory (112), which proposes that one function of the immune system is to recognize and destroy malignant cells as they arise, has gradually been modified and expanded to take into account broader possibilities for additional types of immune action against malignant cells (488).

Attempts to measure and interpret alterations in immune function are central elements of many current PNI studies. Investigators have tried various ways of testing the hypothesis that the immune system mediates among emotions, personality, behavior, and disease onset and progression. However, a major difficulty in interpreting the significance of alterations in particular immune functions is that the clinical implications-benefit or impairment with regard to disease-are not yet known (93). A statistically significant increase in circulating levels of disease-fighting cells could, for instance, reflect normal variability, or could have only short-term effects, or could be compensated for by changes in other immune processes (93). The critical associations needed to interpret immune system alterations and changes in cancer onset or progression have not been demonstrated (12,461,564,834).

For the most part, PNI research has focused on correlations between psychosocial characteristics, such as personality, emotions, and stress, and specific biochemical measures of immune function, or between psychosocial characteristics and disease onset and progression. A handful of studies have been carried out to assess possible effects of psychological interventions on immune function or on disease onset and progression.

So far, PNI research on links between psychosocial characteristics and disease has suggested that stress, or the ways in which individuals cope with stress, may influence immune function. It is not known if stress acts directly, via physiologic processes, or indirectly, via altered health-related behaviors, such as alcohol drinking, a poor diet, lack of exercise, etc. Of critical importance, it is not known whether these altered immune responses are directly linked to the onset or progression of cancer (564).

Other studies have examined effects of psychosocial factors on the risk of disease onset. There are conflicting data on relationships between psychosocial factors, e.g. "cancer-prone personalities," and cancer onset and progression. For instance, clinical depression has been found to have little or no effect on the risk of developing cancer in large segments of the population (300,990). A recent review of these studies concluded that "the results of prospective studies [on psychosocial risk factors and cancer onset] do not yet permit firm conclusions about the cancer-prone personality" (564).

Many studies have examined effects of psychosocial factors on the course of cancer, with mixed results. In general, four types of factors have been examined: adjusting to illness, emotional expression, will to live, and emotional stress. A number of studies have reported correlations between one or more of these factors and cancer outcome (542,735).

A recent study of 36 women with recurrent breast cancer found that signs of joyful attitudes were associated with longer disease-free intervals (543). Two other recent studies did not find a correlation between psychosocial factors and length of survival or time to relapse in patients with advanced disease (176,460).

At present, one of the most controversial areas of PNI research concerns effects of behavioral interventions on immune function and cancer. Preliminary evidence suggests that some psychological or behavioral interventions, such as hypnosis (370) and relaxation (476), can alter immune function in healthy individuals. Another study in progress is examining effects of relaxation and imagery techniques on immune function in cancer patients (808). Whether psychological and behavioral methods may influence the onset or progression of cancer is still an open question. Studies that have approached this issue are discussed in the last section of this chapter.

UNCONVENTIONAL USE OF PSYCHOLOGICAL AND BEHAVIORAL APPROACHES IN CANCER TREATMENT

Psychological and behavioral interventions for which an assertion of tumor reduction or life extension is made involve relatively few techniques. As discussed above, these same approaches are also used for helping patients reduce pain or distress, and inmost of these cases are not claimed to have a direct anticancer effect. Given the popularity of psychological interventions for a wide range of purposes, the unconventional use of these methods appears to be a relatively small, but quite visible, part of the overall field.

This section summarizes information on the psychological approaches that are most prominently associated with direct anticancer claims in the popular and professional literature. Three techniques are discussed: the psychotherapeutic method developed by Lawrence LeShan, meditation as described by the late Ainslie Meares, and imagery and visualization as developed by the Simontons. These approaches are the best documented examples and are the ones cancer patients are most likely to hear about, even though many other practitioners have adopted and modified them.

There is overlap in practice among imagery, meditation, and a variety of other self-regulation techniques, such as relaxation, hypnosis, and biofeedback. Hypnosis, for instance, is probably very similar to meditation and imagery in its effect on consciousness (669,844). It is commonly stated in the popular literature that these psychological techniques facilitate the achievement of a particular state of consciousness, and thereby enhance the immune system and the body's natural healing abilities. As discussed in the previous section, PNI research is just beginning to address this issue.

LeShan's Psychotherapy

One of the most prominent examples of an unconventional psychological approach is a form of one-on-one psychotherapy developed by Lawrence LeShan, a researcher and clinical psychologist, as an adjunct to conventional treatment for cancer patients. LeShan's two most prominent books (537,539) explain the basis for his view that patients with advanced, metastatic disease can sometimes undergo tumor regression and can sometimes increase the length and quality of their lives under his psychotherapeutic regimen (538). His conclusions are based on personal experience over several decades with patients he has treated.

LeShan received his Ph.D. from University of Chicago and began clinical research in 1952 at the Institute for Applied Biology in New York. He has published widely in psychological literature. For many years, his research focused on relationships among personality factors, traumatic life events, and cancer onset and progression. In his earlier research, he focused on the notion of a "cancer-prone personality" and concluded that the interplay between personality and events can so weaken the body's cancer defense mechanism that a cancer is likely to appear (537,538,539).

The approach LeShan describes in his 1989 book, Cancer as a Turning Point, *is a psychotherapeutic process used to identify the creative potential and self-healing ability of each patient. LeShan attempts to develop 'the perception and the expression of the individual's special song to sing in life" and "the cause of his or her loss of contact with enthusiasm and joy' (537). He describes his method as a process of self-examination and growth that delves deeply into the patient's past in order to 'analyze the blocks*

that keep the patient from being able to live out his or her true nature" (537).

Rejecting a traditional Freudian psychoanalytic approach early on in his career (537), LeShan chose instead to find ways of helping cancer patients make their disease a "turning point" in their lives, an opportunity to fulfill their dreams. LeShan explains this guidance toward inner development and fulfillment in the following way:

> *What is right with this person? What are his (or her) special and unique ways of being, relating, creating, that are his own and natural ways to live? What is his special music to beat out in life, his unique song to sing so that when he is singing it he is glad to get up in the morning and glad to go to bed at night? What style of life would give him zest, enthusiasm, involvement?*
>
> *How can we work together to find these ways of being, relating, and creating? What has blocked their perception and/or expression in the past? How can we work together so that the person moves more and more in this direction until he is living such a full and zestful life that he has no more time or energy for psychotherapy? (537)*

Leshan believes that some cancer patients have undergone tumor regression and have increased the length of their lives as a result of his psychotherapeutic approach. He states his conclusion this way:

> *Ever since I learned how to use this approach some twenty years ago, approximately half of my "hopeless," "terminal," patients have gone into long-term remission and are stiIl alive. The lives of many others seemed longer than standard medical predictions would see as likely. Nearly all found that working in this new way improved the 'color" and the emotional tone of their lives and made the last period of their lives far more exciting and interesting than they had been before starting the therapeutic process. (537)*

Speculating that the psychotherapy might bring about changes inpatients' immune function, LeShan writes that his treatment is often "sufficient to halt or reverse the direction of growth of a serious neoplasm.' He believes that "if we recover our hope for the ability to live our own life" our "cancer-defense mechanism [will] recover its strength and come to the aid of the medical program. As we move toward living this life, [our] own self-healing powers [will] act more strongly and raise our 'host-resistance' to the cancer" (537).

Meditation

Meditation can be defined as "any activity that keeps the attention pleasantly anchored in the present moment" (92). Although there are many forms of meditation, one common feature is the absence or near absence of logical thought and emotional experience (608). Different approaches to meditation may consist of quieting the mind, concentrating on a single subject such as breathing or a repeated word, observing passing thoughts, or visualizing active healing processes (a Process similar to the practice of imagery, described below). The purpose of meditating is not primarily to relax, although relaxation may be a side effect of meditating, but to raise awareness, which is seen as the prerequisite to "getting the mind back under control" (92). By calming the body and fixing the mind through 'dropping the anchor of attention,' meditation is believed to be an important tool of self-healing and self-regulation (92).

In the 1970s and early 1980s, meditation directed against tumors received public attention as a result of the work of the late Ainslie Meares, an Australian psychiatrist. Meares used a form of meditation aimed at producing a profound stillness of mind (608). He characterized the practice as one of simplicity and naturalness (609). Cancer patients reportedly experienced "a profound and prolonged reduction" in anxiety and a nonverbal understanding of life and death (609). Meares believed that intensive meditation "enabled the immune system to function more effectively by inducing changes in blood supply to particular parts of the body and in endocrine function and neural activity" (610).

Based on his experience treating 73 patients with advanced cancer who attended at least 20 sessions of intensive meditation, Meares believed his treatment reduced anxiety, depression, discomfort, and pain in about half his patients. Meares believed that intensive meditation was associated with tumor regression in at least 10 percent of the advanced cancer patients he treated (607). He also published a number of case reports of regression of cancer after intensive meditation and in the absence of conventional treatment (603,604,605,606). (These cases are summarized in ref. 608.)

Imagery and Visualization

Imagery refers to various psychological techniques that involve the creation and interpretation of mental images (6). It has been described as a tool for communicating with the subconscious mind (583). Imagery can be used as a tool for articulating ideas, beliefs, and experiences and for replacing fears and negative expectations with positive ideas and beliefs. In cancer treatment, guided imagery often consists of visualizing the symbolic destruction of cancer cells and has been used to reinforce patients' beliefs in their ability to recover. Other imagery techniques used in cancer treatment, e.g., gentle imagery, focus on imagining peaceful, pleasant scenes (102). Imagery is often used along with relaxation, meditation, or hypnosis.

A broad psychological approach to cancer treatment centering on the use of imagery was popularized in the 1970s by O. Carl Simonton, a radiation oncologist, and Stephanie Simonton-Atchley, a psychotherapist. The Simontons' best-selling 1978 book, *Getting Well Again* (583), described their clinical experience treating cancer patients with imagery and other psychological approaches at the Cancer Counseling and Research Center in Dallas (continued now at the Simonton Cancer Center in Pacific Palisades, CA). Their regimen was described as a "whole-person approach to cancer treatment' and included interventions designed to "restore the physical, mental, and emotional balance so that the whole person returns to health' (583). The rationale was reportedly based on theories concerning the role of personality characteristics and psychological factors in the etiology of cancer. Relaxation and mental imagery were presented as tools for cancer patients to motivate themselves to recover their health and to make creative changes in other areas of their lives. overall, the regimen was presented as an adjunctive approach to conventional cancer treatment, but claims for direct antitumor effects were also made (see below).

The process of imagery, as outlined by the Simontons, begins with a period of relaxation. The patient is then instructed to visualize the tumor as a weak, disorganized, soft mass of cells. Conventional treatment is visualized as powerful and effective, capable of shrinking tumors and helping the patient overcome the disease. The patient is encouraged to visualize defending himself or herself against cancer through a strong and aggressive immune system, a symbol of the body's natural healing processes. White blood cells are visualized as a vast army of defenders easily overwhelming the weak malignant cells. Dead and dying cells are visualized as being flushed out of the body by natural processes, until no more tumor cells remained. The patient is then instructed to imagine himself or herself as healthy, energetic, and fulfilled (583). The Simontons recommended that cancer patients repeat the process three times a day.

According to the Simontons, the process of relaxation and imagery reportedly helped patients lessen fears, tension, and stress; change attitudes; strengthen the will to live; confront depression, hopelessness, and helplessness; and gain a sense of confidence and optimism (583). It was also believed that relaxation and imagery could "effect physical changes, enhancing the immune system and altering the course of a malignancy" (583). The Simontons claimed significant life extension as a result of relaxation and imagery techniques. The claim was apparently based on a preliminary analysis of their patients compared with national statistics, as explained in the following excerpt from *Getting Well Again*:

> In the past four years, we have treated 159 patients with a diagnosis of medically incurable malignancy. Sixty-three of the patients are alive, with an average survival time of 24.4 months since the diagnosis. Life expectancy for this group, based on national norms, is 12 months. A matched control population is being developed and preliminary results indicate survival comparable with national norms and less than half the survival time of our patients. With the patients in our study who have died, their average survival time was 20.3 months. In other words, the patients in our study who are alive have lived, on the average, two times longer than patients who received medical treatment alone. Even those patients in the study who have died still lived one and one-half times longer than the control group. (583)

In a 1980 paper describing an uncontrolled, exploratory study, the Simontons used a similar approach to describe outcomes in another, possibly overlapping, series of cancer patients (806). Out of 130 patients with breast, lung, or colon cancer, 75 patients with advanced disease were included in the analysis. Median survival time (the time at which half have died and half are still alive) since diagnosis was 35 months for the 33 breast cancer patients, 21 months for the 18 colon cancer patients, and 14 months for

the 24 lung cancer patients. These survival times were compared to published data on other groups of metastatic breast, colon, and lung cancer patients: 16, 11, and 6 months, respectively. The Simontons noted that their patients lived twice as long as those reported in the literature and speculated that better patient motivation, greater confidence in the treatment, and overall positive expectancy as a result of their regimen may have contributed to the results.

The design of the Simontons' study was such that valid conclusions could not be drawn from it about increased survival as a result of relaxation and imagery, since other possible intervening variables were not accounted for. It is not known how the Simonton patients might have differed in physical and psychological characteristics from the patients with whom they were compared.

ATTEMPTS AT EVALUATING SURVIVAL OUTCOMES

Despite anecdotal reports of tumor regression or life extension in patients treated with imagery, meditation, or Leshan's psychotherapy, possible anticancer effects of these interventions in other patients have not been confirmed. Researchers in this area have, in general, focused more on the evaluation of quality of life issues than on antitumor effects. The few studies that have addressed the issue of survival--one on Bernie Siegel's ECaP program, and two others on different forms of psychotherapy—are summarized in this section.

A study of the ECaP program was conducted in the early 1980s by Hal Morgenstern and colleagues in collaboration with Bernie Siegel (639). The study attempted to assess the impact of the ECaP program on survival of patients with breast cancer. The ECaP program consisted of groups of 8 to 12 participants who met once a week for 90 minutes. Sessions included discussions of patients' problems, meditation, and mental imagery using drawings. The investigators designed a retrospective followup study comparing survival in a group of 34 ECaP participants with a group of 102 nonparticipants. The group of patients to whom the ECaP participants were compared were matched for age at histologic diagnosis, stage of disease, surgery, and course of disease.

The study found a small, but not statistically significant increase in survival time among ECaP participants compared to nonparticipants. As noted in the published report, though, the study did not control for the lag period among ECaP participants from the time of diagnosis to the time of ECaP entry, a period that reportedly ranged from less than 1 month to 10 years. Morgenstern and colleagues used two statistical methods to adjust for this error. In one case, the adjustment produced a result showing a positive effect on survival in these women, and in the other case, a negative effect on survival, neither result being statistically significant.

A more important limitation in interpreting the results of this study is its overall design, in which an attempt was made to control retrospectively for known and unknown differences between the two groups of patients by a matching procedure. Despite the matching, there could still have been major differences in personal characteristics, treatment variables, and disease characteristics that were not or could not have been identified. For this reason, this type of study design is not generally considered acceptable for detecting effects on survival, unless the difference in survival between the treatment and control groups is so great as to outweigh the possible effects of bias or confounding.

The effect of different forms of psychotherapy in women with metastatic breast cancer was evaluated by Ronald Grossarth-Maticek and colleagues (363). The study included 100 women, 50 of whom chose to receive chemotherapy and 50 of whom refused chemotherapy. Half of each group of 50 was assigned by randomization to receive psychotherapy. Little information is given on how the groups compared in stage at diagnosis, time to entry into the study, and other characteristics after randomization. The investigators found that the women randomized to psychotherapy survived 18.6 months foIlowing diagnosis compared with 12.6 months for women randomized to no psychotherapy. The results suggest there may have been a small survival benefit for patients participating in psychotherapy.

Another randomized study evaluating the effect of psychotherapy on survival and quality of life of patients with metastatic breast cancer was recently described by David Spiegel and colleagues (824). In this study, psychotherapy consisted of weekly 90-minute supportive group sessions and self-hypnosis for pain control. The sessions were conducted for 1

year and were led by a psychiatrist or social worker and a therapist who herself had breast cancer in remission. Eighty-six women with metastatic breast cancer, who were also receiving conventional treatment, were randomized to psychotherapy or no psychotherapy (yielding 50 women in the treatment group and 36 in the control group). Patients in the two groups were comparable in age, marital status, type of surgery, degree of metastatic spread, number of mastectomies, exercise activity, and number of treatment courses. The groups did differ in stage of disease at initial diagnosis, with the psychotherapy group having fewer women with advanced disease. That difference was reportedly controlled for in the analysis of the data. Survival was measured 9 years after psychotherapy ended.

There was a significant difference in survival time between the two groups: women who underwent psychotherapy lived an average of 36.6 months after randomization to the intervention, while women in the control group lived an average of 18.9 months following randomization. Divergence in survival time between the two groups began to appear 8 months after psychotherapy ended. Spiegel and colleagues also found that psychotherapy significantly reduced anxiety, depression, and pain among participants. The investigators suggested that involvement in the support group may have allowed patients to better mobilize their resources, to improve compliance with conventional treatment, or to improve their appetite and diet through reduced depression. They also suggested that patients who learned self-hypnosis for pain control may have been better able to remain physically active.

The results of Spiegel's study lend support to the practice of psychotherapy in cancer treatment, but more information is needed before the practice could be adopted confidently on a broader scale. Spiegel's provocative findings are difficult to generalize to other types of psychosocial intervention and other patient populations, since the study included a relatively small number of subjects. One other factor limiting the interpretation of the results is the possibility that other, unidentified variables occurring during the 9-year followup period had some influence on survival time. The women in the study were not contacted after their initial year, and it was not known what other factors, e.g., further conventional treatment or psychosocial support, may have intervened during that time to create more differences between the groups. A larger randomized study will be needed to verify the results, and is clearly warranted by Spiegel's conclusions.

Chapter 3

Dietary Treatments

CONTENTS

Boxes

Chapter 3
Dietary Treatments

A specified diet is the primary component of some unconventional cancer treatments. This chapter reviews three examples of unconventional treatments with dietary regimens as the primary or central component: the treatment regimen developed by the late Max Gerson, M. D., currently offered at a clinic in Tijuana, Mexico; the treatment regimen developed by William Kelley, D. D. S., and recently modified by Nicholas Gonzalez, M. D., who treats patients in New York; and the macrobiotic regimen, whose educational resources and specialized food products are widely available to patients in the United States. Coffee enemas, which are included in two of these regimens, are also discussed separately in box 3-B later.

In other chapters of this report, treatments are described that also include dietary elements, but in those cases, the diet may be one of several major elements in the approach, with a non-nutritional treatment usually considered primary in the regimen. In the Livingston-Wheeler regimen (described in ch. 5), e.g., dietary guidelines are specified, but the regimen is centered on its original anti-infective treatment. In addition, many of the clinics in the United States and Mexico that promote "metabolic" treatment for cancer specify particular foods to include or avoid as part of a regimen that also includes pharmacologic and biologic agents, exercise, and spiritual and psychological components (289).

Other dietary approaches used in unconventional cancer treatment for which more limited information is available are not covered in detail in this chapter. One of these is wheatgrass, a component of a regimen that has been available for several decades in the United States. Originally developed by Ann Wigmore, the wheatgrass regimen is advocated for prevention and treatment of a variety of conditions and for general health maintenance. Individuals attending one of three U.S. centers that offer instruction in following the wheatgrass regimen (289) are taught "an enlightened approach to the understanding of health and various cleansing and rebuilding techniques to restore and/or maintain a vigorous life" (198), according to promotional literature. One of the centers, the Hippocrates Health Institute in Florida, describes itself as a "health resort" offering "a multi-dimensional program for the serious health seeker" (405). The wheatgrass diet is described as a "nutritional lifestyle that embraces an all natural way of eating" (405). Using books and products commonly available in health food stores and through mail order houses, patients can also follow the wheatgrass regimen on their own.

The wheatgrass regimen eliminates all meat, dairy products, and cooked foods from the diet, while emphasizing "live foods" (including uncooked sprouts, vegetables, fruits, nuts, and seeds), wheatgrass juice, "detoxification" (enemas and high colonies), enzyme supplements and chlorella (green algae tablets). Proponents believe that wheatgrass is the key element of the program and claim that it bolsters the immune system, kills harmful bacteria in the digestive system, and rids the body of waste matter and toxins (405,959). Anecdotal case reports of tumor regressions and life extension among cancer patients who followed the wheatgrass regimen have been published in the proponent literature (see, e.g., (344)), but thus far, no studies of its clinical role in the treatment of cancer have been reported.

GENERAL COMMENTS ABOUT UNCONVENTIONAL DIETARY APPROACHES COMPARED WITH OTHER FORMS OF NUTRITIONAL TREATMENTS

By relying for the most part on vegetarian, low-fat, high-fiber foods, the dietary regimens described in this chapter share certain characteristics with the kinds of foods currently recommended by mainstream groups for lowering the risk of developing cancer and heart disease. Recent American Cancer Society (ACS) guidelines for cancer prevention, e.g., suggest reducing the intake of fat, alcohol, and salt-cured and smoked foods, while increasing the intake of fruits, vegetables, and whole grains (681). One way they differ, however, is that the unconventional cancer treatment diets may emphasize a few particular foods and limit or totally eliminate others. The macrobiotic regimen, e.g., advises against consuming vegetables and fruits that

are not grown locally, such as bananas and other tropical fruit, and against certain types of vegetable, such as those in the nightshade family (including tomatoes, green peppers, eggplants, e.g.). The wheatgrass diet excludes all cooked vegetables and fruits in favor of raw foods exclusively. The Kelley regimen emphasizes certain categories of food, e.g., vegetables or red meat, over others, on an individual basis. (The Kelley diet does not necessarily conform to current mainstream dietary recommendations.) It has been noted that in some circumstances, cancer patients who follow overly restrictive diets of any kind, whether unconventional or not, maybe at risk for malnutrition and uncontrolled weight loss (8,84). It has also been noted that diets that may be useful in preventing cancer are not necessarily effective in treating cancer, since substances in food that may play a role in the initiation of cancer may be different from those that may contribute to tumor progression (84).

The goals of the unconventional dietary treatments also overlap with the goals of conventional nutritional support for cancer patients in that both try to counteract the metabolic and nutritional effects of the disease and of some forms of treatment. The unconventional treatments go beyond the conventional support measures, however, by claiming to reverse the course of the disease, to enhance host function, and to improve quality of life.

The fact that the unconventional treatments spec@ particular dietary regimens for cancer patients at all, regardless of their condition, stage of disease, or type of tumor, separates them from mainstream cancer treatment. Nutritional support has a well-established place in conventional cancer treatment, but generally does not include dietary recommendations for patients with cancer. At present, no diet is recommended publicly by NCI or ACS for use in cancer treatment. In practice, patients are not commonly given nutritional advice at the time of diagnosis or initiation of treatment by mainstream physicians. Nutritional support in mainstream oncology focuses instead on the provision of nutrients under special and usually more extreme circumstances. Nutritional support given in conjunction with conventional cancer treatment often involves the use of total parenteral nutrition (nutrient solutions given intravenously) or enteral nutrition (nutrient solutions provided (e.g., through a nasogastric tube). These measures are normally limited to cachexic patients in advanced stages of disease, to patients who have particular cancer- or treatment-related nutritional problems that prohibit normal intake of food, or to malnourished patients undergoing major surgery (34,473,798).

It is well accepted that cancer and its treatment can cause malnutrition and that malnutrition itself predicts a poor outcome (253). A number of physiologic factors associated with cancer are believed to contribute to malnutrition, including the metabolic state of the tumor and its effects on the body's metabolism, catabolic effects of conventional treatment, and physiologic stress associated with rapid tissue growth and cell destruction (407), although the ways in which these factors influence nutritional status are still poorly understood. The issue of how to ensure that patients obtain an optimal daily intake of nutrients and calories in order to preserve lean body mass without stimulating tumor growth is considered unresolved (407). Total parenteral nutrition has been found to be of limited use, and in some cases even detrimental (798). In general, oral dietary treatments have not been evaluated for possible prevention of malnutrition or for possible effects on the course of the disease in cancer patients, although the initial stage of a multicenter study involving a low fat dietary intervention in patients with breast cancer was recently begun (35).

ADJUNCTIVE USE OF DIETARY APPROACHES IN CANCER TREATMENT[1]

The unconventional dietary treatments for cancer described in this chapter are also distinct from the adjunctive use of dietary treatment in other contexts, e.g., in the more numerous and diverse practices where physicians and other practitioners offer what is often referred to as "alternative" or "holistic" health care. The issue of dietary treatment in conjunction with conventional treatment by these practitioners is commonly raised in the popular literature, but detailed information is scarce. The actual dietary regimens, their rationales, and the outcomes have not yet been reported, so the extent and nature of their use cannot be characterized precisely.

[1]This section is based, in part, on a paper written by Keith I. Block and Charlotte Gyllenhaal, "Nutrition: *Unessential Tool* in Cancer Therapy (84)."

Box 3-A—An Example of an Adjunctive Nutritional Approach to Cancer Treatment

A program developed over the past 10 years by Keith I. Block M.D., illustrates one approach to nutritional treatment that can be used in conjunction with mainstream cancer care. The program, as described by its developer, is intended to be used adjunctively and not as a substitute for medical treatment. At present, it is used in Block's private medical practice in Evanston, Illiniois, and at an independent medical center in Chicago.

According to Block's protocol, individualized dietary guidelines and nutritional treatment are used in combination with mainstream cancer treatment, exercise, and psychosocial support strategies for stress reduction. Overall dietary guidelines are made on the basis of nutritional assessments, including the use of body composition analysis, blood and laboratory studies, determinations of nitrogen balance, and other biochemical and clinical evaluations. Patients are given a range of food choices within an overall framework that covers five food groups (cereal grains, vegetables, fruits, fats, and proteins). Foods are divided into exchange lists so patients can select foods according to their tastes while still satisfying the overall nutritional requirements of the program.

The semivegetarian diet Block recommends consists of high-fiber, low-fat, protein-restricted foods along with specific items such as soybean products, shiitake mushrooms, and sea vegetables. In general, Block recommends that 50 to 60 percent of calories be derived from complex carbohydrates, 12 to 25 percent of calories from fat, and the remainder from protein sources. The diet, which is modified on an individual basis, emphasizes foods high in vitamins, trace minerals, and substances thought to reduce cancer risks. Developed in part from macrobiotic principles, the diet has been modified to incorporate information from other sources, primarily experimental data from the scientific literature on substances that maybe active in inhibiting tumor growth or stimulating immune responses. Nutritional analysis has reportedly shown Block's nutritional program to be nutritionally adequate; the Recommended Daily Allowances (RDAs) were met or exceeded for almost all nutrients for which RDAs have been established and for which nutrient analyses are available, and the diet reportedly exceeds requirements for vitamins A, C, and B12, calcium, iron, magnesium, and several other elements.

Block's use of an adjunctive dietary program for cancer patients has several goals, some of which he believes have been met in many cases, based on observations of patients treated with this regimen. One goal is to maintain adequate nutritional support through oral feeding as much as possible, in order to improve patients' quality of life and help them retain 'a sense of self-empowerment and clinical autonomy. "He notes that few of the cancer patients on his program experience weight loss, except those with anorexia in late stages of disease, or experience hair loss during chemotherapy. Another goal is to enhance patients' resistance to the disease by focusing on improving immune function and inhibiting tumor growth through the provision of a low-fat diet, which may decrease the intake of tumor-promoting substances. The high intake of vitamin A-containing vegetables in the diet is believed to enhance patients' responses to conventional cancer treatment. Overall, Block believes his program to be of benefit in diminishing the side-effects of conventional treatment and in improving patients' quality of life. The treatment protocol has been described in some detail in unpublished manuscripts (83,84), but thus far, it has not been studied systematically so that its effects on patients cannot be judged adequately.

One practitioner's approach that he uses currently as an adjunctive nutritional approach to cancer treatment is described in box 3-A. It is unknown how representative that example is of other efforts to use nutritional approaches adjunctively. In the judgment of some of the members of the Advisory Panel for this project, however, the adjunctive use of dietary interventions in cancer treatment is gradually becoming incorporated into conventional treatment and becoming accepted as a potentially valuable supportive measure (8). The stated aim of such adjunctive nutritional treatment is to maintain adequate levels of critical nutrients (assisted by close monitoring for deficiencies and abnormalities) in order to enhance the patient's natural resistance to the disease, to increase the ability to respond to conventional treatment, to improve the patient's quality of life, and ultimately, to lengthen his or her survival time (84).

A number of factors maybe involved in stimulating efforts to combine nutritional intervention with cancer treatment before the development of overt deficiencies, metabolic abnormalities, and cachexia. One factor may be the public interest in self-help regimens and in health effects of diet, as shown by the wide range of books and articles in the popular literature concerning diet and cancer. This is paralleled by the large and expanding scientific literature on links between specific nutritional factors and cancer processes (361,660,661). Strong evidence is emerging from laboratory and population studies suggesting a substantial dietary contribution to a

large proportion of human cancers (866), though in some cases the data are not unequivocal and many specifics remain to be determined. Major efforts in this area at NCI are currently conducted in two research programs: the Chemoprevention Program, which focuses on the role of natural and synthetic micronutrients (e.g., beta carotene, vitamin A and related retinoids, vitamins C and E, and certain selenium compounds) in preventing or inhibiting cancer development; and the Diet, Nutrition, and Cancer Program, which focuses on macronutrient factors (e.g., fiber and fat) in cancer development (361).

THE GERSON TREATMENT

The *Gerson treatment, consisting of a low sodium, high potassium, vegetarian diet, various pharmacologic agents, and coffee enemas, is one of the most widely known unconventional cancer treatments. As one of the first unconventional approaches now commonly referred to as "metabolic,"[2] it may have spawned the development of many other currently used unconventional dietary and pharmacologic approaches.*

Max Gerson, M.D., a German-born physician, spent the last 23 years of his 50-year medical career in the United States. He died in 1959 leaving no apparent system in place to continue his treatment program. In 1977, Gerson's daughter, Charlotte Gerson Straus, co-founded (with Norman Fritz) the Gerson Institute now based in Bonita, California. The Institute oversees a clinic in Tijuana, Mexico, where the Gerson treatment is offered. According to one outside report, that clinic treats approximately 600 patients per year (569).

Background and Early Use

Max Gerson was born in Germany in 1881 and graduated from the University of Freiburg medical school in 1907 (875). He practiced medicine in Germany, Austria, and France before emigrating to the United States in 1936. He received his New York medical license in 1938 and his U.S. citizenship in 1944 (875). He opened a private medical practice in New York City and in 1946 also began treating patients at nearby Gotham Hospital. Gerson was a member of the American Medical Association (AMA), the New York State Medical Society, and the Medical Society of the County of New York (875).

In 1958, after a long investigation, the Medical Society of the County of New York suspended Gerson's membership. The Society charged that Gerson's participation in a 1946 radio broadcast, during which the show's commentator, Raymond Gram Swing, described beneficial results of Gerson's treatment for cancer, constituted personal advertising (387,465,956). Gerson reportedly also lost his hospital privileges and malpractice insurance (387,569), although no details of these actions are available.

In 1946, during a hearing on a proposed bill to authorize increased Federal support for cancer research in general, Gerson testified before a subcommittee of the Senate Committee on Foreign Relations. In his statement to the subcommittee, Gerson described his background, the development of his treatment for cancer, and submitted written case histories of 10 patients treated with his regimen, 5 of whom were questioned in person at the hearing (875). Gerson claimed that these patients were cured of advanced cancer as a result of his treatment.

Both Gerson's testimony and radio appearance drew national attention. The same year, an editorial appeared in The Journal of the American Medical Association *in response to numerous requests for information about Gerson. The editorial criticized Gerson and his sponsors at the Robinson Foundation, New York, for 'promotion of an unestablished, somewhat questionable method of treating cancer. The editorial stated AMA's view that Gerson had provided only "clinical impressions as to benefits secured but nothing resembling scientific evidence as to the actual merit of the method" (465). A 1949 report of the AMA Council on Pharmacy and chemistry reiterated AMA's view of the Gerson treatment, concluding that "there is no scientific evidence whatsoever to indicate that modification in the dietary intake of food or other nutritional essentials are of any specific value in the control of cancer' (39). The American Cancer Society's Committee on Unproven Methods of Cancer Management published its first statement on the Gerson treatment in 1957 (90).*

[2]In the unconventional cancer treatment literature, "metabolic" treatment generally refers to treatments intended to stimulate patients' immunologic and biochemical processes to fight cancer. The term is used nonspecifically to refer to both particular treatments and to collections of unconventional treatments (e.g., combination pharmacologic and nutritional treatments).

While certain aspects of Gerson's regimen-e.g., the intake of fresh fruits and vegetables and the reduction or elimination of sodium and fat—are consistent with current knowledge about reducing the risk of contracting certain types of cancer and other illnesses, Gerson's thesis that regression of cancer can result from dietary treatment and 'detoxification" is unconfined.

Rationale for the Treatment

Gerson developed his dietary treatment over the course of several decades. His approach was largely empirical. By his own account, he tried variations and combinations of foods and other agents on his patients, noted the ones that reacted favorably, and adjusted subsequent patients' regimens accordingly (336). All along, he reasoned why some agents seemed to work while others did not and developed hypotheses to account for his observations. Gerson described the development of his treatment regimen and presented case histories of patients he believed were treated successfully in his 1958 book, A Cancer Therapy: Results of Fifty Cases (337), and in a number of published articles in German and in English (403). By the late 1950s, Gerson had produced an overall approach and rationale for treating cancer that diverged significantly from conventional medical thought and practice.

It is unknown whether Gerson's formal medical training included study of the therapeutic use of diet (939). Early on in his medical career, he devised a dietary regimen to treat his own severe migraine headaches. After reported success with his condition, he used his diet in the treatment of a variety of other disorders, including skin tuberculosis (lupus vulgaris), asthma, pulmonary tuberculosis, and arthritis (337). In 1928, he began treating cancer patients with the diet he used on tuberculosis, at the insistence of a patient with cancer of the bile duct, who reportedly recovered following Gerson's treatment (336). By the time he established his practice in New York in the mid-1940s, he concentrated on treating cancer patients. His frost paper published in English[3] on dietary treatment for cancer appeared in 1945 (331). In that paper, Gerson outlined his high potassium, low sodium,' fatless diet regimen, which included foods, mineral and vitamin supplements, and crude liver injections (preparations of raw calves liver). He reported on 10 patients treated with the regimen in whom he observed improvements in "general bodily health" and, in some cases, tumor reduction.

In a subsequent publication, "Gerson described other agents that he added to the regimen, including an iodine solution (' 'Lugol''), thyroid extract, potassium solution, pancreatic, and vitamin C (333). Gerson noted that in six additional patients his treatment appeared to reduce inflammation around tumors, relieve pain, improve psychological condition, and provide at least temporary tumor regressions (333). In the mid- 1950s, Gerson first published explanations of the components of his regimen and the rationale for their use, along with some of the clinical outcomes he observed.

Gerson described cancer as a "degenerative disease,' fundamentally similar to many other disease states; he believed that an "impaired metabolism" was the underlying problem in degenerative disease and that proper liver function was critical to maintaining metabolic order (334). He believed that several physiologic functions were impaired in cancer patients, including the metabolism of fats, proteins, carbohydrates, vitamins, and minerals; the activity of oxidative enzymes; and the activity of intestinal bacteria (335). Gerson believed that the impairment in these functions created an internal climate favorable to the growth of malignant cells (334).

Gerson believed that his treatment regimen reversed the conditions he thought necessary to sustain the growth of malignant cells. He attached great importance to the elimination of 'toxins' from the body and to the role of a healthy liver in recovery. Gerson noted that if the liver were damaged, e.g., by cancer or cirrhosis, the patient had little chance of recovery on his treatment regimen (333,337). He observed that patients who died showed a marked degeneration of the liver, which he presumed was due to unspecified toxic factors released into the bloodstream by the process of tumor regression. He believed that these toxic tumor breakdown products poisoned the liver and other vital organs (229).

According to this view, Gerson believed that detoxification-preventing patients from dying of self-poisoning—was the most important frost step in treatment (336). In support of detoxification, he cited a passage from Hippocrates that described

[3]Gerson published many articles in German before 1945 (see bibliography cited above).

drinkmg a "special soup" and administering enemas (336). Gerson prescribed coffee enemas, initially at the frequency of one every 3 or 4 hours, as part of his cancer treatment regimen. He maintained that the coffee enemas helped to stimulate the flow of bile (336), thereby increasing the rate of excretion of toxic products from the body.

Gerson believed that the need to detoxify resulted not only from the internal generation of poisonous substances but also from the external supply of toxins created by the use of insecticides and herbicides in commercial agriculture. Accordingly, his dietary regimen emphasized the use of food grown organically. He reasoned that treatment for cancer must replenish and detoxify the entire body to allow its innate healing mechanisms to be restored (337).

Another central component of Gerson's approach concerned the balance of potassium and sodium in the body. An imbalance in the concentration of these substances contributes to the internal environment supporting the growth of tumors, Gerson believed. He sought to eliminate sodium in patients' diets and to supplement with potassium (in the forms of potassium gluconate, potassium phosphate, and potassium acetate). Several papers published since Gerson's death have elaborated on Gerson's ideas regarding physiologic implications of the potassium-sodium balance in cancer states. Those papers suggest various biological and theoretical rationales for Gerson's theory that potassium supplementation and sodium restriction act against tumor formation (229,551,590,991).

The role of oxidation in the treatment of cancer was another central element of Gerson's theory. He believed that tumor cells thrive in an environment depleted of oxygen and can be destroyed when oxidative reactions occur. He believed it was essential to supply intact oxidative enzymes in the diet, in the form of vegetable and fruit juices prepared by a stainless steel grinder and press (rather than by centrifugal juicers or liquefiers, which he believed destroyed the foods' oxidative enzymes) (336). He also recommended avoiding food that had been canned, processed, bottled, powdered, frozen, or cooked in aluminum pots (336).

The combined effect of these treatment components was intended to "normalize the biological function of damaged cells" (334). Gerson wrote:

> . . . the end result is to return the body to its physiologic functions as they existed before the development of malignancies. In this state of the normal metabolism, abnormal cells are suppressed and harmless again. (334)

Current Gerson Treatment Regimen

Current patient literature from the Gerson clinic states that the treatment "restores the patient's healing mechanism so that the body can heal itself and overcome degenerative disease.' In addition to treating patients with cancer, heart disease, diabetes, arthritis, multiple sclerosis, and other diseases, the clinic also treats "some people with no apparent serious disease [who] come to the Center simply to detoxify and build themselves up in order to feel good, to improve their health, and to prevent disease" (329).

The regimen is said to have two main components: 1) "an intensive detoxification program to help the body eliminate toxins and waste materials which interfere with healing and metabolism" and 2) "an intensive nutrition program which floods the body and its cells with easily assimilated nutrients needed for improving the metabolism and healing" (329). After a period of treatment at the clinic, each patient is instructed to continue the regimen at home for 1½ years or more "until the liver, pancreas, oxidation, immune and other systems have been restored sufficiently to prevent the recurrence of cancer and other degenerative diseases" (329).

At present, the dietary part of the Gerson treatment offered at the clinic consists of low-sodium, low-fat, low-animal protein and high-carbohydrate foods, with vitamin and mineral supplements. The diet relies on large amounts of fresh and raw fruits and vegetables. Until late 1989, raw fresh calves liver juice was included in the regimen (see discussion below). The current patient brochure lists the dietary components as: "13 glasses daily of various fresh raw juices prepared hourly from organically grown fruits and vegetables" and "three full vegetarian meals, freshly prepared from organically grown vegetables, fruits, and whole grains" (328).

The Gerson treatment also consists of a variety of other substances, including potassium supplements, thyroid hormone, Lugol's solution (an inorganic solution of iodine plus potassium iodide), injectable crude liver extract with vitamin B 12, pancreatic

enzymes, and enemas of coffee or chamomile tea (317,328).

Other treatments, beyond the ones Gerson specified, have been added to the current protocol in recent years. According to materials distributed by the Gerson Institute, these substances include:

- ozone treatment (328) (given by enema (3 18) or via infusion in autologous, heparinized blood or directly into patients' blood vessels (401));
- hydrogen peroxide (topically, rectally, or orally) (328);
- intravenous "GKI drip' (glucose, potassium, and insulin solutions) (328);
- "live cell therapy" (328);
- castor oil (328);
- clay packs (328);
- Lincoln bacteriophage (a vaccine made from killed *Staphylococcus aureus* bacteria) and influenza virus vaccine, both reportedly to stimulate "allergic inflammation," a process Gerson believed contributed to healing (387); and
- laetrile (328,329).

The Gerson treatment is time-consuming and restrictive, and can be difficult to follow in areas where fresh fruits and vegetables are not widely available (530). To assist with the rigors of the treatment, the clinic advises patients to have a "helper,' since patients "need time and energy and rest to heal and if they do the therapy alone it will reduce their chances of healing" (325).

Potential and Reported Adverse Effects

Two aspects of the Gerson treatment have attracted attention as possible causes of adverse effects-the use of raw calves liver juice, and coffee enemas.

Ingestion of raw calves liver juice has been associated with infection with *Campylobacter fetus* subspecies *fetus,* an organism that is carried in the intestinal tract of cattle and sheep. Infection with C. *fetus* subsp. *fetus* is treatable if detected early, but can lead to sepsis and death if undetected or inadequately treated (339).

An outbreak of C. *fetus* subsp. *fetuis* infection among cancer patients, some of whom were thought to have been treated with the Gerson regimen, was reported in 1981 (339). Between January 1979 and March 1981, nine cancer patients and one lupus patient with sepsis were reported to the San Diego County Department of Health Services. C. *fetus* subsp. *fetus was* isolated from blood cultures from nine patients and from peritoneal fluid from one patient. Upon admission to the hospital, five of the patients were comatose and all had severe electrolyte abnormalities. The nine cancer patients died shortly after admission (338).

After learning of the outbreak from a newspaper article, members of the Gerson staff contacted the San Diego Department of Health Services to discuss the problem, assuming from the description of treatments taken that at least some of the 10 patients had been treated at the Gerson clinic (401). Ackmowledging the possible link between the raw liver juice and the Campylobacter infection in these patients, Gerson staff subsequently improved the handling and storage of the calves liver to reduce the likelihood of contamination and instituted routine tests for C. *fetus* among their patients at the first sign of infection; patients testing positive would then be treated with an appropriate antibiotic (e.g., erythromycin) (401). No further reports of this type of infection in Gerson patients have been published in the literature. The clinic discontinued the use of raw liver juice in late 1989, however, because of potential problems with infection (326).

Coffee enemas have been associated with serious fluid and electrolyte abnormalities, although none have been reported specifically in patients undergoing the Gerson regimen. One report in the literature noted the death of two Seattle women, one of whom had cancer, due to fluid and electrolyte abnormalities following coffee enemas (273). One of these women reportedly took 10 or 12 coffee enemas in one night, and continued at a rate of one per hour, while the other woman took them four times daily; in both cases, the enemas were taken much more frequently than is recommended in the Gerson treatment. Another report of serious adverse effects associated with coffee enemas cited three cases (579). The overall risk of fatal electrolyte disturbance associated with coffee enemas is unknown, and may depend to some extent on frequency and conditions of use (see also discussion in box 3-B).

Claims of Effectiveness

Gerson wrote (and rewrote, after the original was lost) *A Cancer Therapy: Results of Fifty Cases* to show that "there is an effective treatment of cancer,

even in advanced cases" (337). In testimony before a Subcommittee of the Senate Committee on Foreign Relations in 1946, Gerson estimated that about 30 percent of 'hopeless cases' of cancer he treated showed a favorable response (875). In a lecture Gerson gave in 1956 (published posthumously in 1978) (336), and in a paper published in 1954, he estimated that his treatment produced "positive results in about 50 percent of so-called generalized, regrowing or final cases" (334).

The current practitioners of the regimen also claim success with the treatment. Patient literature from the Gerson Institute claims:

> . . . the Gerson Therapy is able to achieve almost routine recoveries in early to intermediate cancers. Even when the disease is advanced and incurable by conventional standards (i.e., involves the liver or pancreas or multiple internal sites) excellent results are possible. The Gerson Therapy has *cured* many cases of advanced cancer in man. (329) Emphasis in original.]

Further, the patient literature states that even for patients with both cancer and other diseases (e.g., arthritis, heart disease, and diabetes), the Gerson treatment "usually heals the body of all diseases simultaneously' (329). This claim is reportedly based on Gerson's belief that the body "will not heal cancer and yet leave arthritis or arteriosclerosis or diabetes unimproved" and that "when the body's ability to heal is restored, the 'physician within' will set about to mend and restore the whole patient" (329).

The vice president of the Gerson Institute, Norman Fritz, republished a book by S.J. Haught (the pen name for Robert Lichello, a writer for the National Enquirer in the 1950s), which was originally titled Has *Dr. Max Gerson a True Cancer Cure? (1962),* renaming it *Cancer? Think Curable! The Gerson Therapy (1983). In* his introduction to the revised edition, Fritz claims that the Gerson treatment "can save about 50 percent or more of advanced 'hopeless' cancer patients' and that "the percentage who recover can exceed 90 percent for early cancers and some 'early terminal' cancers. " Fritz's claims are apparently not made by others in the Gerson Institute, but the Haught book is still widely available to patients and is one of the most easily accessible sources of information about the treatment (401). The Gerson Institute's newsletter often describes case histories of patients believed to be cured through the Gerson treatment (see, e.g., a description of "cure of a partially removed, inoperable, radiation-resistant, adult astrocytoma through the Gerson Therapy" (327)).

Attempts at Evaluating the Gerson Treatment

Since the 1940s, there have been several attempts by a number of groups and individuals to assess the effects of Gerson's regimen, and at least one attempt is currently in progress.

Gerson's Case Presentations

In 1947, Gerson submitted 10 case histories of cancer patients treated with his regimen to the National Cancer Institute (NCI) for review (332,822). The only available information about that review comes from a current NCI statement on the Gerson treatment, which states that the NCI review "found no convincing evidence of effectiveness, particularly since the patients were also receiving other anticancer treatments" (893). It was also noted that Gerson "was invited to submit additional data but did not do so." Further information about the nature of the 1947 review is unavailable, since NCI cannot locate any records concerning it (766).

In 1959, NCI reviewed 50 case histories presented in Gerson's book A *Cancer Therapy :Results of Fifty Cases.* NCI concluded that, in the majority of cases, the basic criteria for evaluating clinical benefit were not met. These criteria were the following:

- The patient must have histologic verification of the presence of a malignant neoplasm, and the diagnostic sections must be available for independent review to verify Gerson's diagnosis.
- If the patient had surgical resection or other previous treatment for a proven malignant neoplasm, the presence of a recurrence or metastasis also must be verified histologically and the sections made available for review.
- If the patient had been previously treated, he must be completely reevaluated and observed for a long enough period of time to verify that this treatment was ineffective, and that the neoplasm is indeed advancing (60).

NCI concluded overall that Gerson's data provided no demonstration of benefit (60,897). In an undated rebuttal, members of the Gerson Institute disputed NCI'S 1959 findings, taking issue with almost every case assessment and charging that NCI dismissed legitimate evidence on the basis of technicalities

(330). No independent assessment of the review has been made.

The Austrian Study

An exploratory study of the clinical effects of some components of the Gerson regimen is currently under way in Austria. According to an unpublished interim report (522), Peter Lechner, M.D., of the Second Department of Surgery of the Landeskrankenhaus in Graz, Austria, is conducting a study using a modified Gerson regimen as an adjunctive treatment. The modified regimen is described as a high fiber, low sodium, high iodine and potassium, lactovegetarian diet with regular coffee enemas. It reportedly omits certain elements of the original Gerson regimen, such as liver juice, thyroid supplements (unless the patient is hypothyroid), and niacin supplements. It also limits the number of coffee enemas to two per day; Lechner noted in previous experience with patients following the Gerson regimen that a higher frequency of enemas was associated with the development of colitis (inflammation of the large intestine, often leading to diarrhea) in some patients.

Twenty-nine patients who chose to follow the modified Gerson regimen were included in the study. An equal number of non-participating patients, matched for tumor type and stage of illness, were paired with the patients following the regimen. Nineteen pairs of patients with breast cancer, eight pairs with colorectal cancer, and four pairs with malignant melanoma were studied. All patients reportedly had previous mainstream treatment (surgery and possibly other treatments) and some of them were taking them concurrently (chemotherapy, radiation, or interferon). While some of the patients are described as having metastatic disease and in advanced stages of illness, the report does not indicate whether all patients had measurable disease at the start of the study or whether previous or concurrent treatment was considered to have had an antitumor effect in any of the patients.

Lechner reported that patients following the modified Gerson regimen showed no side-effects attributable to the treatment and did not become malnourished. One of the patients with inoperable liver metastasis who followed the Gerson treatment showed a temporary regression. In Lechner's opinion, there were subjective benefits from the modified Gerson regimen: patients needed less pain medication, were in better psychological condition, and experienced less severe side-effects of chemotherapy than did the patients with whom they were compared. Without claiming definitive results, Lechner stated that the patients with breast and colon cancer with liver metastasis benefited more than others in the study. According to the report, those patients 'seem to live longer, and their quality of life is apparently better" than patients with whom they were compared, although he noted that his conclusions were subjective and "of no statistical relevance at all.

Lechner's description indicates that the study was not designed to generate definitive conclusions about changes in survival or in quality of life among patients following the modified Gerson regimen. The fact that the patients following the regimen chose to undergo a relatively rigorous and demanding program suggests that there may well be differences between those patients and the ones who did not participate in the program. In this case, the comparison between participating and nonparticipating patients does not provide a legitimate basis for judging differences in turner response, survival, or quality of life. In addition, based on the information provided in the report, it is impossible to separate the effects of the modified Gerson regimen from the effects of previous or concurrent treatments. The study does, however, provide preliminary qualitative information on the experiences of the 29 patients who followed a modified Gerson regimen along with conventional treatment. It is unclear from the report how much longer the study would continue or what endpoints were being measured.

The British Review

In 1989, three British researchers visited the Gerson Clinic on behalf of a British medical insurance company (805) "to assess its basis as a claimed dietary cure for cancer" (459). The investigators observed patients and their treatment freely and were offered information from the clinic's files on a group of patients considered by the Gerson staff to represent "best responses" to the Gerson treatment. They conducted two studies: the first was a review of the best responses, and the second was a psychological study of patients at the clinic at the time of the visit.

For the review, the investigators were presented with 149 cases from among all patients treated at the clinic since it opened in 1977. Of those, 27 were

alive and well and had sufficient documentation for assessment. Nearly all had had mainstream treatment of some kind before beginning the Gerson regimen, and a number continued to receive it in addition to the Gerson treatment.

The investigators reported that nine of the patients had melanomas, and the course of their disease "fell within what we would consider the limits of the 'natural history' of this disease. " Two patients reportedly had early stage prostate cancers which had been removed surgically, and their survival was also judged to be consistent with what would have been expected without further treatment. Another patient with prostate cancer having "clinically significant disease' had survived beyond the expectation of the investigators, given his disease and prior treatment. Two patients with breast cancer and two with endometrial cancer were considered to have had disease courses consistent with their cancer and other treatment. A third patient with biopsy-proven endometrial cancer who had had no conventional treatment subsequently underwent a hysterectomy, at which time no evidence of malignancy remained, representing a case of tumor regression. One patient with non-Hodgkins lymphoma (NHL) had extensive radiation treatment, which could have accounted for a favorable outcome, and another had no followup scans, so tumor status could not be determined. In another patient with low-grade NHL, a biopsy-confirmed mass regressed with no other treatment. The remaining patients were described as having "slowly progressive disease. "

The investigators concluded:

> *Although several of these cases would have been expected to have a poor prognosis on the basis of their histology and stage . . . a proportion of poor prognosis patients do fare better than the average. Any large series of 6,000 poor prognosis patients treated conventionally would produce similar results.*
>
> *A small number of the patients appear to have had disease regression that cannot be explained as being an extreme of the natural history of the disease. There may thus be a small antitumor effect in some patients. However, it must be stressed, if the anticancer effect of the Gerson Therapy was substantial, we would have expected to find evidence of a larger number of responses-if an effective new anti-cancer treatment had been given to 6,000 patients we would expect it to have been easier to find successful cases to present.*

In the second study, 15 patients completed a questionnaire that elicited information about their background and disease history and their feelings about their physicians, their physical and mental health, the Gerson Clinic, and their interpersonal relationships. It was found that, in general, the patients had very positive feelings and experiences; they felt well supported by family and other patients at the clinic, had a' 'high degree of control over their health," and had high "mood" and "confidence" scores. The investigators noted particularly that none of the patients was taking opiates for pain, though several had taken them previously, and they had low "pain" scores. The investigators concluded overall that there was a "significant subjective benefit" to patients and their families from the treatment:

> *The nature of the therapy requires a positive contribution to be made by the patient to his or her health and meets a need not satisfied by conventional therapy. There are therefore lessons for oncologists to learn in the management of desperate cancer patients and their families.*

Gerson Institute Case Review

An effort to document possible tumor remissions among patients treated at the Gerson clinic in Tijuana is currently being conducted under the direction of Gar Hildenbrand of the Gerson Institute (402). Since 1987 (400), a "best case" review has been in progress to assemble relevant data from Gerson patients believed to have benefited from the treatment. As planned, the review would include patients who either had no previous treatment or who failed previous treatment, and would collect details from each patient's medical records (including all cancer-related discharge summaries, pathology reports, slides, radiology summaries, films, laboratory reports, and surgery summaries). Provision was made for blind reevaluation of the pathology material by the U.S. Armed Forces Institute of Pathology and of the medical records by experts at the University of California at Los Angeles. Where necessary, followup evaluations on patients would be conducted (including scans or other evaluative procedures). The collected data would then be reviewed by an expert panel to determine whether objective responses to the treatment had been documented. As of August 1989, OTA had no further information on the status of the Institute's review.

Box 3-B--Coffee Enemas

Several of the current unconventional cancer treatments, e.g., the Gerson treatment and the Kelley regimen, include a recommendation that patients take coffee enemas several times a day. Proponents believe that coffee enemas stimulate the secretion of bile and the action of the liver, helping to "detoxify" the body of waste products and poisons accumulated in the gastrointestinal tract (337,472). "Colonic irrigation' and 'high colonies" are terms referring to a related procedure that involves flushing a larger portion of the colon with water. Colonic irrigation is used in the context of physical cleansing and general detoxification in many unconventional settings (450,959), but is usually distinct from the use of enemas in cancer treatment.

A few studies examining the theory of self-poisoning through the accumulation of toxins and waste products in the body were published in the 1920s (21,259) as a result of a belief common at the turn of the century that impacted feces in the colon produced pathogenic toxins. The specific causative toxins have apparently never been identified or measured and possible physiologic effects of the "detoxifying" enemas have not been studied systematically. In general, there is no scientific evidence to support the claim that coffee enemas detoxify the blood or liver. It has been suggested, however, that coffee taken by this route is a strong stimulant and can be at least as addictive as coffee taken regularly by mouth (947).

The occasional use of enemas, usually consisting of plain water, is conventional practice for a number of medical purposes, e.g., to prepare for x-rays of the intestines, surgery, or childbirth (649), or to relieve constipation (613c). The enema procedure is reportedly not without certain risks, however (970). Case reports of serious adverse effects associated with enemas used in conventional and unconventional treatment have appeared in the medical literature. Coffee enemas have been associated occasionally with fatal electrolyte imbalances. Transmission of enteric pathogens (835), fatal bowel perforation and necrosis (1%,454), and toxic colitis (478,727,793) have been associated with various other types of enema (soapsuds, water, barium, herbal, etc.). Colonic irrigation has been linked with fatal amebiasis resulting from contaminated equipment (450).

Proponents often point to the recommendation of coffee enemas in relatively recent editions of the Merck Manual of Diagnosis and Therapy, a general health care guide, as evidence of the medical appropriateness and conventionality of coffee enemas (355). Up to and including its 1972 edition, the Merck Manual did recommend coffee as one type of ingredient for occasional use as a retention enema, the purpose of which was to "soothe or lubricate rectal mucosa, to apply absorbable or local medications, or to soften feces" (613). No mention was made of the use of coffee enemas to remove toxins from the body. In addition to coffee, other agents mentioned for the same purposes were starch, olive oil, cottonseed oil, mineral oil, and whiskey in isotonic saline. Retention enemas using coffee or any of these other substances were not being recommended for frequent use, however (76), and coffee enemas were not recommended for use as a part of treatment for cancer or any other serious illness-only for temporary, specific problems such as constipation. In the 1977 and later editions of the Merck Manual, the mention of coffee enemas was dropped. In the *three most recent editions, enemas using olive Oil, mineral oil, or, isotonic saline are recommended for constipation and fecal impaction (613a,613b,613c).*

THE KELLEY REGIMEN

In the 1960s, William Donald Kelley, an orthodentist by training, developed and publicized a nutritional program for cancer patients based on dietary guidelines, vitamin and enzyme supplements, and computerized metabolic typing. The Kelley regimen became one of the most widely known unconventional cancer treatments. Although Kelley is no longer practicing his treatment, the regimen has been continued in a variety of forms by his followers. There are three distinct phases or interpretations of the Kelley program: the first, which Kelley described in his book *One Answer to Cancer; the* ***second, Fred Rohe's expansion and reinterpretation as published in his book*** *Metabolic Ecology;* ***and the third, Nicholas Gonzalez's metabolic typology based on Kelley's ideas, which is currently being offered by Gonzalez in New York.***

Background and Rationale

In 1964, Kelley was told he had metastatic pancreatic cancer, although he reported that the diagnosis was never confirmed by biopsy. Applying one of his own "biochemical tests" (one of which he called the "Protein Metabolism Evaluation Index," a test intended to diagnose cancer before it was clinically apparent), he concluded that he had had cancer for several months, if not years, and that his wife and two of his three children also had cancer (472). Kelley claims that his doctor told him he had

2 months to live and advised surgery, which Kelley refused. Based on his own experience, he felt that the wrong foods caused tumors to grow, while proper foods allowed the body to fight off the tumor. By trial and error, he regulated self-administered doses of various enzymes, vitamins, and minerals to achieve his recovery. He proceeded to apply his dietary program to his family and others, and eventually published his recommendations and the beliefs underlying them in a 1969 book entitled *One Answer to Cancer (472),* ***which achieved a wide distribution.***

In his book, Kelley wrote that cancer represented "nothing more than a type of placenta growing at the wrong place and time in the body. ' He characterized cancer as a deficiency disease-a deficiency of active pancreatic enzymes, in particular. He believed that an indication of inadequate protein metabolism signified early stages of cancer and that cancer could be controlled by supplying adequate doses of pancreatic enzymes, a key component of his "ecological" treatment (472). He claimed that this treatment could halt the growth of tumors from within 3 hours to 12 days of initiation. The difficult part, he concluded, was clearing the body of accumulated toxins and the toxic poisons that are released as the tumors are dissolved and excreted (472).

Development and Use of the Treatment

Kelley described his treatment as ecological since "the total person and his total environment must be considered in order to give proper treatment. " The program consisted of five components: taking suffi cient nutritional supplements (vitamins, enzymes, minerals, etc.); detoxifying the body (purging, fasting, coffee enemas, colonic irrigations, cleansing the kidneys, the lungs, and the skin, and exercising); maintaining an adequate diet;[4] providing proper neurological stimulation (e.g., osteopathic manipulation, chiropractic adjustments, 'mandibular equilibration to re-shape the skull," or physiotherapy); and taking a positive spiritual attitude ("purifying the emotions and spirits") (472).

The Kelley nutritional program gained popularity in the 1970s, when Kelley gave many interviews and made unequivocal claims that his program was regularly able to cure a wide range of cancers: "It is extremely effective and rather inexpensive. Those who are willing to faithfully and tediously follow it will be successful. Those who follow it in part or haphazardly will be completely unsuccessful' (472). He also developed a rnail-order approach to nutritional-metabolic treatment in which he was able to use "technicians" who assisted patients in getting on and following his program. Specific recommendations for patients were generated by his computer system. In addition, Kelley developed his own supply houses for the supplements,[5] water filtration systems, and even the coffee ('"Kelley Koffee'"). An updated and expanded version of his treatment was published in 1983 by Fred Rohe with Kelley's input (761). Kelley endorsed Rohe's book, stating that it represented his most up-to-date findings and recommendations.

In this second phase, Kelley's spiritual philosophy had taken on a strong "New Age" tone. He wrote:

> ***. . . there has to be some purpose to human life on this planet. That purpose seems tome to be the development of understanding and inner growth. I define inner growth as the expansion of our whole being, particularly our spirit, as we interact with each other and with the environment . . . This new positive foundation supports a new paradigm for the field of health care, allowing for the influx of great new streams of intelligence, experiences, and creativity. Millions of people who come along in future generations will be able to build and react upon this new paradigm. It is an ultra-holistic model with a completely realistic and scientific framework. We are moving from a left-brain dominant system to a left/right balanced brain system, with plenty of heart mixed in. I don't know if I understand it all-I don't think anybody can completely grasp such a comprehensive process of change. But it's a beautiful thing to watch. (761)***

According to Rohe, Kelley had noticed that not everyone he treated responded the same way, and modified his original idea of "one answer to

[4]This refers to a low protein diet and proper protein timing. Kelley claimed that "if people would not eat protein after 1:00 p.m., 83% of cancer in the United States could be eliminated" (472); no pasteurized milk, no peanuts, nothing cooked or processed, no white flour or white sugar; lots of vegetable and fruit @ices, plenty of raw almonds, fresh raw salads, whole grain cereals.

[5]Kelley believed that the supplements commercially available in health food stores and drug stores did not meet his standards of purity and potency, so he initiated a custom-made line of products made according to his specifications (353).

cancer. He came to believe that there was no single, perfect diet for all patients. To account for each individual's unique metabolic makeup, Kelley devised a system of metabolic typing or classifying each individual and coordinating a unique set of recommendations for each.

One of the elements of the Kelley program that evolved substantially from the first phase was his use of diagnostic tools. The "Kelley Enzyme Test," one of the many tests used in the program, was designed to provide a very early diagnosis—1 month to several years before clinical signs of cancer (761). The test consisted of taking ten "Ultra-zyme" tablets over a 4-week period. The presence or absence of cancer was indicated by the person's observation of whether they felt better, worse, or no different during this period. Feeling either better or worse indicated the presence of cancer, whereas feeling no different meant that the person was probably free of cancer (but in this case Kelley recommended that the test be repeated with a double dose of the enzyme tablets to be sure). The test was not intended to indicate the location of cancer in the body or the type of tumor (761).

According to Rohe, Kelley believed that environmental pollutants were being incorporated into our bodies and becoming internal toxins, and that exhaustion of the fertility of the Nation's farmlands was depleting our foods of nutritive value. All of this led, he reasoned, to pancreatic and immune system breakdowns, leading ultimately to cancer.

The diet recommended by Kelley as stated in the Rohe book outlines the following guidelines: restrict intake of meat (except liver); consume no protein after lunchtime; no refined foods, pasteurized milk, peanuts, tea (except herbal), coffee (except in enemas), soft drinks, tobacco, liquor, white rice, or fluoridated water. He recommended that patients eat fresh, raw salads, vegetable juices, whole grain cereals, raw liver (liver must be taken raw to preserve the "enzymes, amino acids, and other intrinsic factors science has not yet identified—which are destroyed when the liver is cooked' '), nuts and seeds, cultured milk products, eggs (preferably soft boiled or raw, except for certain types of cancers), beans, etc. In summary, the diet consisted of increasing one's consumption of raw foods, decreasing protein intake, and eliminating refined foods and additives.

The only classification system used by Kelley at the time of the Rohe book was a breakdown between "soft" and "hard" tumors. "Hard" tumors included all except leukemia, lymphomas, melanomas, and multiple myeloma, which were classified as "soft."

The nutritional supplementation recommended by Kelley consisted of 25 supplements (enzymes, vitamins, glands, minerals, hydrogen peroxide, aloe vera, bile salts, freeze-dried liver, etc.) that were to be taken for a 2-year period. In the standard protocols, patients were classified as "hard tumor" and "soft tumor" patients and were recommended the same list of supplements, although "soft tumor" patients were advised to take a few extra foods. Some patients were given specific recommendations tailored to them and in these, patients often were advised to take additional supplements beyond the 25 listed in the standard protocol. Patients were referred to Kelley's Nutritional Counseling Service in Texas for additional information.

These supplements were intended to stimulate the release of "wastes and debris" from the body. Ridding the body of these wastes through detoxification was advised as essential to the program's success. Kelley recommended that patients take at least one strong coffee enema each day, to clean out the liver and gallbladder and to rid the body of toxins produced during tumor digestion (see also discussion in box 3-B). In addition to coffee enemas, Kelley recommended regular purging, fasting, and colonic irrigation (high enemas, between 18 and 30 inches into the body). He also advised cleansing the kidneys, nostrils, lungs, and skin (761).

As in Kelley's original description, other components of the program as described by Rohe were neurological stimulation and spiritual growth. Kelley advised patients to "reactivate nerve function through structural alignment": osteopathic manipulation, chiropractic adjustments, cranial osteopathy, mandibular equilibration (to reshape the skull and take stresses from the brain), and reflexology.

Kelley considered matters of the spirit an integral part of his program: "Just as the body must be purged and cleansed, so must the emotions and mental attitudes be purified." He advised removing "all false teachings, false doctrines, fruitless activities, fears, and misunderstandings. Your spirit and very being hunger for truth-the truth that can be

found only in the proper understanding of the Word of God." (761)

To support his program and make his teachings more widely known, Kelley created the International Health Institute in Dallas, consisting of a group of doctors, dentists, chiropractors, naturopaths, metabolic technicians (nutritional counselors certified by the institute), and attorneys. Under the umbrella of this institute, Kelley's Nutritional Counseling Service was developed, whereby patients attended workshops to find out about the Kelley program and then answer the 3,200-question Metabolic Evaluation Survey (which reportedly took about 8 hours to complete). This questionaire, analyzed entirely by computer, formed the basis for the Kelley nutritional prescription, a program designed according to each patient's individual nutritional needs. Questions were answered on computer cards and sent to Kelley's headquarters. Kelley claimed that the cards gave him a detailed picture of the patient's metabolic type and of the efficiency of 50 physiological functions. In response to the questionnaire, patients received a lengthy, detailed computer printout of their metabolic status along with step-by-step instructions for following their particular version of the Kelley regimen--covering foods, supplements (in the range of 100 to 200 pills per day), detoxtification techniques, psychological approaches, and lifestyle changes (341). With the cooperation of physicians unaffiliated with Kelley's institute, cancer patients were advised by Kelley to submit the questionaire every 6 months until, according to Kelley, their nutrient levels reach normal ranges, and after that, about once a year.

For most early localized cancer, Kelley advised frequent oral doses of pancreatic enzymes taken between meals; the enzymes were said to destroy cancerous and other defective cells (353). Kelley maintained that patients with metastatic disease require prolonged therapy (1 to 2 years at least). In patients with very advanced malignancies involving many organs, Kelley did not claim that the tumors could necessarily be eliminated, only that the enzymes often shrink much of the tumor mass and could prevent the cancer from spreading further (353).

Kelley designed a mail-order form for an intensive nutritional-metabolic program for cancer that reached many patients who may not have had access to other unconventional treatments. The idea that cancer could occur as a result of inappropriate nutrition and could be treated with intensive nutritional supplementation and detoxification, as articulated in his book One Answer to Cancer, *brought Kelley a great deal of attention from the public, the medical profession, and State medical examiners. In 1971, Kelley was issued a restraining order forbidding him from treating non-dental disease and was prohibited from distributing copies of his book. Gonzalez reported that following this restraining order, Kelley became more cautious in his claims and practice; he required all patients to sign a form acknowledging that he was a dentist, not a medical doctor and that his nutritional programs were intended for nutritional support, not as therapies for any disease (353).*

Kelley's International Health Institute and his Computer Health Service (934) were closed in the mid-1980s. A computerized metabolic typing service similar to Kelley's is offered by Healthexcel in Winthop, Washington, although Kelley is not identified as being directly involved in the service (390).

Current Applications of the Kelley Regimen

In recent years, Nicholas Gonzalez, M.D., has examined the Kelley regimen and has provided an additional analysis of Kelley's individual metabolic profiles. Since Kelley's ideas and results are known only from his 1969 book and the 1983 book by Rohe, it is not known whether Gonzalez's descriptions match Kelley's most recent interpretations of his program. However, Gonzalez is practicing this regimen in New York (354) and Kelley is apparently not, so Kelley's metabolic typology as interpreted by Gonzalez is presented herein summary (353).

According to Gonzalez, Kelley believed that human beings can be divided into three genetically based categories-' 'sympathetic dominants," "parasympathetic dominants,' and ''balanced types. '[6] "Sympathetic dominants" will have highly efficient and developed sympathetic nervous systems. "In addition, the tissues, organs and glands nor-

[6]The autonomic nervous system, made up of the opposing sympathetic and parasympathetic nervous systems, innervates smooth and cardiac muscle and glandular tissues, governing actions that are more or less automatic, such as actions of the heart, secretion, constriction of blood vessels, and peristalsis. The parasympathetic nervous system tends to induce secretion, increase the tone and contractility of smooth muscle, and cause blood vessels to dilate. Effects of the sympathetic nervous system are opposite.

really stimulated by the sympathetic nerves-the heart for example-will be well developed. However, in this group the parasympathetic nervous system will be relatively inefficient, and all the tissues and organs normally activated by this system will be physiologically sluggish." In "parasympathetic dominants," the opposite is the case; and in "balanced types," both branches of the nervous system and corresponding tissues, organs, and glands are equally developed.

Sympathetic dominants are hypothesized to have evolved in tropical and subtropical ecosystems on plant-based diets. Parasympathetic dominants evolved in colder regions on meat-based diets. The balanced types evolved in intermediate regions on mixed diets. While modern migrations have extensively mixed the three types, Kelley believes people tend to belong definitively to one of the three categories.

Kelley thus evolved a diet for each type based on its hypothesized historical origins. And he traced a characteristic path of "metabolic decline" for each group when they consume the wrong diet. He associates "hard tumors" with severely compromised sympathetic dominants, and 'soft tumors'—cancers of the white blood cells and lymph system-with severely compromised parasympathetic dominants.

Gonzalez dispenses with the neurological stimulation and spiritual components of the original Kelley regimen, and now divides the Kelley therapy into several components. Gonzalez's regimen consists of:

- *An individualized diet, "as determined by an experimental blood test,' that ranges in content from entirely vegetarian to entirely meat, with about 90 variations in between. Gonzalez stated in a recent interview that he has 'patients who will not get well unless they eat fatty red meat three or four times a day" (356).*
- *Large doses of nutritional supplements, as many as 150 pills a day (356), including vitamins, digestive enzymes (e.g., pancreatic enzymes, pepsin, hydrochloric acid, bile), and concentrates in pill-form of beef organs and glands.*
- *Coffee enemas.*

Attempts at Evaluating the Kelley Regimen

In his 1987 manuscript *One Man Alone: An Investigation of Nutrition, Cancer, and William Donald Kelley (353), Gonzalez* ***presents case histories of 50 patients he selected from Kelley's files. This case series has been singled out by proponents as one of the most convincing in support of an unconventional treatment (530,596). As a means of finding out whether the evidence presented in these cases would be convincing to the medical community, OTA asked six physicians who are members of the Advisory Panel for this OTA study to each review a portion of Gonzalez's case histories. Three of the physicians were supportive of some unconventional treatments (though none was associated particularly with Kelley or Gonzalez), and three were mainstream oncologists. (For convenience, these physicians are referred to, in this section, as "unconventional" and "mainstream.") The three unconventional practitioners are not oncologists, though each treats some cancer patients.***

Each of the 50 cases was assigned to one "unconventional' and one "mainstream" physician for review. Assignments were made randomly within each group of three physicians, so all possible pairings of reviewers could occur. The reviewers were asked to assume that Gonzalez's reports were accurate, and then comment on whether the course of the disease described for each patient was beyond reasonable expectation, and whether attribution of benefit to the Kelley program appeared justified.

The cases include a variety of cancers: seven lymphomas (various types); six pancreatic; five prostate; four breast; four melanoma; three Hodgkins disease; three leukemia; two each of colon, lung, ovary, rectosigmoid, and testicular; and one each of bile duct, brain, cervix, metastatic liver (primary unknown) myeloma, kidney, stomach, and uterine.

Each case history consists of a narrative by Gonzalez and copies of some supporting medical records. The criteria for including cases were: they had to have been evaluated by "competent specialists" so that the diagnosis would not be in doubt; patients should have been given a prognosis of ''poor' or 'terminal' and there had to be evidence of regression of disease or "long-term survival that might logically be attributed to the Kelley program." The patients were chosen from more than

1,000 selected patient records that Gonzalez determined were "potentially suitable." He contacted 455 of them, and 160 seemed to satisfy the stated criteria. For each of these, Gonzalez reports that he "obtained complete medical records," and the 50 cases were then selected. Gonzalez refers to these cases as "representative' of Kelley's patients, rather than his "most 'impressive' cases."

In addition to making general comments (discussed below), five of the six reviewers responded with a narrative on each case; one categorized cases as "seem legitimate," "suggestive but not definitive," "somewhat suggestive," and "definitely not convincing." In all cases, however, documentation presented in the manuscript was inadequate to confirm critical details of the narrative, and in many cases, it appeared that critical pieces of information did not exist in the medical record at all (e.g., conflation of metastatic disease), mainly because the patients had not been followed up with tests and scans to determine the status of their disease.

Fifteen cases were judged by unconventional reviewers as definitely showing a positive effect of the Kelley program; the mainstream reviewer of each of these cases found 13 of them unconvincing and 2 unusual. Nine cases were judged unusual or suggestive by unconventional reviewers; the mainstream reviewers found these cases unconvincing. Fourteen cases were judged by unconventional reviewers as having been helped by a combination of mainstream plus Kelley treatment; the mainstream reviewers found 12 of these cases unconvincing and 2 unusual. Twelve cases were considered unconvincing to both the unconventional and mainstream reviewers.

Specified criticisms of the case presentations included the lack of histologic diagnosis in several cases, the assumption that disease was metastatic without biopsy, discrepancies between the narrative and the medical records (e.g., in one case, the surgical pathology report states that the tumor arose "in the colonic mucosa infiltrating into the wall," Gonzalez describes the tumor as "growing through the wall," which would have a much poorer prognosis), discounting the effects of prior mainstream treatment (e.g., hormonal treatment, which, unlike cytotoxic chemotherapy, may take months to take full effect), and the general lack of reassessment of patients' conditions once begun on the Kelley treatment. Three illustrative cases are discussed below.

Discussion of Three Cases

In one case history, a woman in her early 40s was diagnosed with a 7-centimeter "infiltrating adenocarcinoma of the colon, intermediate differentiation with full thickness involvement of bowel wall but no evidence of regional lymph node metastasis.' It was removed surgically. She did well, except for chronic fatigue, until about a year and a half later, at which time she had a car accident and then developed severe abdominal pain with significant weight loss. Outpatient studies "revealed a large, restricting tumor in the remnant of her descending colon." The narrative reports that the patient said her doctor told her that the cancer "had metastasized widely." She refused recommended surgery. Shortly, she began the Kelley program, at a time when she appeared to be "critically ill." Within a week, her bowel obstruction cleared and she improved gradually. "Eleven months after beginning her protocol, she reports passing a large globular mass of tissue which she and Dr. Kelley assume was the remnants of her tumor.' Seventeen years after diagnosis, she is alive and in "excellent health and apparently cured of her cancer.

The medical records accompanying this narrative include the discharge summary from the original surgery and corresponding radiology, surgery, and pathology report.

The mainstream physician who reviewed this case judged that this patient's localized tumor was probably cured by the initial surgery. No documentation of the reported recurrence is supplied, and the cause of her later medical problems could not be determined. He commented that the globular mass of tissue, which was apparently seen only by the patient, was a unique but uninterpretable feature of this case.

The unconventional physician who reviewed this case noted that the recurrence was not confirmed by pathology, but felt that the Kelley program probably was instrumental in her survival.

In a second case, a man in his late 30s had an early stage (Clark's level II) malignant melanoma removed from his back. A "livermass' was described in the hospital record as a "space occupying lesion inferior portion right lobe of liver," but was not thought to represent metastatic disease. About 3 months later, he noticed a nodule under his left arm, which upon removal was found to be malignant.

Sixteen lymph nodes were subsequently removed, of which five were positive for melanoma. Four months later, he had another nodule near the previous one, and had it removed; it also was positive for melanoma. No other treatment was recommended. According to the narrative, the patient developed fatigue and anorexia. After another 6 months, he noted another nodule on his forehead, and shortly thereafter began the Kelley program. He gained weight and the forehead nodule regressed, disappearing after 6 months. At his last followup 2½ years later, he had no evidence of cancer and was in "excellent health. '

Supporting records for this case include the biopsy report from the first recurrence in the left axilla, a letter that appears to be from the treating oncologist to the patient's personal physician written about 6 months after the forehead nodule was noticed (letter on plain paper, no letterhead), and a letter written about 6 months later from the same oncologist to what appears to be the patient's insurance group discussing his history.

The unconventional reviewer found this narrative "highly suggestive" of benefit from the Kelley program, but that the absence of continued followup weakened the case. The mainstream reviewer commented that a waxing and waning course for malignant melanoma is not unusual, and mentioned a patient of his own with a similar history, whom he has followed for 10 years. He also commented that the cause of the fatigue was unclear, but could have been related to depression. In addition, the letter to the patient's personal physician notes in relation to the forehead nodule that had disappeared, "this was not thought to be metastatic melanoma when he was examined by my colleague . . . at that time. "

In a third case, a man in his mid-60s was diagnosed with well-differentiated infiltrating adenocarcinoma of the prostate during a routine physical. An abnormality of the right eighth rib was noted on a bone scan, which the narrative notes was "initially believed consistent with metastatic disease. " On x-ray, an infiltrate was noted in the lower region of the left lung, which the narrative states "appeared to be an additional area of metastasis. ' The patient refused further testing and treatment. During a hospitalization a little over a week later for removal of two superficial skin cancers, a chest x-ray showed some improvement in the lung infiltrate but the records stated that "the possibility of an underlying neoplasm could not be excluded." He began the Kelley program shortly after that. Nine years later, the patient, when contacted, said that his prostate was found to be completely normal on a recent physical examination. The narrative concludes that this was a "most remarkable patient," and that "it seems reasonable to attribute . . . prolonged survival to the Kelley program."

Supporting records for this case include the discharge summary and biopsy report from his original hospitalization.

Neither the unconventional nor the mainstream reviewer found this a case inconsistent with the expected course. Both commented that there was no real evidence of metastatic disease. The mainstream reviewer added, "The survival of nine years with localized adenocarcinoma is not at all unusual, and such cases are identified fairly frequently inpatients who seek medical attention for obstructive symptoms related to their associated benign prostatic hyperplasia" (271).

General Comments

The mainstream reviewers had similar general comments about the cases. A general theme in their remarks was that, based on the material presented, it was not possible to relate the reported results to the Kelley treatments. Nearly all the patients had had mainstream treatment, which, along with the natural variability of the disease, might also have been sufficient to account for the observed outcome. Two reviewer comments include:

> *My impression of these cases overall is that most of them represent better than average survival from their respective diseases, and to persons who are not familiar with the breadth of individual disease survival spectra they might seem unusual. For the most part, however, they are not and they do not as a group represent any basis for further pursuit of the Kelley treatment per se. (271)*

> *Those of us who have worked over the years with cancer patients have come to respect the vagaries of human biology wherein there are cancer patients who for unclear reasons fare better than we would have expected. (544)*

In several instances, reviewers commented that they had in their care patients whose courses are as exceptional, for reasons not immediately apparent, as the Kelley cases they reviewed.

Another common criticism was that comparing an individual patient's survival with average group statistics is misleading and an invalid use of the group data,

> . . . it is an elementary statistical principal that retroactive or retrospective reviews of groups of patients such as that surveyed by Dr. Gonzalez of necessity are fraught with the bias imposed by the ways in which the patients selected themselves for referral to the Kelley program . . . . These patients can hardly be considered representative of the entire spectrum of cancer patients. Secondly, in critiquing the cases, Dr. Gonzalez is highly selective in marshalling references and supporting assertions which are limited and clearly chosen to support his point of view. His review of each case is not a neutral exercise, but is slanted to support his assertion that the Kelley program has had an impact on the outcomes of these patients. (544)

General comments of the unconventional reviewers were significantly different:

> As an overall assessment, I would judge that the patients under my review appear probably, but not certainly, to have presented for the most part an unusual course, that the outcome exceeded normal expectancies with current contemporary conventional management and that the effect of the Kelley treatment contributed significantly, although not necessarily exclusively, to the outcome. (271)

> I have . . . found 5 which seem legitimate; 5 suggestive but not definitive, 2 somewhat suggestive; 8 definitely not convincing. If we can extrapolate to the 50 cases there might be 12 which seem on the basis of the info presented, to represent genuine unexpected "cures" or remissions. Certainly, even 25% is striking. It obviously does not rule out expectancy and great motivation as the "cause" of the remission.

> . . . in the cases I have marked legitimate, based upon the facts presented and beyond any reasonable medical doubt, it appears that totally unexpected remissions occurred. If there is such a thing as "best cases,' these appear to fulfill that definition. It would be unscientific to ignore such data. (795)

Another comment had to do with the difficulty of assessing best cases attributable strictly to unconventional treatment, because patients so often use both mainstream and unconventional treatment (218).

This limited OTA review of Gonzalez's case histories suggests that physicians generally supportive of unconventional treatments found some of the cases supportive of benefit from the Kelley regimen, whereas mainstream physicians did not find such suggestion of benefit, for several reasons. Key reasons appear to be lack of adequate documentation of the course of disease and reliance in most cases on unusually long survival rather than documented tumor remission. (See ch. 12 for a discussion of "best case" series, including discussion of medical documentation and endpoints.)

MACROBIOTIC DIETS

Macrobiotic diets, consisting largely of cooked vegetables and whole grains, are among the most popular unconventional approaches used by cancer patients (177,530,781). Books and magazines, special food items, macrobiotic cooking classes, and other macrobiotic products and services have, for the past decade or more, been easily accessible through local health food stores and regional macrobiotic teaching centers ("East-West Centers"). General bookstores are now also a common source of information about macrobiotic beliefs and practices, often carrying at least a few of the many available books by macrobiotic teachers and by individuals who initiated a macrobiotic regimen following diagnosis of disease. One recent example is a widely publicized book (777) (and excerpted magazine articles (634,635,776)) recounting a physician's personal use of a macrobiotic diet as an adjuvant treatment for prostate cancer.

During the past three or four decades in the United States, a small group of proponents has been active in developing and teaching macrobiotic beliefs and practices, drawing at first from elements of Japanese culture and Eastern philosophy. During this time, the dietary recommendations have been modified, and continue to evolve. One of the most prominent leaders in the macrobiotic movement is Michio Kushi, who, in 1978, founded the Kushi Institute near Boston, the aim of which is to "provide the education necessary to achieve our common goal of a healthy and peaceful world' (501). The overall goals of macrobiotic education include teaching people to take responsibility for their state of health and to develop natural, balanced ways of living seen as essential to recovery from disease. Kushi and his staff offer courses covering a diverse array of practical and theoretical issues, including physical and psychological health and well-being, environmental concerns, spiritual evolution, and international peace. Another prominent leader in the U.S.

macrobiotic movement is Herman Aihara, president of the California-based George Ohsawa Macrobiotic Foundation, a group whose aim is to spread the teachings of macrobiotics and its practical application in daily life. The Foundation publishes writing pertaining to macrobiotic principles and diet, along with a monthly magazine, and teaches macrobiotic cooking methods (16).

Macrobiotics is defined as the way of life according to the greatest or longest possible view (509). Kushi believes that through its practice, i.e., the "selection, preparation, and manner of eating of our daily food, as well as the orientation of consciousness,' it is possible to apply "the order of the universe, nature, and life' to our daily lives (507,509). According to Kushi, "macrobiotics is neither a treatment nor a therapy, but rather a common sense approach to daily living" (506) and a comprehensive approach to the maintenance of health (507).

The central and most prominent element of the macrobiotic belief system is its dietary practice. Most of the recent popular literature, including much of Kushi's own writings, focuses on the use of macrobiotic diets not only to promote general health and well-being, but to relieve illnesses such as cancer (509) and AIDS (636). One effect of that literature is that many U.S. cancer patients initiate a macrobiotic regimen following a diagnosis of cancer and do so with the hope of obtaining direct health benefits related to their cancer; many who recover believe that their renewed health was a result of the macrobiotic diet they followed.

While the macrobiotic diets were not developed primarily as a treatment for cancer, they are, nevertheless, promoted actively and followed by many as a treatment for cancer. Accordingly, this section of the report focuses on current macrobiotic practices as applied to cancer treatment. The adoption of a macrobiotic regimen in other primary contexts, e.g., as a general lifestyle choice, as a preventive measure against cancer, or as treatment for conditions other than cancer, is not covered in this report.

Background and Philosophy

The introduction of macrobiotic practices into the United States is usually attributed to George Ohsawa (1893-1966), the pen name for Yukikazu Sakurazawa, a Japanese teacher who studied the writings of Sagen Ishizuka (1850-1910), a Japanese physician. Ohsawa is said to have cured himself of serious illness by changing from the modem refined diet then sweeping Japan to a simple diet of brown rice, miso soup, sea vegetables, and other traditional foods (509). He initiated the development of macrobiotic philosophy, reportedly integrating elements of Eastern and Western with 'holistic' perspectives on science and medicine (509). Ohsawa made his frost of several visits to the United States in 1959.

Through his writings and teachings, Ohsawa combined elements of Zen Buddhist philosophy with macrobiotic principles. He popularized his approach through advocacy of the 'Zen macrobiotic diet'—the diet from which the current (and different) macrobiotic regimen was developed. Ohsawa advocated simplicity in diet as a key to good health. He believed that personal happiness and health could be achieved by following a predominantly vegetarian dietary plan consisting of unprocessed, organically grown grain products, especially cereal grains (which he referred to as "principal food"), vegetables, beans, fruit, and seafood. In his 1965 book, Zen Macrobiotics *(693),* Ohsawa outlined 10 stages of diet (designated numbers -3 to +7), with diet -3 consisting of 10 percent cereals, 30 percent vegetables, 10 percent soups, 30 percent animal products, 15 percent salads and fruits, 5 percent desserts, and beverages 'as little as possible.' With each higher number diet, Ohsawa reduced the percentages of food from some of these categories or eliminated the category entirely and increased others, so that, e.g., in diet +3, 60 percent was cereals, 30 percent was vegetables, and 10 percent was soups. Ohsawa regarded diet +7, which consisted of 100 percent cereals, as the "highest" way of eating for treating illness, including cancer, or as a short-term exercise in dietary simplicity (592).*

A 1971 report of the AMA Council on Foods and Nutrition noted various types of serious nutritional deficiencies, some of which were fatal, among individuals restricting themselves to Ohsawa's +7 diet for extended periods of time. These included cases of scurvy, anemia, hypoproteinemia (low serum protein), hypocalcemia (low serum calcium), emaciation due to starvation, and loss of kidney function due to restricted fluid intake (43). Publicity surrounding these cases led to the development of a strongly negative stereotype of the macrobiotic regimen in the 1960s. The American Cancer Society Committee on Unproven Methods of Cancer Man-

agement published its first statement on macrobiotic diets in 1972 (90).

In the 1970s and 1980s, changes in the content and focus of the macrobiotic movement were led to a great extent by Michio Kushi, who had studied with Ohsawa, and who came to the United States from Japan in 1949 (499). Kushi, along with Herman Aihara and other leaders in the macrobiotic movement, preserved elements of Ohsawa's philosophy while incorporating a variety of broader and more complex components into macrobiotic philosophy and practice (16). Most notably, Ohsawa's 10-phase dietary levels were replaced with the general 'standard macrobiotic diet," which Kushi described in detail in his 1983 book, The Cancer Prevention Diet (509). Aihara recommended his own macrobiotic dietary guidelines for cancer patients in his books Basic Macrobiotics *(16) and Acid and Alkaline (15). Those books, along with Anthony Sattilaro's 1982 book,* Recalled by Life, *highlighted a new aspect of macrobiotic practice, at least from a public perspective, by asserting a fundamental relationship between current macrobiotic diets and cancer remission.*

Rationale

Kushi and his associates have become prominent spokespersons for the ideas underlying macrobiotic practices and for the rationale for applying them to the treatment of cancer. From Kushi's perspective, the development of cancer is determined by dietary, environmental, social, and personal factors; by extension, existing cancers may be influenced by these same factors.

Kushi cites a number of specific factors he believes are Iinked fundamentally to the development of cancer, including patients' "overall blood quality,' consumption of excess nutrients, exposure to toxic substances, "mentality and way of life, ' as well as more general factors, such as unfavorable trends in the food industry and our "increasingly unnatural and sedentary way of life. He emphasizes the role of personal behavior in the development of cancer: "cancer is not the result of some alien factor over which we have no control," he writes, but rather "the product of our own daily behavior, including our thinking, lifestyle, and daily way of eating" (509).

The development of cancer is described as a long-term, multistep process that begins well in advance of actual tumor formation. Kushi writes:

> *Cancer is only the terminal stage of a long process. Cancer is the body's healthy attempt to isolate toxins ingested and accumulated through years of eating the modern unnatural diet and living in an artificial environment. (509)*

He believes that these accumulated toxins result from overconsumption of milk, cheese, meat, eggs, and other fatty, oily, or greasy foods (509), and of foods with a cooling or freezing effect, such as ice cream, soft drinks, or orange juice (509). Depending on their location in the body, these accumulated toxins are manifested initially as, e.g., allergies, earaches, coughing and chest congestion, a' 'bulging abdomen," periodic swelling and weakness in the legs, dry skin, hardening of the breasts, prostate abnormalities, vaginal discharge, or ovarian cysts—problems Kushi believes are indications of potentially precancerous conditions (509). As he explains it:

> *As long as improper nourishment is taken in, the body will continue to isolate abnormal excess and toxins in specific areas, resulting in the continual growth of cancer. When a particular location can no longer absorb toxic excess, the body must search for another place to localize it, and so the cancer spreads. This process continues until the cancer metastasizes throughout the body and the person eventually dies. (509)*

In Kushi's view, the central error in our behavior that leads directly to an imbalance and unnatural state in the body and thereby to cancer development, is the consumption of food that is overly expansive and contractile (509). He uses the traditional Oriental concepts of yin (expansive) and yang (contractile), described as antagonistic and complementary forces that create and balance all phenomena on earth (509), to devise a framework for explaining and formulating a set of dietary recommendations to treat each type of cancer.

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[7]Kushi uses the traditional Oriental practice of "physiognomy" to diagnose cancer and to monitor its progress in individual patients. Correlations are made between external appearances (e.g., facial features, posture, and skin color) and disorders of specific organ systems, and particular attention is paid to certain markings in the eyes and to skin color, since a *greenish* skin color on certain areas *of* the body is *claimed* to indicate the existence of a tumor (509,776).

A macrobiotic approach to treating cancer would first classify each patient's illness[7] as predominantly yin or yang, or sometimes as a combination of both, based in part on the location of the primary tumor in the body and the location of the tumor in the particular organ. In general, tumors in peripheral or upper parts of the body or in hollow, expanded organs are considered yin; examples include lymphoma, leukemia, Hodgkins disease, and tumors of the mouth (except tongue), esophagus, upper stomach, breast, skin, and outer regions of the brain. Tumors in lower or deeper parts of the body or in the more compact organs are considered yang, e.g., cancers of the colon, rectum, prostate, ovaries, bone, pancreas, and inner regions of the brain. Cancers thought to result from a combination of yin and yang forces include melanoma and cancers of the lung, bladder, kidney, lower stomach, uterus, spleen, liver, and tongue (509).

Macrobiotic dietary treatment would attempt to correct the perceived excess of yin, yang, or both tendencies. For cancers classified as predominantly yang, Kushi recommends the standard macrobiotic diet (explained below) with a slight emphasis on yin foods, and for cancers classified as predominantly yin, the same diet with a slight emphasis on yang foods. Patients with cancers classified as resulting from both yin and yang forces are advised to follow "a central way of eating," as suggested in the standard macrobiotic diet. Different cooking styles are also recommended based on this disease classification (509).

Beyond dietary guidelines, a number of additional recommendations are emphasized in the macrobiotic regimen, e.g., obtaining regular exercise, avoiding electromagnetic radiation, synthetic fabrics, and chemical fumes, and maintaining a good mental attitude. Kushi writes:

> *A person with cancer must understand that he or she was directly responsible for the development of the disease, through his or her daily diet, manner of thinking, and way of life. The patient should be encouraged to reflect deeply, to examine those aspects of modern mentality that have produced the problem of cancer and a host of other unhappy situations. These reflections should include a review of the rich heritage of traditional wisdom developed by many cultures over thousands of years, an appreciation of the endless wonders of the natural world, including the body's marvelous self-protective and recuperative mechanisms, and a respect for the order of the universe that produces these phenomena. (509)*

The overall purpose of these various changes in diet, exercise, attitude, and family interactions is reportedly to bring every aspect of the patient's life into balance. Macrobiotic philosophy teaches patients to be grateful and assume responsibility for everything in their lives, including their illness. By doing this, patients are encouraged to believe that since they had the power to create their illness, they must also have the capability to recover from it (667).

According to his 1983 book, Kushi does not encourage cancer patients to combine the macrobiotic diet with mainstream cancer treatment, except in immediately life-threatening circumstances, such as an inability to eat normally or an obstruction in the digestive system (509). Although he does encourage patients to keep their physicians informed of their macrobiotic practices and to have periodic medical checkups, he recommends in his book that patients gradually reduce their reliance on mainstream medicine as their health improves. He notes that patients who follow a macrobiotic diet while taking mainstream treatment might have a slower recovery than they would have with the macrobiotic approach alone. After an initial 1 to 4 months of both conventional and macrobiotic treatment, patients are advised to "reduce the frequency of outside treatment" (509). Kushi encourages patients to find physicians who are also trained in macrobiotic dietary practices and offers referrals to macrobiotic physicians through the Kushi Institute. According to information supplied to OTA by one of Kushi's associates, Kushi no longer recommends against cancer patients' combining the macrobiotic diet with mainstream treatment and encourages them to seek ongoing conventional care (652a).

In practice, there could be wide variation in patients' interpretations of Kushi's dietary guidelines, although no systematic information is available to document how patients are using macrobiotic

[7] Kushi uses the traditional Oriental practice of "physiognomy" to diagnose cancer and to monitor its progress in individual patients. Correlations are made between external appearances (e.g., facial features, posture, and skin color) and disorders of specific organ systems, and particular attention is paid to certain markings in the eyes and to skin color, since a greenish skin color on certain areas of the body is claimed to indicate the existence of a tumor (509,776).

diets in cancer treatment. In addition to consulting the Kushi Institute in Boston, local East-West Centers, or other national macrobiotics groups, a variety of approaches may be taken in following a macrobiotic regimen. For instance, patients may rely primarily on information obtained from books or magazines written by Kushi and others, with little or no guidance from physicians or macrobiotic counselors. They may receive instruction in cooking methods without more general guidance about the regimen. Patients may also be treated by physicians unaffiliated with the Kushi Institute who advocate an individualized version of the macrobiotic diet as an adjunctive approach to conventional treatment.

Macrobiotic Dietary Guidelines

The standard macrobiotic diet forms the basis for recommendations for individual patients and is adapted according to the individual's age, sex, level of activity, personal needs, and native climate. Kushi advises that such individual recommendations be made with the supervision of a qualified macrobiotics counselor and with a medical or nutritional professional although patients may devise their own dietary plans or modify the initial ones devised by a macrobiotics counselor. Kushi's 1983 book, *The Cancer Prevention Diet* describes specific dietary recommendations for most major types of cancer.

Kushi recommends a general dietary plan for cancer prevention and treatment in addition to guidelines for specific types of cancer. The standard macrobiotic diet emphasizes the intake of complex carbohydrates over simple sugars; high fiber foods over low fiber foods; unsaturated fats over saturated ones; sea salt over refined salt; natural vitamins and minerals found in food, rather than supplemental vitamins and minerals; natural, organically grown foods over chemically fertilized foods; whole, unrefined foods over processed foods, vegetable protein over animal protein, and foods cooked by gas and wood-burning stoves rather than by microwave ovens or electric stoves (507).

The standard macrobiotic diet is adjusted on a case-by-case basis, taking into account geographic, seasonal, and individual situations. The diet consists of the following types of food, identified as ones for regular or daily use, for occasional use, for infrequent use, and to avoid:

- 50 to 60 percent by volume of daily food includes cooked, organically grown, whole cereal grains (e.g., brown rice, barley, millet, bulgur, oats, corn, rye, wheat, and buckwheat, with a small portion of whole wheat pasta, unyeasted whole grain breads, and other partially processed whole cereal grains) prepared in a variety of ways.
- 5 to 10 percent soups (about 1 to 2 bowls per day), made with vegetables, seaweed, grains, or beans, seasoned with miso or tamari soy sauce.
- 25 to 30 percent local, organically grown vegetables, which may include a small amount of raw vegetables and pickled vegetables. The diet specifies vegetables to be eaten frequently (e.g., green cabbage, kale, broccoli, cauliflower, collards, pumpkin, watercress, Chinese cabbage, bok choy, dandelion, mustard greens, daikon greens, scallion, onion, daikon, turnips, acorn squash, butternut squash, buttercup squash, burdock, and carrots, among others), ones "for occasional use" (e.g., celery, cucumber, iceberg lettuce, mushrooms, snow peas, and string beans), and ones to be avoided (e.g., potatoes, tomatoes, eggplant, peppers, asparagus, spinach, beets, zucchini, and avocado).
- 5 to 10 percent beans of various types (e.g., azuki beans, chickpeas, lentils), bean products (e.g., tofu, tempeh, and natto), and sea vegetables (e.g., wakame, hiziki, kombu, nori, arame, agar-agar, Irish moss).
- Occasional foods 'if needed or desired' one to three times per week include a small amount of fresh whitemeat fish (e.g., flounder, haddock, herring, scrod, snapper, sole, cod, carp, halibut, or trout), locally and organically grown fruit, dried or cooked (individuals living in temperate climates are advised not to eat tropical or semitropical fruits); seeds and nuts, grain sweeteners, and vinegars.
- Non-aromatic and non-stimulating teas, such as bancha twig tea, stem tea, roasted brown rice tea, or cereal grain coffee, or plain, non-iced water.
- Foods generally avoided on a macrobiotic diet include: meat and poultry; animal fat; eggs; dairy products; refined sugars; chocolate; molasses, honey, and refined sugar; tropical or semitropical fruits; soda; artificial drinks; aromatic or stimulating tea or coffee; all artificially colored, preserved, sprayed, or chemically treated foods; all refined and polished

grains and flours; canned, frozen, and irradiated foods; hot spices; and alcohol (500,505).

Kushi recommends that people with cancer, or with a "serious precancerous condition" emphasize certain types of food in the diet for an initial period "until vitality is restored" (509). In general, foods are identified as belonging on a scale from extremely yin (alcohol, tropical fruits, and dairy products) to the center (grains, beans, vegetables, and nuts), to extremely yang (fish, cheese, poultry, meat, and eggs). Patients with a tumor type categorized as predominantly yin would be advised to avoid, e.g., fruits, while occasional small amounts of white fish, a moderately yang food, would be encouraged. Patients with a yang cancer would be advised to avoid fish altogether, at least initially, but would be encouraged to eat small amounts of dried or cooked fruits, which are thought of as moderately yin foods. Foods categorized as extremely yin (e.g., sugar) or extremely yang (e.g., red meat) are considered inadvisable on a macrobiotic diet for patients with any type of cancer (509).

Possible Adverse Effects

The issue of possible adverse effects of the macrobiotic regimen has been a longstanding controversy in the medical and macrobiotic communities. Case reports of serious nutritional deficiencies and disorders resulting from extreme use of the Zen macrobiotic diet +7 and some types of vegetarian diets not specifically associated with macrobiotics have been published in the medical literature (267,760,797,799). The relevance of those case reports to currently recommended macrobiotic practices has been greatly reduced since the introduction of the general "standard macrobiotic diet" outlined above. Partly in response to the evidence of nutritional deficiencies, however, macrobiotic instructors reportedly adjusted some of the dietary recommendations (502,550). In current macrobiotic recommendations, for instance, small amounts of whitemeat fish and seafood are allowed a few times per week, although dairy products, eggs, poultry, and red meat are generally excluded (509). Vitamin and mineral supplements are not recommended in the macrobiotic regimen.

Advocates point out that a wide range of possible combinations of particular grains, beans, vegetables, fish, and fruit exist in individual macrobiotic diets, and that the standard macrobiotic diet is lower in fat and cholesterol and higher in fiber, complex carbohydrates, vitamins A and C, and beta carotene than a typical U.S. diet (504). It is also acknowledged, however, that macrobiotic guidelines can be interpreted too narrowly, resulting in overly restrictive food choices (276), and, in some individuals, possible deficiencies of certain nutrients (550). (These possibilities are not unique to macrobiotic diets, and apply equally to other diets.)

Although vegetarian diets similar to the macrobiotic diet have been acknowledged as potentially healthful and nutritionally adequate when appropriately planned (30,83), such diets are believed to carry a risk of nutritional deficiency under certain circumstances, notably in individuals with increased nutritional requirements (e.g., infants and children, pregnant and lactating women, and the seriously ill (95)) and in cases in which the diet is unplanned, unsupervised, or followed too restrictively (83,457). Critics of macrobiotics have suggested that seriously ill cancer patients, particularly those with cachexia,[8] have special nutritional and caloric requirements that may not be met by a macrobiotic regimen and that may actually be exacerbated by it (30,53,95). Such effects have not been documented, however.

One possible adverse effect of an overly restrictive macrobiotic diet is a deficiency of vitamin B12, an essential nutrient normally supplied by meat, poultry, and other animal sources. Kushi maintains that his recommendation that a small amount of certain types of fish be included in the diet greatly reduces or eliminates this risk. In the dietary recommendations for certain tumor types (e.g., those he believes are caused by an excess consumption of animal products), fish is excluded, however, at least for an initial period in some cases (509). Kushi believes that vitamin B12 is supplied by other components of the macrobiotic diet, e.g., by sea vegetables and certain fermented foods (504). While the vitamin may be present in some sea vegetables (nori, seaweed, etc.) and in some fermented soya products (tempeh, tamari, rice miso, tofu, etc.) used in the diet, there is doubt about its availability in these foods in a form that the body can use (515).

[8]Cancer cachexia refers to general physical wasting and malnutrition often associated with advanced cancer.

Another possible adverse effect of a macrobiotic diet is a deficiency of vitamin D, which is essential for growth and development. Kushi acknowledges that an adequate supply of vitamin D might be a problem for some individuals, particularly young children, since most of the common sources of vitamin D-dairy products-are not included in the diet (924). A recent study of Dutch children fed with macrobiotic diets showed that growth curves for these children were below the Dutch standard after about 5 months of age and did not catchup later on in childhood (925). For children, Kushi advocates the addition of fish liver oils to the diet, other foods containing vitamins D and B 12, and exposure to sunlight. For adolescents and adults, he recommends adequate exposure to sunlight without supplemental vitamin D unless deficiencies develop (924). It is not yet known whether these measures, if followed, are successful in averting vitamin D deficiencies in individuals eating macrobiotically.

In its recent summary statement on macrobiotics, ACS noted that cancer patients following a macrobiotic regimen should take care to ensure adequate intakes of vitamins B 12 and D, but that with proper planning, the diet could provide sufficient nutrition (30). Another summary article also expressed concern about vitamins B 12 and D and about the adequacy of total calories and complete protein intake on the macrobiotic diet, and advised that cancer patients following Kushi's recommendations be medically supervised and monitored for potential nutritional deficiencies (95).

Claims of Effectiveness

In his book, *The Cancer Prevention Diet*, Kushi claims that macrobiotic diets have 'helped relieve' patients with a variety of tumor types, but notes that the "best responders" have been cancers of the breast, cervix, colon, pancreas, liver, bone, and skin (509). He believes that cancers of the lung, ovaries, and testes have responded poorly to the macrobiotic approach (509). Clinical data in support of these claims are not provided.

Kushi qualifies his claims of effectiveness by noting that certain conditions and personal attitudes must be present for a patient to recover while following a macrobiotic diet. These include: a spiritual awareness and an attitude of gratefulness for the illness and for the opportunity it affords to correct previous errors in diet and lifestyle; an informed and careful interpretation of the macrobiotic dietary guidelines and cooking methods; a will and determination to overcome one's illness; support of family and friends; and maintenance of one's "natural healing ability" (509).

Attempts at Evaluating Macrobiotics in Cancer Treatment

OTA reviewed the available information concerning the efficacy of macrobiotic diets in cancer treatment. This information consists of retrospective case reviews and anecdotal reports, some of which come from the popular literature, and two unpublished retrospective studies. A number of individual accounts of patients who attributed their recovery from cancer to their adherence to a macrobiotic diet have been written in recent years (73,107,483,508, 686,777,782). Although these various accounts reflect the authors' beliefs that they were helped by following a macrobiotic diet, they are nevertheless inadequate to make an objective assessment of the efficacy of the diet in treating cancer.

In an unpublished study supplied to OTA by its authors, Carter and his colleagues discuss what they describe as "two retrospective studies," one of patients with primary pancreatic cancer, the other of patients with advanced prostate cancer (171). The stated purpose of the pancreatic cancer study was "to determine whether pancreatic cancer patients who adopted the macrobiotic dietary approach survived longer than those who did not."

Patients included in the pancreatic cancer study were those who had been counseled by a particular counselor about macrobiotics during the period January 1980 through June 1984, and who (or whose next-of-kin) reported having modified their diet for at least 3 months. Of 109 patients who had been counseled during the relevant period, 36 could be reached, and of those, 23 reported having modified their diets for at least 3 months. The mean survival (the average) and median survival (the point in time after diagnosis by which half the group had died) of these 23 patients was compared with the survival times of all pancreatic cancer patients diagnosed during that same period through the National Cancer Institute's Surveillance, Epidemiology, and End

Results (SEER) program.[9] Statistical tests of significance were performed to determine whether the macrobiotic patients lived significantly longer.

The authors report that the mean survival for the 23 macrobiotic patients was 17.3 months, and for the SEER population, 6 months. Median survival was 13 months for the macrobiotic patients and 3 months for the SEER patients. They concluded from this comparison that the macrobiotic patients lived significantly longer.

Unfortunately, serious flaws in Carter's analysis make that conclusion unsupportable and misleading. A comparison such as Carter makes between the length of survival of a selected group of patients and the length of survival among a national sample of patients would not indicate whether the selected group of patients lived longer than they would have had they not followed a macrobiotic diet. The analysis overlooks the fact that treatment with a macrobiotic diet was only one of numerous known and unknown differences between the groups that could have affected survival time. It is impossible to determine by their method whether it was, in fact, the diet, or whether other treatments or the patients' characteristics or a number of other possible factors contributed to their survival with pancreatic cancer. For this reason, comparisons between the survival times are uninformative in suggesting a possible treatment effect in the selected group of patients.

In addition, the way in which survival times are determined in Carter's study skews the results in favor of an effect of macrobiotics. According to the eligibility requirements, patients following a macrobiotic regimen had to survive for at least 3 months to be included in the study in the first place. The SEER patients, with whom the macrobiotic patients were compared, included all patients from the time they were diagnosed. For pancreatic cancer patients, this is an important difference, since the SEER statistics showed that 50 percent of this national population had died by 3 months after diagnosis.

In the second study described in Carter's paper, 11 patients with prostate cancer who followed a macrobiotic regimen along with conventional treatment were examined. No information is given about the way in which they were selected for inclusion in the study. The paper states that "length of survival free-of-progression, overall median survival rates, and other characteristics of stage D2 prostate cancer patients, receiving conventional therapy and on a macrobiotic diet" were compared with stage D2 prostate cancer patients reported in the literature, and with "matched controls receiving conventional therapy and following a standard American diet." No other information is provided about these controls. The only comparison reported in the paper states that "the median survival of the macrobiotic group was 81 months, whereas those using the standard American diet had a median survival of 45 months.

It is impossible to interpret the results of the study, since details of the patients' selection factors are not reported in the manuscript. In general, however, conclusions in Carter's second study about survival time among prostate cancer patients following macrobiotic diets are subject to the same critical limitations as those in the study of pancreatic cancer patients described above. A randomized study, which could minimize differences between study and control populations, would be needed in the future to generate valid evidence on possible effects of macrobiotic diets on cancer patients' survival. Certain types of non-randomized studies could also be used to detect possible antitumor effects of the diets. (See ch. 12 for a discussion of such studies.)

In another unpublished manuscript (668), Newbold presents six case histories of patients with advanced cancer who adopted a macrobiotic diet in addition to using mainstream treatment. These cases are well described medically, including reference to appropriate diagnostic tests (all but one case was definitely biopsy-proven) and followup scans and tests.

At OTA's request, several physicians on the project Advisory Panel reviewed and commented on Newbold's cases. As was the case with the review of Kelley's cases, discussed earlier in this chapter, the reviews split along mainstream/unconventional lines. The three mainstream reviewers did not find these cases compelling, however they did not find them lacking in technical detail, as they did the Kelley cases. One reviewer suggested the need for a randomized trial of the diet before any conclusions could be drawn. He also commented that "restora-

[9] The SEER program covers about 10 percent of the U.S. population in various cities and States, and attempts to gather reports of all new cases of cancer diagnosed in those areas.

tion of harmony and balance to the lives of people with terminal illnesses and those without terminal illnesses is a reasonable goal," but he did not necessarily think that a diet could achieve this. The reasons given for skepticism about the cases were that the effects of mainstream treatment could not be ruled out as explanations for the observed effects; in one case, that there had been no scan to verify continued presence of disease before the patient adopted the macrobiotic diet; and in another case (an astrocytoma), the mainstream reviewers believed that the scans on which the reported regression rested could not have provided definitive evidence.

The two unconventional physicians were more positive about these cases. One concluded that five of the six cases (all except the one without biopsy-proven diagnosis) showed positive effects of the macrobiotic diet. The other physician found two cases that seemed "legitimate," two "highly suggestive," one 'suggestive," and one not convincing (a different one from the other physician).

If cases such as Newbold's were presented in the medical literature, it might help stimulate interest among clinical investigators in conducting controlled, prospective trials of macrobiotic regimens, which could provide valid data on effectiveness. It has also been suggested that improvements in recordkeeping and followup-e.g., monitoring compliance with dietary recommendations and health status among patients-could facilitate the funding and conduct of randomized clinical trials needed to study the efficacy of macrobiotic diets in cancer treatment (503).

Chapter 4

Herbal Treatments

CONTENTS

Chapter 4
Herbal Treatments

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 approved 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 veriscolor, 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 summarizs 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.[1] 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

[1]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 L121O 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 sigificant 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 L121O 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 NGDA 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 Brusch 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.[2] 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 apparently 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

[2]Many of these are collected by Stan Darling, Member of Parliment, 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)[3] and from the published literature (as collected by the NAPRALERT database,[4] 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-

[3]These data are unpublished, though publicly available from NCI on request.

[4]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"[5] 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).

[5]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).[6] 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.***

[6]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 vaseleline 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)*, pokeroot *(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).[7] 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***

[7]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,[9] 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.

[8]These data are unpublished, though publicly available from NCI on request.

[9]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). Pokeroot, 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' fries (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 Plenosol (208), but the oldest and most widely used is a product marketed by Weleda AG (Switzerland 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 inverventions 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 ofsummer 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.[10] 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

[10]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 (PapanicolaouIII 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 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[11] (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 aspolysaccharides (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 L121O (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[12] 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.

[11] 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.

[12] 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 products, 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), L121O 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 'he 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.*

Chapter 5

Pharmacologic and Biologic Treatments

CONTENTS

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Pharmacologic and Biologic Treatments

A large and diverse group of unconventional cancer treatments has as its central component a pharmacologic or biologic substance, including biochemical agents, vaccines, blood products, and synthetic chemicals. Some of these pharmacologic and biologic treatments are offered at single sites under the direction of a developer or other chief proponent. Others are more widely available, are not necessarily associated with particular proponents, and may be used in combination with a variety of other unconventional and conventional treatments.

Examples of unconventional pharmacologic or biologic cancer treatments associated with a single practitioner include: "Antineoplastons" offered by Stanislaw Burzynski, M.D., Ph.D., at his clinic in Houston; an autogenous vaccine developed by the late Virginia Livingston, M.D., at her clinic in San Diego; "eumetabolic" treatment offered by Hans Nieper, M.D., in Hannover, West Germany; and "biologically guided chemotherapy" practiced by Emanuel Revici, M.D., at his office in New York. Each of these treatments is discussed in detail below. Another pharmacologic treatment, "Immuno-Augmentative Therapy" offered by Lawrence Burton, Ph.D., at his clinics in the Bahamas, West Germany, and Mexico, is discussed in chapter 6.

Examples of pharmacologic approaches offered at a number of places, either singly or in combination, include laetrile, megavitamins, dimethyl sulfoxide (DMSO), cell treatment, digestive enzymes, hydrogen peroxide, ozone, and a variety of other agents. When used in various combinations and with special diets, enemas, and instructions about avoiding substances thought to be harmful, these treatments become part of a general approach often referred to as 'metabolic therapy,' a non-specific term used by many unconventional practitioners to refer to a combination of unconventional approaches aimed at improving the physical and mental condition of cancer patients (96). Many of the best known "metabolic clinics' are located in or near Tijuana, Mexico, not far from the U.S. border, e.g., Centro Medico del Mar, American Biologics, the Manner clinic, St. Judes International, and Hospital Santa Monica. Practitioners associated with these clinics include Ernesto Contreras, Robert Bradford, Jimmy Keller, and Kurt Donsbach. Some of the major components of the 'metabolic' treatments (vitamin C, laetrile, DMSO, cellular treatment, hydrogen peroxide, and ozone) are also discussed in this chapter. The treatments are presented in alphabetical order according to the name of the main practitioner or the substance used.

STANISLAW BURZYNSKI: ANTINEOPLASTONS

In *the late 1960s, Stanislaw R. Burzynski, M.D., proposed that a naturally occurring and continuously functioning biochemical system in the body, distinct from the immune system, could "correct" cancer cells by means of 'special chemicals that reprogram misdirected cells. He called these chemicals 'Antineoplastons, and defined them as naturally occurring peptides[1] and amino acid derivatives that inhibit the growth of malignant cells while leaving normal cells unaffected (124,133). Burzynski developed a treatment regimen for cancer based on the administration of various types of Antineoplastons, which he originally isolated from urine and subsequently synthesized in the laboratory. He currently treats patients with Antineoplastons at his clinic and research facility in Texas.*

Burzynski received his M.D. in 1967 and his Ph.D. in biochemistry the following year, both from the Medical Academy of Lublin in Poland. He moved to the United States in 1970, and obtained a license to practice medicine in Texas in 1973. From 1970 until 1977, he held the positions of research associate and assistant professor at the Baylor College of Medicine in Houston. In 1977, he left Baylor to establish his own research institute. He is now president of the Burzynski Research Institute in Stafford, Texas, where he and his colleagues conduct in vitro and animal research on Antineoplastons. Burzynski's clinical practice focuses on treatment of cancer patients with Antineoplastons, which he administers at his outpatient clinic in Houston. His current regimen for cancer patients includes oral and intravenous use of approximately 10 types of

[1]Peptides are a broad category of molecules, including many biologically active proteins, that are made Up of combinations of amino acids.

Antineoplastons, all of which are manufactured at the Burzynski Research Institute.

From 1974 to 1976, Burzynski received funding from the National Cancer Institute (NCI) for research involving gel filtration techniques to isolate peptides from urine and for testing their ability to inhibit in vitro growth of several types of cultured human cells (142). In 1976, Burzynski applied unsuccessfully for renewal of this grant, although he did receive supplemental finding until July 1977 (245). In 1983, he applied to the Food and Drug Administration (FDA) for an Investigational New Drug exemption (IND), which would allow him to use Antineoplastons in human studies designed to determine the efficacy and safety of Antineoplastons. That application was put on "clinical hold," the action taken by the FDA in cases where data submitted are insufficient to just@ the investigational use of a substance in cancer patients. In March 1989 the clinical hold was removed for one study, allowing a study of the oral form of Antineoplaston A10 in a small number of women with advanced, refractory, breast cancer (125). That study, which was planned to be conducted at a U.S. medical center, was later "delayed," according to a public notice from Burzynski's staff, "due to the high cost' ' of conducting clinical trials in the United States (858). To date, no form of Antineoplaston has received FDA approval for use on patients outside of that specific study.

Burzynski first isolated Antineoplastons from blood and then the urine of individuals without cancer.[2] He reportedly obtained dozens of fractions (128), each containing many different Antineoplastons (133). Burzynski and other researchers reported testing each fraction for anticancer activity in cultured human cells and then for toxicity in animals. His first fraction, Antineoplaston A, which he used to treat 21 cancer patients at a hospital in Houston (143), was later subdivided into fractions A1, A2, A3, A4, and A5 (132,133). Fraction A2 was reported to contain an "active' ingredient which was named Antineoplaston A10; Burzynski identified the chemical structure of A10 as 3-phenylacetylarnino-2,6-piperidinedione (131). In addition to using it to treat patients, Burzynski supplies this product to the Sigma Chemical Co., which offers it for sale through its catalogue for research purposes. Two degradation products of Antineoplaston A10, identified as Antineoplastons AS2-1 and AS2-5 (130), have also been administered to cancer patients (see discussion below).

Burzynski believes that a variety of Antineoplastons are present naturally in the tissue and body fluids of healthy people, but that, possibly as a consequence of cachexia (a metabolic process that results in physical wasting), cancer patients excrete excessive amounts in the urine, leaving them with low circulating levels. He states that treatment with Antineoplastons reduces the amount of endogenous Antineoplastons excreted, and that excretion of Antineoplastons decreases with tumor regression (133). Burzynski hypothesizes that Antineoplastons may act by interfering with the action of certain enzyme complexes (methylation complex isozymes) that allow malignant cells to gain a growth advantage over normal cells (546). He has also suggested that Antineoplastons may interact directly with DNA (524).

Burzynski believes that Antineoplastons represent a "completely new class of compounds' (516). It is unclear whether or how Burzynski's Antineoplastons relate to a variety of known growth factors and inhibitors that are the focus of considerable mainstream research in biochemistry and oncology. Burzynski's theory of a biochemical antitumor surveillance system in the body mediated by endogenous Antineoplastons has not been recognized in the broader U.S. scientific community. However, Burzynski has recently supplied some scientists with Antineoplastons which they are testing for biochemical and physiologic properties, particularly antitumor activity, in cultured tumor cells and in animal tumor models (see discussion below).

Burzynski's Treatment Regimen

At present, oral and intravenous forms of 10 types of Antineoplaston are made by the Burzynski Research Institute; most patients reportedly take the oral form (124). Treatment starts with small doses and increases gradually until Burzynski determines that an optimal level has been reached. In some cases, Burzynski also prescribes low-dose chemotherapy (124) and a variety of common prescription drugs (134,136,138). Burzynski claims that following initial treatment with Antineoplastons, some patients produce sufficient quantities of endogenous Antineoplastons and no longer need treatment, while

[2]Burzynski developed the laboratory methodology to make at least one type of Antineoplaston (A10) synthetically.

others continue taking oral doses of Antineoplastons to "guard against future recurrence of cancer" (124).

The patient brochure from the Burzynski Research Institute states that the treatment is "nontoxic" (124), but that a "small percentage of patients had some adverse reaction sometime during the course of treatment. " Side-effects cited include "excessive gas in the stomach, slight skin rash, slightly increased blood pressure, chills and fever" (124).

There are no reports of adverse effects from Burzynski's treatment in the published literature. One unpublished report based on a site visit to the Burzynski Research Institute noted two patients who developed sepsis after treatment, one of whom died, although it did not include information confirming the association between the patients' death and Burzynski's treatment. The authors of that report noted that one possible route of infection is through intravenous injections into an indwelling subclavian catheter; infections of the indwelling lines would be likely if aseptic technique is not followed; this is more likely if the patient is not thoroughly instructed in the techniques of aseptic injection (79). Walde, who visited Burzynski's facilities in 1982, also noted this risk of catheter sepsis and air emboli resulting from patients administering their own intravenous doses through indwelling subclavian catheters, but concluded that "the number of complications that [Burzynski and his associates] have been aware of, or have been notified of, have been extremely low" (933).

Claims

While treatment success rates are not specifically cited in the Burzynski Research Institute patient brochure, such rates are widely quoted in the popular literature. An article in *Macleans* magazine, for example, credits Burzynski with a 46 percent rate of "total remission for cancer of the colon" from the use of one type of Antineoplaston. That article also reports that Burzynski has had the most success with cancers of the bladder, breast, prostate, and bone (291). A recent newspaper article quotes a spokeswoman for the Burzynski clinic as saying that "preliminary studies show that 80 percent of tumor patients respond positively to the treatment" (721).

Burzynski does claim that the 'majority of cancer patients treated at [the Burzynski Research] Institute showed positive response to treatment" (124). His patient brochure states that Antineoplaston treatment makes it "possible to obtain complete remission of certain types of cancer' and that "the number of patients who are free of cancer over five years as the result of Antineoplaston therapy is steadily increasing" (124). In addition to their postulated therapeutic role, Antineoplastons are claimed to be useful in diagnosing cancer. Burzynski believes that measuring the levels of naturally circulating Antineoplastons in blood and urine "may help to identify individuals who are more susceptible to the development of cancer or to diagnose the cancer at the early stages" (129,133).

These claims are based on a number of recent clinical studies in which Burzynski reported favorable clinical outcomes, including complete remissions, partial remissions, and stabilization of disease, in patients with various types of advanced cancer, following injection of Antineoplaston A2 (137), A3 (140), A5 (141), A 10 (138), AS2-1 (136), and AS2-5 (134). Burzynski reported that three of these Antineoplastons (A3, A5, and A10) will be studied in phase II trials.

Burzynski occasionally publicizes his treatment via press releases. In a recent statement, for example, it was announced that "dramatically improved results in the treatment of prostate cancer due to a recent discovery made within the past year' had been obtained through Burzynski's administration of Antineoplastons given orally. It noted that "with this route of administration, some prostate cancer patients, even those whose cancer failed to respond to conventional therapy, have experienced a complete remission of their cancer in as little time as five months" (126). In that press release and another one (127), it was claimed that Burzynski's methods "may also be effective in diagnosing and preventing some types of cancer," citing results from experimental animal studies conducted at the Burzynski Research Institute and at the University of Kurume, Japan.

Published Clinical Studies

Burzynski and his colleagues at the Burzynski Research Institute have a long list of published papers and presentations at meetings in which they report on animal and biochemical studies of Antine-

oplastons, as well as on studies of their use in cancer patients. Most of Burzynski's recent clinical papers (studies of the effects of Antineoplastons on cancer patients, as opposed to laboratory research) appear in supplements to the journal *Drugs Under Experimental and Clinical Research,* ***one in 1986 and one in 1987. These supplements were devoted entirely to Antineoplastons and all publication and printing charges for these supplements were borne by Burzynski (840).***[3]

Burzynski's list of publications (124) includes a number of "phase I clinical studies," along with several other types of study that also include clinical outcome data, such as "initial clinical studies," and "toxicology studies." Many of these studies are listed as presentations made at conferences outside the United States; these reports are not readily available in the open literature. Many of the published studies appear in the *Drugs Under Experimental and Clinical Research* ***supplements, one appears in a journal or a book cited as*** *Advances in Experimental and Clinical Chemotherapy* ***(which is not listed at the National Library of Medicine), and one appears in a book, which presents the same data as a paper in one of the supplements.***

Despite the fact that these are reported as early stage studies, which in mainstream research would concentrate on toxicology (i.e., safety more than efficacy), they also report on clinical outcomes, including partial and complete remissions. Burzynski's reputation for success rests at least in part on these reports. OTA's concern with these studies is that, among other problems, Burzynski's definition of a remission, while not stated in any of the papers, appears to be discrepant from the generally accepted definition,[4] making the results difficult if not impossible to understand. Three papers from the 1987 *Drugs Under Experimental and Clinical Research* ***supplement are representative ('Initial clinical study with Antineoplaston A2 injections in cancer patients with five years' follow-up" (139), 'Phase I clinical studies of Antineoplaston A3 injections" (140), and "Phase I clinical studies of Antineoplaston A5 injections' (140)). These are discussed below.***

These three papers have similar formats and have a similar level of detail, so some general observations can be made about them. First, the reports raise a question about whether these studies were actually planned prospectively, with protocols including patient selection criteria, specific recordkeeping requirements, etc. (a "clinical trial"), or whether they represent groups of patients studied retrospectively. Details concerning a protocol, which would be expected in reporting a clinical trial, are generally lacking. In addition, there is little systematic information about patients' treatment prior to Antineoplastons, except in specific cases, some of which are discussed below. A table with certain information about each individual patient (diagnosis, age, sex, length of Antineoplaston treatment, highest dosage, adverse reactions, desirable side-effects, and anticancer effect) is included in each of these papers.

A particular difficulty with these papers is that some important terms--e.g., "completer regression" and 'partial regression,' terms used to describe the effectiveness of Antineoplastons in these papers—are not used in accordance with their generally-accepted definitions. In the first Burzynski study cited above, six "complete remissions' were reported among 15 patients described as having "advanced neoplastic disease. " Three of these six patients were reported to have non-metastatic transitional cell carcinoma of the bladder, grade II, which would not be described as "advanced" by mainstream definitions. These three patients are described in some detail. Two of them reportedly had no measurable malignant disease when they began Antineoplaston treatment. According to the article:

> ***Patient D.D., diagnosed with transitional cell carcinoma of the bladder, Grade II, had seven transurethral resections of the tumours and six recurrences in 16 months preceding the treatment with Antineoplaston A2. Her treatment began shortly after the last transurethral resection, therefore she did not have measurable tumour at that time. The patient was incomplete remission and free from recurrences for two years and six weeks as the result of treatment with Antineoplaston A2 intravenous injections. She developed recurrence one year and two months after discontinuation of Antineoplaston A2 injections.***

[3]Though most medical journals do not charge authors for publishing papers, it is not uncommon for authors to pay a fee for publication and printing.

[4]In conventional terminology, regressions may occur in patients who initially have "measurable disease," which means that tumors that can either be felt during physical examination or can be seen clearly on some type of diagnostic film or scan, and which can be measured in at least two dimensions. A complete regression is said to occur when the disease measured can no longer be found at all. Partial regression describes the condition where the measurable tumor is reduced by at least 50 percent in size.

> Patient J.J. . . . underwent transurethral resection of the tumour shortly before the beginning of the treatment with Antineoplaston A2 injections. He was found to have no recurrence after 56 days of treatment and decided to discontinue the therapy at that time. Five months later, he developed recurrence and underwent transurethral resection of the tumour and instillation of Thiotepa. The patient was disease-free for over five years.

Neither of these patients had measurable malignant disease when treatment began and both had recurrences after treatment. Patient J.J. had curative conventional surgery and chemotherapy as treatment for the recurrence. Burzynski counts both of these patients as complete remissions, and J.J. as a five-year survivor, as a result of Antineoplaston treatment. However, the evidence presented does not substantiate the claimed benefit to either patient from the treatment.

In the second paper, another patientin"complete remission' is described as having "adenocarcinoma of the colon, status post resection,' meaning that the tumor had been removed surgically before the patient started treatment with Antineoplastons:

> The patient . . . maintained complete remission during the treatment with Antineoplaston A3 . . . After discontinuation of this form of treatment he developed recurrence with liver metastasis, which responded to treatment with different formulations of Antineoplastons and 5-fluorouracil. This patient is alive, well and free from cancer over six years after his participation in Phase I studies with Antineoplaston A3.

This patient evidently had no measurable disease when Antineoplaston A3 treatment started, but reportedly had a "recurrence," was treated with conventional chemotherapy plus Antineoplastons, and then was reported free of cancer. There is no evidence that this patient was helped by Antineoplastons, and the case does not describe a "complete remission' attributable to that treatment.

Another unusual feature of these studies is the section describing increases in platelet and white blood cell counts as "desirable side-effects." In each case, the post-treatment levels are not just increased, but are abnormally high. In the case of platelet counts, levels are high enough (ranging from about 500,000 to 3.4 million) to lead to possible blood clotting. The authors do not explain why these effects should be considered desirable; physicians would usually consider these levels as indicators of underlying disease or as risks for serious medical complications.

Attempts at Evaluating Antineoplastons

In 1983 and 1985, at the request of the Canadian Bureau of Human Prescription Drugs, NCI tested three of Burzynski's Antineoplastons for antitumor effects in the mouse P388 Leukemia assay, a test that NCI used routinely as a prescreen for antitumor activity until 1985 (2,602) (see ch. 12 for details). No antitumor activity (as measured by a statistical increase in survival) was found for Antineoplastons A2 and A5. Both showed toxicity at the highest dose given, while at lower doses, neither antitumor effect nor toxicity was found. Both Antineoplastons were found inactive over wide dose ranges (602). Antineoplaston A 10 was also tested in a range of concentrations in this mouse system, and the results indicated that there was no increase in survival at any concentration and there was toxicity at the higher dose levels (360).

More recently, Antineoplaston A10 has been studied in several experimental animal tumor systems. Researchers at the Medical College of Georgia reported on results indicating that oral Antineoplaston A10 delayed the development of viral-induced mammary tumors in C3H+ mice and inhibited the growth of carcinogen-induced mammary tumors in Sprague-Dawley rats (393). Eriguchi and colleagues at Kurume University, Japan, presented results suggesting antitumor effects of Antineoplaston A10 on the development of urethane-induced pulmonary adenomas in A/WySnJ mice (275). A second group at Kurume University reported that Antineoplaston A10 reduced the growth of human breast cancer cells in athymic mice (385). Recent experiments using human and mouse tumor cell lines were summarized in an abstract written by researchers at the Uniformed Services University of the Health Sciences, Maryland. It was noted that Antineoplaston AS2-1 promoted cell differentiation in human promyelocytic leukemia HL-60 cells grown in culture and suppressed some of the neoplastic properties of mouse fibrosarcoma V7T cells in culture (775).

A 1981 television news report ("20/20") on Burzynski's cancer treatment, followed by numerous inquiries from patients about the treatment, reportedly prompted David Walde, a physician practicing in Ontario, to visit Burzynski's facilities

in April 1982. In his written report (933), which he sent unsolicited to Health and Welfare Canada and to NCI, Walde described Burzynski's clinical and research facilities and summarized the treatment regimen. He reportedly also reviewed about 60 patient records, but did not report on them in detail. He concluded that there was sufficient information about Burzynski's treatment to warrant evaluating "then nature and action of [Antineoplastons]. . . even if these eventually do not result in any major therapeutic advances" and recommended that Burzynski apply for investigatory new drug clearance in Canada so that Walde could coordinate clinical studies with Canadian health officials. He also suggested that outside funding sources be sought to support clinical studies, and advised against 'sensationalism through the public media, ' to avoid disruption to ongoing and future clinical studies.

In November 1982, consultants to the Ontario (Canada) Ministry of Health visited Burzynski's clinical and research facilities in Houston for the purpose of providing information to the Ministry of Health about the treatment because some Ontario residents had sought reimbursement under the Ontario Health Insurance Plan (79). After reviewing Burzynski's published papers and viewing the clinic and laboratories, the consultants, Martin Blackstein and Daniel Bergsagel, asked Burzynski to select examples of patients who he believed had had a good response to Antineoplaston treatment. They specified that each case had to satisfy the following conditions to be considered: 1) proven histologic diagnosis of cancer; 2) complete record of all cancer treatment before Antineoplastons (some of which might be responsible for a delayed response); 3) complete record of additional treatment; and 4) original X-rays, CT, or isotope scans used to document a response.

Burzynski presented them with about 12 cases at the clinic, and sent them additional cases afterward. According to the report, there were original X-rays for only one case; for two others, selected CT scans were available. The case with X-ray evidence was a patient with metastatic nodules in the lung from a colon cancer, which, from his history, appeared to be a slowly progressing disease. The consultants concluded that the X-rays showed no documentable change, though there were difficulties in interpretation because the films were reportedly taken on different machines with different magnifications. They also concluded that the two patients for whom some CT scans were available showed no definite response to Antineoplaston treatment. In those cases, they believed that the views on the scans were not the same, making direct comparison impossible.

In other cases, the consultants reported that Burzynski's patients had had effective treatment for treatable cancers before starting Antineoplaston treatment, and they described two specific examples. The first was a woman who had had radiation treatment for stage III cervical cancer, and had gone to Burzynski when there was still necrotic tumor in the cervix; a cytologist was unsure whether any viable cancer cells remained, but noted extensive radiation changes. The turner gradually disappeared, which the consultants felt could be attributed to the prior radiation, rather than to Antineoplastons. The other patient had prostatic cancer with bone metastases who had had an orchiectomy 3 months before beginning Antineoplastons. His bone scans improved, which the consultants attributed to the delayed effects of the orchiectomy, which commonly takes months for full effects to become evident.

On the basis of the cases they reviewed, Blackstein and Bersagel reported that they found no examples of objective response to Antineoplastons. In addition to reviewing the cases, they asked about four patients reported by Burzynski in 1977 to have had complete remissions with treatment. According to the report, three of those patients had progressed fairly rapidly and died. The fourth patient was still alive at the time of the review (1982), but the consultants felt his disease (a solitary bladder tumor) had been removed during the biopsy. In conclusion, Blackstein and Bersagel's report recommended that the Ontario Health Insurance Plan not cover the cost of Antineoplaston treatment for Ontario residents.

Burzynski wrote a detailed rebuttal (135) to their report, charging that Blackstein and Bersagel "completely distorted the research, production, and clinical data presented to them. " He disagreed with each individual assessment, concluding:

> *Out of the initial nine cases presented in the clinic, six patients obtained complete remission and two remaining patients were very close to complete remission. Only one patient was treated with radiation and chemotherapy and one additional patient* received a very small dose of palliative radiotherapy before coming for the treatment with antineoplas-

tons. Two patients died from causes unrelated to cancer like multiple emboli in the lungs and perforation of the stomach ulcer. (135)

Burzynski contested the report's judgments on the quality and content of the clinical data. He cited clinical records (photocopies of which he included) to show that each case was confirmed by biopsy and that "the remission of each of them was confined by at least one other doctor not associated with our clinic. "

In 1985, in a separate and more limited effort to gather information about Burzynski's treatment, the Canadian Bureau of Prescription Drugs reportedly contacted 25 physicians with patients who had visited Burzynski's clinic in Houston for treatment with Antineoplastons. According to a memo summarizing the effort (829), information on clinical outcomes in 36 patients from five provinces reportedly consisted of tumor type and clinical status as reported by telephone from the physicians (actual records were apparently not obtained). Of the 36 patients noted by the physicians, 32 had died with "no benefit" from the treatment, one had died after having a "slight regression for two months," one died after having been stable for a year, followed by progression of disease, and two were alive at the time of the survey. Of the two who were alive, one had metastatic lung cancer and the other had cervical cancer, and both had received radiotherapy prior to Antineoplaston treatment. The memo does not indicate the existence of more detailed data on the clinical course of these patients (including time between treatment and outcome recorded) or the basis for selecting the 25 physicians for the survey. OTA's requests to the Canadian Bureau of Prescription Drugs for further information about this survey have been denied. It is not possible to draw conclusions about efficacy or safety of Antineoplaston treatment from this limited information, since it was a retrospective analysis of self-selected patients and there may have been bias toward reporting poor outcomes.

Despite a substantial number of preliminary clinical studies presented by Burzynski and his associates describing outcomes among the patients he treated with Antineoplastons, and an attempt at a "best case" review, there is still a lack of valid information to judge whether this treatment is likely to be beneficial to cancer patients. Thus far, prospective, controlled clinical studies of Antineoplastons, which could yield valid information on efficacy, have not been conducted.

CELLULAR TREATMENT

Cellular treatment refers to a group of related procedures that may be referred to as "live cell therapy,' "cellular therapy," "cellular suspensions, " "glandular therapy," or "fresh cell therapy." In general, cellular treatment involves injections or ingestion of processed tissue obtained from animal embryos or fetuses. It was developed in Switzerland in the early 1930s by Paul Niehans, M.D., and became widely known when various public figures received the treatment and claimed it restored their youth or extended their lives (26). One of Neihans' colleagues, Wolfram Kuhnau, M.D., introduced the treatment in Tijuana in the late 1970s (238,490). Currently, at least 5 Tijuana clinics offer cellular treatment as a component of "metabolic therapy" (289,968). To OTA's knowledge, cellular treatment is not widely practiced in the United States, although no Federal or State law prohibits physicians from preparing his or her own cellular treatments for patients. FDA has issued an import alert concerning the detention of shipments of foreign cellular treatment products to the United States (887).

Cellular treatment uses a variety of materials, including whole fetal animal cells (derived, e.g., from sheep, cows, and recently also sharks (491)) and cell extracts from juvenile or adult animal tissue. The organs and glands used in cell treatment include brain, pituitary, thyroid, adrenals, thymus, liver, kidney, pancreas, spleen, heart, ovary, testis, and parotid (261). Several different types of cell can be given simultaneously-some practitioners routinely give up to 20 or more at once (489).

A number of different processes are used to prepare cells for use. One form of the treatment involves the injection into the buttocks of fleshly removed fetal animal tissue, which has been processed and suspended in an isotonic salt solution. The preparation of fresh cells then maybe either injected immediately into the patient, or preserved by being lyophilized (freeze-dried) or frozen in liquid nitrogen before being injected. In the latter process, the preserved cells can be tested for pathogens, such as bacteria, viruses, or parasites, before use. Fresh cells, in contrast, are used before such testing can be performed. Other types of cellular treatment may use

dehydrated concentrates in tablet or capsule form taken orally.

The types of cell given are reported to correspond in some way with the organ or tissue in the patient that is diseased or malfunctioning ("like cells help like cells" (261)). Proponents claim that the injected cells "travel to the similar organ from which they were taken to revitalize and stimulate that organ's function," an effect which is said to have been "validated by scientifically controlled laboratory and clinical experiments' (322).

Proponents of cellular treatment believe that embryonic and fetal animal tissue contains active therapeutic agents distinct from vitamins, minerals, hormones, or enzymes, and "the fact that these active agents have not yet been identified seems of little consequence" (261). Kuhnau claims that cellular treatment "stimulate[s] weak organ function and regenerates] its cellular structure" (489). Proponents claim that cellular treatment is accepted by the body because "embryonic cells from unborn animals. . . are immunologically inactive and hence not recognized as 'nonself' by the patient's immune system' (238). It is stated that the cellular treatment using cells from endocrine organs "harmonize hormones . . . [and] balance the intricate hormone-producing and feedback mechanisms of the endocrine system" (238). Cellular treatment is also claimed to stimulate the immune system.

Although cancer is not one of the primary conditions for which cellular treatment is promoted, cellular treatment is included in the array of treatments offered to cancer patients at "metabolic" clinics in Tijuana (490). Positive results following cellular treatment have been claimed for a wide variety of genetic, necrologic, and multifactorial conditions, including Down syndrome, Klinefelter's syndrome, Alzheimer's disease, Parkinson's disease, epilepsy, multiple sclerosis, lupus, arthritis, muscular dystrophy, and infertility (238). At one Tijuana clinic where cancer patients reportedly make up 70 percent of the caseload, cellular treatment, using umbilical cord tissue in particular, is "increasingly being given in cancer therapy" at a frequency per patient of several "rounds" per year (238).

Kuhnau claims that "in the hands of a physician trained in this form of therapy, the proper selection of cells and their appropriate administration provides a well-tolerated treatment which is virtually free of side effects" (489). He claims never to have seen a fatality or toxic reaction to the material (238).

A number of adverse effects could, however, be associated with cellular treatment. Allergic reactions to calf thymus tissue derived from 5-day-old animals were noted in patients with histiocytosis-X, a heterogeneous group of rare disorders, and cellular treatment was stopped in these patients (698). A recent report in the British Medical Journal *described a case of a 79-year-old man who developed antibodies against human skin antigens and signs of an autoimmune skin disease following injections of extracts of human placental tissue (778). Cellular treatment also poses a risk of transmitting bacterial or viral infections, such as brucellosis (a generalized infection characterized by fever, sweating, and pain in the joints) or encephalomyelitis (a viral infection characterized by inflammation of the brain and spinal cord), from donor animals to recipient patients, as noted in a 1984 FDA "talk paper" (885).*

A number of serious immunological reactions to cellular treatment in West Germany were noted in a recent report in Lancet *(514). In one example cited, a woman athlete reportedly received several hundred injections of cellular therapy and subsequently went into fatal anaphylactic Shock.[5] Other adverse effects were also noted in that report, including immune vasculitis, encephalitis, and polyradiculitis following cellular treatment, and a delayed effect of chronic progressive neurological disease with perineural inflammation and demyelination. A 1957 survey of 179 West German hospitals reportedly revealed 80 cases of serious immunological reactions, 30 of them fatal, in cellular treatment recipients. On the basis of these findings, the West German Federal Health Office suspended the product licenses of a number of commercial cellular preparations (including lyophilized or freeze-dried whole-cell preparations and cell extracts), and "strongly recommended" that the use of fresh cell preparations, which are made in the clinics themselves and do not come under pharmaceutical regulations, also be stopped.*

[5]Anaphylaxis is an immediate, exaggerated immunologic (allergic) reaction to a foreign protein to which the body has become hypersensitized as a result of past exposure. Anaphylaxis is frequently treatable with appropriate medical care, but in the absence of treatment, it can be fatal.

DIMETHYL SULFOXIDE (DMSO)

Dimethyl sulfoxide (DMSO) is a commonly available product with a wide variety of non-medical uses. In industry, it has been used as a chemical solvent. In laboratory research, it is often used as a cryopreservative for cultured cells. One of the properties of DMSO is that it is absorbed very rapidly through the skin and cell membranes, carrying along almost anything else (particularly low molecular weight molecules) dissolved in it that would not otherwise be able to cross those barriers. Intravenous and oral administration of DMSO allow it to penetrate rapidly into vascular and non-vascular tissues in the body (854). Its popular use among athletes, people with arthritis, and others have stemmed from claims that topical DMSO reduces pain, decreases swelling, and promotes healing of injured tissue. The FDA approved the use of bladder instillations of a 50 percent solution of DMSO (sold under the trade name "Rimso-50") to relieve symptoms of interstitial cystitis, a painful chronic bladder disorder (884). At present, "Rimso-50" is still the only DMSO product approved by FDA for use in humans. DMSO available in health food stores or by mail order is an industrial form of the chemical, consisting of about 99 percent DMSO, and is not labeled for human use (45).

DMSO is commonly used in unconventional cancer treatments, particularly in 'metabolic' treatments, such as those offered at several clinics in Tijuana and in the United States (e.g., at a hospital in Zion, Illinois and at clinics in Nevada, Pennsylvania, and California (289)). DMSO is often combined with laetrile and vitamin C, among other substances, and administered to patients intravenously. For example, the "Manner Cocktail," consisting of 10cc of DMSO, 25 grams of vitamin C, and 9 grams of laetrile dissolved in a 250cc bag of a 5 percent dextrose solution (574), is used to treat cancer patients at the Manner Clinic in Tijuana.

DMSO has been studied in mainstream research for a variety of possible therapeutic uses. As a possible cytotoxic agent, DMSO has been studied in human tumor cell lines and in human tumor model systems in animals, and in each case, DMSO demonstrated no activity (243). As a possible tumor differentiating agent (942) (a substance that stimulates tumor cells to undergo development to mature, benign cells (827)), DMSO was found to be active in mouse and human leukemic cell cultures and in human solid tumor cell cultures (243,827), but it did not improve survival in animals implanted with human tumor cells (243); this lack of an effect in vivo is the basis for NCI classifying DMSO as a relatively weak differentiating agent, compared to other available agents (243).

As a potential enhancer of the activity of known cytotoxic agents, DMSO was found to increase the activity of some of these agents in tumor-bearing rats (854). DMSO has been tested experimentally for antitumor effects, both in various tissue culture and in animal systems, and was found to be inactive. In a clinical study using DMSO in combination with the chemotherapeutic agent cyclophosphamide in patients with squamous cell carcinoma of the lung, DMSO did not enhance the effect of cyclophosphamide (319).

One of the most widely available sources of information about the use of DMSO in unconventional cancer treatments is the booklet found in many health food stores, Dr. Donsbach Tells You What You Always Wanted to Know About DMS0 (263). In this booklet, it is claimed that "while DMSO has not brought 'cure' for health problems, it has been and is now the source of comfort for millions of medical consumers." Donsbach states that DMSO acts by making cancer cells "behave more normally by bringing about a mitotic turnabout." He proposes its use as a treatment to relieve pain, to slow the growth of bacteria, viruses, and fungi, to control inflammation and swelling, to relieve burns and sprains, and to relieve the symptoms of arthritis, herpes, tuberculosis, sinusitis, and cancer. Another source in the popular literature discusses the use of DMSO in combination with conventional chemotherapeutic drugs (593).

Mildred Miller, an advocate of DMSO use in cancer treatment (616), claims that intravenous DMSO "dissolves the protein shell surrounding the cancer cells and begins to restore the abnormal cell to normalcy" (615) and that it "stimulate[s] the body's own immune system, as well as altering the cancer cell, causing it to become mature or burn out" (617). Miller is associated with a clinic in Las Vegas that uses DMSO as one of its main components of cancer treatment.

Topical application of DMSO has been associated with redness, itching, and inflammation of the skin and a garlic-like taste and odor on the breath. Intravenous administration of DMSO has been

reported to cause transient hemolysls (breakdown of red blood cells), resulting in urinary excretion of hemoglobin (45,983). Several additional adverse effects of DMSO are mentioned in the Donsbach booklet (263), including "possible damaging effects to the liver, the kidneys, bloodforming organs, and the central nervous system"; and "headache, dizziness, nausea, and sedation. "

Toxic effects to the lens of the eye were reported in studies involving the use of DMSO in dogs, rabbits, and pigs, although no such effects have been noted in studies with human subjects (45). The safety of prolonged use of DMSO in humans has not been established.

HYDRAZINE SULFATE

In the mid- 1970s, one of the commonly discussed unconventional cancer treatments was hydrazine sulfate (646,682), a chemical agent proposed to treat cancer cachexia, the progressive weight loss and debilitation characteristic of advanced cancer. On the basis of animal data and preliminary human studies conducted in the United States and the Soviet Union (described below), hydrazine sulfate was also claimed to cause tumor regression and subjective improvement in cancer patients. According to one observer (743), hydrazine sulfate was publicized in the news media as a "dramatic breakthrough—bringing people back from the dead." The American Cancer Society (ACS) published its first 'Unproven Methods" statement on hydrazine sulfate in 1976 (24). In 1979, however, it was taken off the ACS list of unproven methods, following the initiation of clinical trials under a new IND exemption (90), although this change was not publicly made until 1982, when the next revised list was published.

While hydrazine sulfate has, in the last few years, been studied by some mainstream researchers, it is still considered an unconventional treatment. Articles in the popular literature continue to highlight controversial issues in hydrazine sulfate's development (416,549,647). Proponents argue that the primary emphasis on treating cachexia, rather than the tumor itself, resulted in hydrazine sulfate being not only ignored but maligned by conventional medicine. In a 1988 interview with a *Washington Post* reporter, the former director of NCI, Vincent DeVita, Jr., reinforced this view of why hydrazine sulfate was not received more enthusiastically by the oncologic community:

> You have to distinguish between good ideas and bad ideas and ho-hum ideas. And hydrazine, I think, is a ho--hum idea. The key thing is not to prevent people from losing weight while they die; the key thing is to get rid of their cancer, and that was always the issue. The trouble was nobody saw the value of pumping a lot of resources into a therapy that gave you plumper people by the time they died (767).

The initial proponent of hydrazine sulfate was Joseph Gold, M.D., director of the Syracuse Cancer Research Institute in New York. Gold proposed a biochemical mechanism for primary tumor growth and progression and for the development of cachexia (345). He hypothesized that cancer cachexia results from a systematic energy-losing cycle involving glycolysis in tumor cells and gluconeogenesis in the liver and kidney, and proposed that an interruption in this metabolic circuit could result in clinical improvement (347). After considering a number of possible agents capable of interfering with the process, Gold settled on hydrazine sulfate as a likely inhibitor of a key enzyme in the process (348,350).

In 1973, Gold reported on results of experimental animal tests indicating that hydrazine sulfate inhibited the growth of various rodent tumors and potentiated antitumor action of some chemotherapeutic drugs (346). Several groups, including investigators at Calbiochem (a pharmaceutical company), Memorial Sloan-Kettering Cancer Center, and the Medical College of Virginia, obtained IND exemptions to study the efficacy and safety of hydrazine sulfate in cancer patients. Positive publicity about hydrazine sulfate at a 1974 meeting of the National Health Federation, an advocacy group for unconventional treatment, led the public to request hydrazine sulfate directly from the company. The FDA later stopped the company from selling it to patients and withdrew all INDs on the agent.

In 1975, Gold reported results of the descriptive study of hydrazine sulfate conducted under Calbiochem's IND (349). Using reports from physicians whose advanced cancer patients were taking hydrazine sulfate, Gold noted several cases of tumor regression and subjective improvement, and some adverse effects, such as numbness in the extremities and transient nausea. An uncontrolled study conducted in the Soviet Union also reported tumor regression and subjective improvement among patients taking hydrazine sulfate (794). This latter study was followed up with a larger descriptive study in the Soviet Union that reported some cases

of partial regression, stabilization, and subjective improvement (324). In contrast, 3 small, uncontrolled clinical studies found no evidence of tumor regression among advanced cancer patients taking hydrazine sulfate (527,690,828).

More recent clinical studies of hydrazine sulfate have examined effects other than antitumor responses. Rowan Chlebowski, M. D., Ph. D., and his colleagues at the University of California at Los Angeles (UCLA) have examined the effect of hydrazine sulfate on metabolism and weight loss in cancer patients. In 1984 and 1987 papers describing biochemical studies, Chlebowski reported that hydrazine sulfate is metabolically active, improves abnormal glucose tolerance, and reduces the increased glucose production rates seen in cancer patients with weight loss (187,849). These studies did not examine clinical outcomes in patients given hydrazine sulfate.

In a separate study, Chlebowski and colleagues examined the effects of a 30-day hydrazine sulfate treatment regimen on weight, appetite, and caloric intake in cancer patients (185). The study was not designed to measure changes in tumor growth, since indicators of measurable disease were not required of patients entering the study, and concurrent chemotherapy was permitted. Sixty-one of the patients entered into the study were randomized to hydrazine sulfate or placebo; 40 additional patients were assigned hydrazine sulfate and included in the study results. Approximately half of the patients were evaluable after 30 days, which greatly reduced the actual size of the study. Unfortunately, results from the randomized and nonrandomized groups were combined, and the report does not state how many patients from the randomized group were in the evaluable group included in the results. Reporting only in percentages, the authors stated that a higher percentage of the patients on hydrazine sulfate maintained or increased their weight, improved their appetite, and increased their caloric intake, suggesting a beneficial effect on these clinical measures. However, valid judgments about such differences could be drawn only from the randomized data, which were not presented apart from data on the serially treated patients. Nevertheless, the study did provide suggestive evidence that hydrazine sulfate might improve outcomes in cancer patients with cachexia, suggesting the need for further research.

Stronger evidence of hydrazine sulfate's effects on cancer patients comes from the most recent study reported by Chlebowski and colleagues (186). A randomized, prospective, placebo-controlled clinical trial was conducted to assess changes in nutritional status and survival time as a result of hydrazine sulfate taken in addition to cisplatin-containing combination chemotherapy. Sixty-five patients with advanced, unrespectable (non-operable) non-small-cell lung cancer were randomized to chemotherapy and hydrazine sulfate (oral doses of 60 mg/day) or to chemotherapy and placebo. These patients had had no prior chemotherapy and were described as being partially or fully ambulatory (performance status O to 2). All patients received the same defined nutritional counseling.

Nutritional status was found to be improved in patients taking hydrazine sulfate: they had significantly greater caloric intake and albumin maintenance. In previous studies, a low serum albumin level inpatients with non-small-cell lung cancer was found to be predictive of poor survival time, while maintenance of serum albumin level was found to be significantly predictive of better 2-year survival in patients with this type of cancer.

Median survival time among patients in the study was found to be greater among those taking hydrazine sulfate (292 days) than among those taking the placebo (197 days), but this difference was not statistically significant. Differences in survival time did reach statistical significance when the patients were separated into two groups-approximately 35 patients in relatively better condition (performance status O or 1), and approximately 30 patients in more impaired condition (performance status 2). Those patients in better condition who took hydrazine sulfate lived significantly longer (328 days) than those taking placebo (209 days). Forty-two percent of these patients taking hydrazine sulfate were alive at 1 year, compared to 18 percent of those taking placebo. There was no similar increase in median survival for patients in relatively worse condition; both treatment groups in this case had a median survival of 132 days. Hydrazine sulfate was not found to have a direct antitumor effect on patients in either group. No complete responses were found, and among the partial responses noted, 23 percent were in patients taking hydrazine, while 29 percent were found in patients taking the placebo. These were presumably attributable to the chemotherapy.

Based on the results showing that hydrazine sulfate improved nutritional status in patients with non-small-cell lung cancer and increased survival time in the subset of those patients who were more fully ambulatory, the authors suggested that hydrazine sulfate warrants further evaluation as an adjunct to conventional treatment. As they noted, the modest size of this trial limits the strength of the conclusions that can be drawn from it. The results were sufficiently promising, though, to have recently prompted NCI to sponsor one or more phase III randomized studies designed to further evaluate the influence of hydrazine sulfate on clinical outcomes in cancer patients (316).

LAETRILE

Laetrile is perhaps the best known unconventional cancer treatment of the past two decades. In the mid-1970s, an estimated 70,000 people had used it for cancer treatment, pain control, or cancer prevention (274), and by 1979, 21 States had legalized its use (722). During the same period, laetrile had become the focus of apolitical and legal controversy about patients' access to unapproved drugs (see ch. 10) (396,525,578,648,705). Since the early 1980s, laetrile has lost much of its popular appeal, but is currently available at many of the unconventional cancer clinics in Mexico used by U.S. patients.

Amygdalin, laetrile, Laetrile (capitalized), sarcarcinase, and nitriloside are some of the names of chemically related substances given to patients as laetrile treatment (903). Proponents have also referred to the treatment as a vitamin ("B-17") even though it has never been recognized as such by the scientific community. One of these names, Laetrile,[6] is the trade name for a substance chemically related to amygdalin, a substance found naturally in pits of apricots and other fruits. In this report, the term "laetrile" is used to refer generally to this group of closely related substance(s) used in unconventional cancer treatment.

Laetrile was developed from an extract of amygdalin by Ernst Krebs Sr., M.D., and Ernst Krebs, Jr., and was frost used to treat cancer patients in California in the early 1950s. Its use in the United States, Mexico, and Canada gradually expanded in the 1960s, as various laboratories were set up to produce and market the substance (985). The popularity of laetrile increased dramatically in the early 1970s when members of the ultraconservative John Birch Society came to the aid of a physician and fellow member who had been arrested for illegally treating patients with laetrile. Using this case as a starting point, several Birch Society members joined together to found the "Committee for the Freedom of Choice in Cancer Therapy," pimarily to advocate the right of cancer patients to use laetrile (722). Other groups, such as the Cancer Control Society and the National Health Federation, actively promoted the use and legalization of laetrile (962). With the support of Andrew McNaughton, a Canadian businessman, several factories around the world were built to manufacture laetrile (101).

Some proponents of laetrile cite a theory of cancer etiology known as the "Unitarian' or "trophoblastic" theory as the basis for treating cancer with laetrile. First proposed by John Beard in 1902 and later expanded on by Ernst Krebs, Jr., in the 1940s and 1950s, that theory draws a connection between cancer cells and trophoblast cells, which are cells present during pregnancy that are thought to protect the fertilized egg from rejection by the woman's immune system. Both cancer cells and the trophoblast cells are described in the trophoblast theory as invasive, erosive, corrosive, and capable of being carried through the bloodstream to other parts of the body. According to the theory, trophoblast cells could develop at various places in the body from precursor cells distributed throughout the body during embryonic development, and that these precursor cells could, under certain circumstances, become cancer cells. Laetrile proponents have also proposed that cancer is a deficiency disease caused by a lack of laetrile ("vitamin B-17") in the diet (362).

When laetrile is subjected to enzymatic breakdown in the body, it breaks down into three chemicals: glucose, benzaldehyde, and hydrogen cyanide (545). Various preparations of benzaldehyde have been studied recently, mainly in Japan, for antitumor activity in experimental animals (581) and in preliminary clinical studies (481,482). Cyanide has well-known toxic effects on human cells, both normal and malignant (197).

[6]Laetrile was named in reference to its biochemical properties; it was laevorotatory, or left-handed, to polarized light and belonged to the mandelonitrile class of chemicals.

Laetrile proponents claim that laetrile kills tumor cells selectively, while leaving normal cells alone. In support of this, Ernst Krebs, Jr., hypothesized that normal cells produce an enzyme, beta glucosidase, that breaks down laetrile, releasing cyanide, which is then converted by a second enzyme, rhodanese, to the less toxic thiocyanate molecule; cancer cells, however, lack the enzyme rhodanese, according to Krebs' theory, and therefore are killed by the free cyanide (704,903).

In the 1970s, proponents claimed that laetrile had direct antitumor effects, relieved pain associated with advanced cancer, and helped to prevent cancer (903). In recent years, specific claims of antitumor activity of laetrile have rarely been made. Instead, laetrile is more often discussed in the context of "metabolic" regimens, with claims made for antitumor responses and life extension resulting from the use of a combination of treatments, including laetrile, DMSO, vitamins, minerals, amino acids, enzymes, oxygen treatment, cellular treatment, and other substances (97,239,576).

Adverse Effects

Since laetrile itself is about 6 percent cyanide by weight, cyanide toxicity is possible when laetrile is broken down in the body. If an excessive amount of laetrile is ingested, or if something is done to accelerate or increase the release of cyanide from laetrile, then toxic and lethal levels of cyanide can be reached. Beta glucosidase, the enzyme that can markedly accelerate the release of cyanide from laetrile, is found in common foods as such raw almonds, other nuts, bean and alfalfa sprouts, peaches, lettuce, celery, and mushrooms (784). When laetrile is simultaneously ingested with a source of the beta glucosidase enzyme, toxic cyanide levels may result. Cyanide toxicity has been observed in patients receiving laetrile, although many patients have taken it without showing any significant clinical signs of cyanide toxicity (620,623). Common adverse effects noted in the studies (described later in this section) by Moertel and colleagues at the Mayo Clinic were nausea, vomiting, headache, and dizziness. Isolated reports of deaths due to cyanide poisoning following the ingestion of laetrile have appeared in the literature (100,585,644,697,768,779,800,8 11). Samples of Mexican laetrile were examined at NCI for potency, content, and quality of manufacture (248,249). It was found that the measured potency of the samples differed substantially from the labeled potency. In addition, of approximately 1,500 ampules that were examined visually, about 400 contained particulate matter, and 20 showed microbial growth (primarily budding yeast and fungal hyphae), indicating contamination of the material. These contaminants pose additional risks of complications, especially when given intravenously to patients who may be immunosuppressed. Bradford and colleagues at the American Biologics clinic in Tijuana have noted the existence of "pure" and "decomposed and degraded" products sold as laetrile or amygdalin (97).

Attempts at Evaluating Laetrile

Since the 1950s, laetrile has been examined for antitumor activity in a variety of experimental test systems. Its use in cancer patients has also been described by several proponents and it has been the subject of clinical trials sponsored by NCI. These efforts are summarized b e l o w .

Animal Studies

Laetrile has been tested for antitumor activity in a variety of transplanted rodent tumor systems. Experiments were conducted in several different laboratories under NCI sponsorship in 1957, 1960, 1969 (twice), and 1973, testing the effects of laetrile alone or in combination with beta glucosidase. These experiments used several different sources of laetrile and a variety of transplanted rodent tumor systems, and in each case, no antitumor activity was found (906). Other investigators have tested laetrile alone (183,404,838) or laetrile with beta glucosidase (519,965) in transplanted rodent tests. No antitumor activity has been found in any of these experiments.

Laetrile alone and in combination with beta glucosidase has also been tested for antitumor activity in human tumor xenografts in athymic (nude) mice. Using MX-1 mammary or CX-2 colon tumor xenografts in these mice, no antitumor effects of laetrile with or without the enzyme were found (701).

Spontaneous animal tumor systems have also been used in a variety of tests involving laetrile. In a study often cited in the proponent literature, Harold Manner and colleagues (575) treated mice that had spontaneous mammary tumors with the following three agents, tested individually and in various combinations: laetrile (50 mg/kg body weight per day injected intramuscularly), vitamin A (333,333

IU/kg body weight per day administered via stomach tube), and digestive enzymes (10 mg injected every other day 'directly into and around the tumor mass' '). The animals were observed for signs of tumor regression during a 30-day period of treatment.

According to the published report, no tumor regressions were observed in the animals treated with laetrile alone, vitamin A alone, or laetrile and vitamin A in combination. Tumor regressions were observed in the four treatment groups receiving the digestive enzymes (and a few in the control groups); in these animals, ulcerations containing necrotic malignant cells in viscous fluid were found at the tumor sites. Fifty-two percent or more of the tumors regressed in the groups treated with enzymes alone, enzymes and vitamin A in combination, enzymes and laetrile in combination, or enzymes, vitamin A, and laetrile in combination. The highest percentage was found in the latter group, in which all three treatments were given. The authors concluded that laetrile given alone is "not effective in tumor regression" but that when all three are given at the same time, "76 percent of the tumors do completely regress." It appears from the results, however, that the main effect observed was the immediate proteolytic effect of injecting digestive enzymes directly into tumor masses.

The largest and most complex set of tests on laetrile in animals was described by Chester Stock and colleagues at Memorial Sloan-Kettering Cancer Center and Catholic Medical Center of Brooklyn and Queens (837). One of the investigators at Sloan-Kettering, Kanematsu Sugiura, conducted six initial experiments using CD_8F_1 mice with spontaneous mammary tumors, and found that the mice treated with laetrile showed no significant prevention of growth of primary tumors, but did show inhibition in the development of lung metastasis. In an unusual sequence of events, unauthorized information about these experiments was made public before the results were confirmed independently, leading to allegations by proponents that "proof" of laetrile's effectiveness had been obtained and then suppressed by the Sloan-Kettering researchers (240,648,813).

These experiments were followed by a series of five experiments designed to replicate Sugiura's initial experiments. In two blinded experiments, the assessment of tumor status was done in such a way that the observer did not know whether the mice had had laetrile or the control treatment. This was intended to address the issue of unintentional bias in observing the presence of metastasis, since the two methods that Sugiura used to detect metastases—gross observation and microscopic analysis-were reported to be inherently subjective, while another method he did not use, bioassay, was reported to be less subject to bias. These independent and blind experiments (including those Sugiura participated in) did not confirm Sugiura's initial results. The authors concluded that in the spontaneous animal tumor system, "laetrile was found to possess neither preventive, nor tumor-regressant, nor antimetastatic, nor curative anticancer activity. "

The report summarizing both Sugiura's work and the independent experiments (on which Sugiura was a coauthor) noted that Sugiura believed his initial results were valid and that laetrile had antimetastatic activity. In an addendum to the paper, Daniel Martin, Chester Stock, and Robert Good added that the negative results of the blind experiments suggested that Sugiura's initial experiments were unknowingly biased, and reiterated their conclusion that laetrile had "no action against the formation of metastasis in the spontaneous tumor system. "

Human Studies

From the 1950s until the late 1970s, laetrile was reported to have been used widely, not only in the United States, but also in Europe, Mexico, and elsewhere. Descriptions by practitioners of its use in cancer patients appeared in various books and journals. These include a 1962 book by Howard Beard on the trophoblastic theory of cancer (381), a 1962 report in a U.S. medical journal written by a New Jersey surgeon (643), numerous reports by a physician in the Philippines (e.g., (662)), an abstract and presentation by practitioners in Italy and Belgium (765), papers by Dean Burk and Hans Nieper (e.g., (110)), and a 1977 book describing patients treated at a California clinic (758). None of these reports describes controlled, prospective trials from which valid judgments of laetrile's effects could be made. They were probably influential in increasing the popularity of the drug, however, since they all reported good results believed to be specifically related to laetrile.

In the mid-1970s, the National Cancer Institute (NCI) attempted to obtain documented evidence of objective responses to laetrile, using an approach designed to collect information from the records of

people who themselves claimed, or whose practitioners claimed, had been treated successfully. The intention was not to try to estimate possible rates of effectiveness, or to document adverse effects, but simply to discover any evidence for an antitumor affect.

Retrospective Review of Cases

NCI sent nearly half a million letters to physicians, other health professionals, and pro-laetrile groups, asking for documented case histories of patients who had shown objective responses to laetrile (274). Consent of the patient or next of kin, confirmatory histologic material, measurable disease, adequately documented history, use of laetrile with or without metabolic treatment for a period of at least 30 days, with at least a 30-day period preceding during which no conventional cancer treatment was given, and records in English were required for cases submitted. Supporting information for each submitted case was sought from physicians, clinics, hospitals, and laboratories.

The solicitation and review of the public record resulted in identifying 230 patients with claimed objective responses from laetrile, all of whom (or the next-of-kin) were asked to authorize release of their medical records. Ninety-three gave permission, and after assembling the records for all cases, 26 were found to be insufficient for review (many because requested records were not sent). The review was based on the 67 remaining laetrile-treated cases (one of whom had two separate courses of laetrile). In an attempt to avoid personal biases against laetrile in the evaluation, 26 case histories of patients with similar types of cancer who received conventional treatment, but not laetrile, were pulled from the NCI files, and added to the laetrile cases. A summary of the clinical course of each of the 93 cases, without specifying whether the patient had or had not received laetrile, was presented to a panel of 12 expert clinical oncologists from outside NCI for their independent review. A group consensus was then reached after discussing the results of the individual reviews.

By consensus, there were two complete remissions, four partial remissions, nine cases of stable disease, and seven cases of progressive disease. Thirty-five cases were non-evaluable, meaning that they did not meet original criteria for cases, and 11 had insufficient data on which to judge response. Of the patients from the NCI files who had not had laetrile, one, who had not had any treatment, was judged to have had a partial response.

Despite attempts to blind the panelists to whether the patients had had laetrile, a higher-than-expected proportion answered correctly when asked to guess whether patients had had laetrile or other treatment. However, the consensus for the six laetrile-treated patients determined to have had partial or complete responses, and three determined to have had an increased disease-free survival, was that they had received conventional chemotherapy.

The discussion in the report of that review illustrates the difficulty in interpreting results such as these. The authors make a number of useful points. First, the rather small number of cases submitted in relation to the solicitation effort, and the loss of cases due to sources not submitting requested information, left a relatively small number of evaluable cases. It is unclear what NCI could have done differently to increase the number of cases submitted. The authors also commented that cases rejected from the review as invaluable were not necessarily examples of poor medical management or of patients who may not have benefited from laetrile. The necessary rigor of NCI'S process alone determined their evaluability. A natural tendency is to want to compute a "response rate' using these data, but, in fact, there is no valid means to do so, therefore these data cannot be summarized in a meaningful statistical sense.

A number of explanations for the six cases determined to have benefited after laetrile treatment are offered in the published report. First, it is possible that the patients responded to laetrile, but in this type of study, that explanation cannot be assumed true:

> Submission of incorrect clinical interpretations, falsified data, intentional or unintentional omission of data (for example, concurrent conventional therapy), the possibility that we were unaware of some physicians treating these patients or non-response to our inquiries must all be considered in interpreting these findings. . . . Spontaneous regressions of tumors, although rare, have been documented. . . with frequency varying according to tumor type. Even in the absence of true spontaneous regression, the well documented variability in the natural history of some

> *tumors may confuse interpretation (904) and, in fact, the panel judged by consensus that a partial response occurred in one patient receiving no treatment during the course evaluated. The patients treated with Laetrile were almost always given concomitant metabolic therapy. . . as well as general supportive-care measures such as improved diet, psychologic support and the unmeasurable ingredient of hope. This fact makes it difficult to attribute any tumor responses to Laetrile alone.*

The authors suggested, however, that the data would be used by NCI in determiningg if further study is needed. A prospective trial, described below, was conducted following the case review.

Phase I and II Clinical Trials

After the laetrile case review described above, NCI sponsored phase I and II clinical trials, which were carried out at the Mayo Clinic. In the phase I study (620), information about dosage and toxicity was gathered in preparation for the phase II study (623), which is described here. One hundred seventy-eight patients with advanced cancers were treated with amygdalin, according to a regimen "representative of current Laetrile practice," and were prescribed a diet and vitamin supplements designed by the investigators to be similar to metabolic regimens offered by many laetrile practitioners. A subgroup (14 patients with colorectal cancer) was given a high-dose regimen of both amygdalin and supplements, resembling high-dose regimens used by some laetrile practitioners.

About a third of the patients had colorectal cancer, the next largest categories being lung, breast, and melanoma, with rare cancers represented by fewer patients. All patients had disease for which no conventional treatment was available, though none was bedridden and all were able to eat normally. Most of the patients were capable of working at least part time. About a third of the patients had had no chemotherapy at all. This is of interest because some metabolic practitioners claim that laetrile and metabolic therapy are more effective in patients whose immune systems have not been damaged by chemotherapy.

The amygdalin was prepared by NCI from apricot pits, corresponding to the laetrile sold by major suppliers to U.S. patients. It was administered intravenously for 21 days, followed by continued oral dosage, and stopped with progression of the cancer or severe 'clinical deterioration.' Amygdalin was also stopped if an extremely high blood cyanide level was reached (3 micrograms per milliliter); this was the case for three patients.

Standard criteria were used to assess patient response. An "objective response" had to meet the following three conditions: 1) at least a 50 percent decrease in a particular measurement of the most clearly measurable tumor area of an originally chosen "indicator lesion" (or if malignant enlarged liver were the measurable disease, a 30 percent decrease in a particular measurement); 2) no increase in the size of other areas of malignant disease; and 3) no new areas of malignant disease. Two criteria had to be met to be classified as in "stable condition": 1) less than 50 percent decrease in the measurement referred to above in the first criterion for an objective response; and 2) no new areas of malignant disease. Meeting any one of three criteria constituted "objective progression' 1) an increase of more than 25 percent in any indicator lesion; 2) new areas of malignant disease; or 3) severe clinical deterioration precluding further therapy and observation.

The study found that 1 of the 175 evaluable patients met the criteria for a partial response (at least 50 percent decrease in size, but not disappearance of lesion), and that response was transient. More than half of the patients had measurable progression at the end of the 3-week intravenous amygdalin course. By the end of 2 months, about 80 percent had measurable disease, and by 7 months, all patients had progressed. The median survival (the point after starting treatment at which half the patients had died) was 4.8 months. The 14 high-dose patients were similar in these outcomes to the entire group.

There was little evidence in this trial population of symptomatic relief. Few people gained weight, and improvements in performance status for those originally impaired were few. Twenty percent of patients claimed some symptomatic benefit at some point during treatment, but this was generally short-lived. After 10 weeks, 5 percent of patients reported still receiving benefit.

Toxicities were generally mild when patients adhered strictly to the treatment schedules. Typical symptoms of cyanide toxicity-nausea, vomiting, headache, and mental dullness-occurred in some cases, particularly when patients took more amygdalin during a specified time period than was

prescribed (e.g., when a dose was missed, and the patient "made it up").

The authors stated that survival times of patients in the trial "appear to be consistent with the anticipated survivals in comparable patients receiving inactive treatment or no treatment." When challenged on this point in a letter to the editor of the New England Journal of Medicine (709), the investigators compared the survival curve of colorectal cancer patients in the trial to survival of colorectal patients who had received new chemotherapeutic agents at the Mayo Clinic, and found no difference (619). The study was not designed, however, to determine if amygdalin causes moderate increases in lifespan (or improvements in well-being or pain control), since it did not include a randomized control group, and thus the author's comparison is not entirely valid.

The study was criticized by laetrile supporters, who claimed that the material NCI used was not "Laetrile," but in fact, a "degradedproduct" (237). However, the NCI product was prepared to correspond to one of several popular formulations being administered to U.S. patients at the time, and the regimen used in the study did reflect then current practices of proponents. If the treatment had the antitumor activity claimed for it, a substantial number of patients in this trial should have shown objective responses. As it turned out, only 1 out of 175 patients studied showed a response-a partial, transient tumor response—which was far below expectations based on proponents' claims of laetrile's efficacy.

THE LIVINGSTON-WHEELER REGIMEN

More than 40 years ago, the late Virginia (Wuerthele Caspé) Livingston-Wheeler, M.D.,[7] reported that she identified a specific microorganism she believed was associated with the development and progression of cancer. During the 1950s, she developed a comprehensive theory of cancer causation based on this common infective agent and designed a corresponding anti-infective treatment-an autogenous vaccine designed to treat and prevent infection with the microbe that she believed causes cancer. The current treatment regimen, offered at an outpatient clinic in San Diego, includes a variety of components intended to bolster patients' immune responses in general and to counteract effects of microbial infection. These components, which have changed over time, include antibiotics, vitamin and mineral supplements, and a special diet. The Livingston-Wheeler treatment was added to the ACS list of unproven methods in 1968 (23). In February 1990, Livingston was issued a cease and desist order by the California Department of Health Services to stop prescribing and administering the autogenous vaccine as part of her treatment regimen (831).[8]

After receiving her M.D. from New York University in 1936, Livingston held a number of academic, clinical, and laboratory positions, including associate professor in the Bureau of Biological Research at Rutgers University and associate professor of microbiology at the University of San Diego (563). In 1969, she established the Livingston-Wheeler Clinic,[9] where she was director, and began treating cancer patients on a full-time basis. Livingston was one of the most widely known practitioners of unconventional cancer treatment in the United States.

Livingston's hypothesis on the role of infectious agents in the etiology of cancer originated from her work in the mid- 1940s on scleroderma, a systemic, autoimmune connective tissue disorder. Comparing tuberculosis, leprosy, scleroderma, and cancer, she noted that "all four diseases are characterized by a simultaneous process of production and destruction of tissue and by a progressive, systemic involvement of the host" (971). She redirected her research from the bacteriology of scleroderma to that of cancer, beginning with tissue from a patient with breast cancer.

In a paper published in 1950 (973), Livingston reported on a group of microorganisms that she isolated from tumor tissue. She referred to these organisms as a single culture and described the various forms in which they appeared: "minute filterable granules beyond the limits of visibility of

[7]Officially, she used the name Virginia C. Livingston, M.D. Dr. Livingston died shortly before this OTA Report was finished.

[8]The Department found that the use of the vaccine by the Livingston-Wheeler Clinic violated California's Health and Safety Code, which "prohibits the sale, providing, or prescribing of any cancer drug, medicine, compound, or device unless it has been scientifically proven to be safe and effective in the diagnosis, treatment, alleviation, or cure of cancer and an application therefore has been approved by the Department or the United States Food and Drug Administration."

[9]Since her death, the clinic has been renamed the Livingston Medical Center.

the light microscope," "larger granules approximately the size of ordinary cocci readily seen with the light microscope," "globoidal forms," "rod-like forms with irregular staining," and "globoidal forms which appear to undergo polar budding.' She reported that she did not find these forms in the tissues of healthy individuals, and suggested that this organism might be of primary or secondary importance in the etiology of cancer.

Although admittedly not the first to culture microorganisms from tumor cells, Livingston believed that she was the first to postulate interrelationships among the observed bacteria, viruses, and mycoplasma. To do this, she examined the ' 'developmental cycle of the organism through each transitional phase" using specific growth media, differential staining, high power microscopic resolution, and electron microscopy. She concluded that these phases represented different developmental forms of the same microorganism (974), which she characterized as "pleomorphic," a term used in microbiology to refer to bacteria that change in size and shape during their lifecycle (also called "cell wall deficient" bacteria) (584). She reported that these different forms included micrococci, diphtheroids, bacilli, fungi, viruses, and host-cell inclusions (977). In 1970, Livingston proposed a formal classification for this microbe and described her method for isolating and culturing it (978). She classified it under the order Actinomycetales, which includes the bacteria associated with tuberculosis and leprosy, and named her microbe Progenitor cryptocides (PC), meaning "the ancestral, or pr[i]-mordial, hidden killer" (563).

Livingston believed that P. cryptocides is ubiquitous in patients with cancer and, contrary to her earlier observation, that it is also present in some individuals without apparent disease (560). She believed that in a healthy person, this microbe is maintained at low levels in the body, but under some conditions, it can multiply in overwhelming numbers and become invasive and tumor-promoting (978). Special staining methods were developed by Livingston and her colleagues to determine the degree of latent or overt infection, an indicator that she used to determine the progress of the disease during treatment (979).

To examine their potential for causing disease, Livingston inoculated mice and guinea pigs with cultures of P. cryptocides and reported a "wide range of neoplastic tissue changes' in the inoculated animals (972,978). These results were confirmed by Irene Diner at the Institute for Cancer Research in Philadelphia (255,256). On the basis of these experiments, Livingston concluded that P. cryptocides was pathogenic in animals, and extrapolated this pathogenicity to humans. She believed that P. cryptocides is the "primary etiologic agent in proliferative and degenerative diseases" (977) and claims that her work proves it to be the causative agent in all cancers. In the absence of clinical studies examining the possible role that P. cryptocides might play in the development of cancer, however, the pathogenicity of this microbe or group of microbes in humans remains unresolved.

There is little support, outside of a few researchers (see, e.g., (106)), for Livingston's belief that the different microbes observed in tissues and blood of cancer patients are actually different forms of the same organism. At present, no independent evidence exists to corroborate her contention that the microbial forms are related to each other as different forms of a single, pleomorphic organism. Evidence does show that the bacterial culture Livingston isolated is not a new and unique species as claimed: P. cryptocides cultures supplied by Livingston were identified as different species of the genus Staphylococcus and Streptococcus (3,4,258). The issue of isolating bacteria of any kind from tumor tissue and urine of cancer patients, however, is generally not disputed, since many groups of researchers have reported isolating various species and strains of bacteria from such sources (see, e.g., (3,62,209)). Some of these bacteria have also been shown to undergo morphologic alterations characteristic of cell wall deficient (or pleomorphic) bacteria (4). Acevedo and others have looked into the effect that these organisms might have on the body's immune response to malignant cells (4).

During the course of her research into the properties of P. cryptocides, Livingston discovered that this microbial culture produces a substance in vitro that is closely related to the human hormone chorionic gonadotropin (hCG) (980).[10] Her report was the first to document the production of a

[10]Human chorionic gonadotropin is a hormone secreted in pregnancy by the trophoblast cells that form the outer part of the embryo and allow implantation. In early pregnancy, this hormone plays a role in maintaining the lining of the uterus and in preventing spontaneous abortion of the fetus.

mammalian hormone-like substance by microorganisms, and this has been confirmed by other investigators (209,580). Others have observed a protein similar to hCG produced *in vivo* by a variety of microorganisms (5). The hormone has been found in tumor tissue isolated from cancer patients, though not from every species of bacteria isolated from cancer patients; it has also been found in bacterial isolates from individuals without clinical manifestations of cancer (3). These findings suggest that the production of a chorionic gonadotropin-like substance by human tissues or microorganisms is not uniquely associated with cancer, although they do not rule out a possible role for the hormone in the development of some cancers. Researchers have suggested the possibility that chorionic gonadotropin, whether produced by human cells (691) or by bacterially infected human tumor tissue, may suppress certain immune responses (517), and that substances acting against hCG may inhibit the growth of malignant cells (471).

Livingston believed that P. *cryptocides* is "an essential but dormant part of all cells, " and is normally kept in check by a fully functional immune system. She believed that ''when immunity is suppressed or weakened, P. *cryptocides* proliferate and allow cancer to gain a foothold, secreting the same (chorionic gonadotropin) hormone found in abundance in all tumors. ' She viewed cancer as an "immune deficiency disease" caused by specific inadequacies in the diet and by toxic chemicals in the environment. She stated in her 1984 book, "the modern diet is simply deficient in providing the nutrition essentials that maintain a healthy, vital immunity to cancer . . . what we put in our mouths either causes or directly contributes to the onset of cancer through the depression of our immunity" (563).

Possible treatment approaches for cancer based on her theory of cancer causation were discussed for the first time in a paper Livingston published in 1965 (977). In that paper, she reported treating 40 patients with a regimen that included an autogenous vaccine-one made from each patient's culture of P. *cryptocides. The* vaccine was designed to promote the production of immunologic cells, to suppress the invading microorganism, and to promote host resistance. Other components of the treatment include laxatives, cleansing enemas, and a special diet low in carbohydrates and high in well-cooked proteins, fresh fruits, raw vegetables, and vitamin and mineral supplements. That paper described how the vaccine was made and administered to cancer patients, although clinical details about the patients, such as tumor type, previous treatment, or outcome, were not provided; it was noted only that, following vaccine treatment, "a number of these patients appear to be improving. Livingston did not publish any other papers in the medical literature presenting data on tumor regression or life extension in cancer patients treated with her regimen. At present, other information about the treatment consists of the materials available from the Livingston-Wheeler Clinic (a patient brochure, a physician handbook, and a compendium of published research papers by Livingston and some of her colleagues), and two books written for a general audience *(Cancer: A New Breakthrough (975)* and *The Conquest of Cancer (563)). The Conquest of Cancer* contains case history Summaries of patients treated at the clinic (see discussion below).

Livingston stated in a deposition (559) that her treatment does not interfere with conventional treatment and can be used adjunctively (559). She stated in her book, however, that she preferred that patients avoid conventional treatment before starting her regimen, since, as she explained it, "often they come to us after having been so heavily treated that their immune systems are all but destroyed, and their turners are far advanced" (563).

Treatment Regimen

The treatment regimen (as of July 1990, before Dr. Livingston's death) used at the clinic included a number of different immunologic, pharmacologic, and nutritional components.

Before the 1990 "cease and desist" order was issued (see above), the autogenous vaccine was administered to all patients. The vaccine was intended to eliminate P. *cryptocides* from the body and was made from each patient's own culture of microorganisms, which were isolated from urine. In the initial treatment period, each patient was supplied with enough vaccine for 9 to 12 months. Thereafter, new cultures were obtained periodically for the production of new vaccines, so that the treatment continued to correspond to any changes in the patient's P. *cryptocides* levels as treatment progressed (559). Gradually, the frequency of autogenous vaccine administration was decreased and eventually, only occasional booster shots were

given. Livingston also gave a "purified antigen" vaccine made at the clinic, consisting of a cell wall extract of a general P. cryptocides culture (562).

Other immunologic treatments included in the regimen are mixed bacterial vaccines, antibiotics, and various commercially prepared nonspecific immune stimulators, such as levamisole (a conventional antiparasitic agent also used as an immune stimulant and recently shown effective in treating patients with colon cancer), and tuftsin (an experimental agent noted for various immune stimulating properties). The bacillus Calmette-Guérin (BCG) vaccine, a vaccine that immunizes against tuberculosis and used as a general immunologic stimulant in some conventional cancer treatment, is also used in many cases. Other treatments are offered on a case-by-case basis.

Progress in reducing infection with P. cryptocides is monitored by examining smears of a patient's blood under a darkfield microscope, an uncommon type of microscope that Livingston believed a key to identifying P. cryptocides microbes. A decrease or increase in the number of visible P. cryptocides microbes in the blood smear is used to indicate increasing or decreasing immune response as a result of treatment. Other tests are also used to assess immune response and progress of treatment (563).

Another component of the regimen is the provision of fresh, whole-blood transfusions from a young, healthy person (preferably a family member), and injections of gamma globulin to increase the number of circulating antibodies. Livingston also used a "custom formula," consisting of an extract of sheep liver and spleen, to "increase the white blood count [and] enhance immunogenic systems." Other immunologic agents that may be used include T-cells, thymosin (a hormone-like factor extracted from calf thymus), interferon, and tumor necrosis factor.

Livingston recommended that patients follow specific nutritional guidelines. The recommended diet emphasizes 'living food' '-whole grains, fresh vegetables, and fruits. She strongly encouraged patients to stop smoking and to eliminate meat and poultry products, alcohol, coffee, refined sugars, and processed foods from their diets. Also included is a nutritional supplementation program, consisting of high doses of vitamins (especially vitamins A, B6, B12, and C), minerals, digestive enzymes, and bile salts.

Another component of the regimen is bowel hygiene and detoxification. Livingston stated that frequent enemas, and sometimes high colonies, are necessary to cleanse the intestinal tract of pathogenic bacteria and toxic materials. She stated also that they help relieve pain and improve appetite and digestion. Daily coffee enemas may be recommended.

In this regimen, emphasis is placed on the use of abscisic acid, a plant hormone and vitamin A analog that Livingston believed neutralizes chorionic gonadotropin in the blood and urine. She stated that abscisic acid is normally produced in the human liver, unless its function is impaired (561,976). This claim has apparently not been examined independently by researchers unaffiliated with Livingston.

There have been no reports in the literature of direct adverse effects from the Livingston regimen. There are some potential risks, however. As with any injection into the body of a foreign substance, the injection of the autogenous vaccine carries the associated risk of sepsis or anaphylaxis. Some risk of contamination in the preparation of the material is also possible, depending on the processes and procedures used to make and assure the sterility of the vaccines manufactured at the clinic. In addition, in any setting, the use of whole blood transfusion, even with directed donors' blood, carries a small risk of transmitting various infectious agents. Livingston's 'custom formula,' consisting of an extract of sheep liver and spleen, carries certain risks associated with all types of cellular treatment. (See discussion of cellular treatment earlier in this chapter.)

Claims of Efficacy

Livingston claimed that her treatment regimen is capable of curing cancer by stimulating the immune system. In support of this claim, she presented in her book, The Conquest of Cancer, a summary of clinical outcomes of patients treated at her clinic. According to Livingston, "someone not employed by our clinic drew 100 charts from our files totally at random," which Livingston then evaluated. Sixty-two of these were considered evaluable by Livingston's criteria: she excluded patients whose records lacked confirmed pathology reports, who discontinued the Livingston-Wheeler treatment, who were "too weak and ill to carry out the program,' and "who had only recently checked into the clinic,

or whose cases were so recent that even the dramatically fast reversals could only be labeled inconclusive. Patients who received previous or concurrent conventional treatment were not excluded.

Livingston concluded from her review that "our success rate has been 82 percent" and "considering the patients we called inconclusive but for whom we were able to be of some help, it is over 90 percent,' although there was no discussion of which cases were included in these percentages and for what reasons. She did not define what she meant by "success" or being of "some help. " Regarding the 18 percent that she did not consider successful, she stated that she "probably could have helped these patients had they not come to us with enormously debilitated immune systems resulting from having already undergone massive chemotherapy and radiation."

The conditions of some of the patients in this review may or may not have improved as a result of Livingston's treatment, but the data presented in her book on this group of self-selected patients do not support calculation of an overall "success rate. " Insufficient information is presented on the clinical course of these patients for readers to arrive at independent judgments about the treatment's usefulness and the complete, original patient data have not been examined by outside researchers.

At present, there is insufficient information to indicate whether this regimen is or is not effective in treating cancer. However, Livingston's ideas have stimulated other researchers to study some aspects of her cancer treatment regimen. For example, Anthony Strelkauskas, M.D., at the University of South Carolina, is reportedly studying the immune responses of breast cancer patients to the autogenous vaccine, but results have not yet been published (559).

A prospective clinical trial of the use of an autogenous vaccine in the treatment of cancer is currently underway in Virginia under the direction of Vincent Speckhart, M.D., and Alva Johnson, Ph.D. (819). The aim of the evaluation is to observe tumor responses following vaccine administration among 33 patients described as having advanced forms of cancer and as either failing previous treatment or having recurrences following conventional treatment. For a 6-month period, patients were given regular doses of an autogenous vaccine prepared from cultures of chorionic gonadotropin-producing bacteria isolated from the patients' urine (820). According to a summary of preliminary results (a full description is not yet available), the study found several cases of tumor regression, some complete and some partial, in this group of patients. No adverse reactions, except localized redness and an occasional rash that were resolved by changing the vaccine dose, were noted. Speckhart and Johnson's full results may contribute information to the further evaluation of the efficacy of such vaccines in cancer treatment.

HANS NIEPER

Another widely known practitioner of unconventional cancer treatment is Hans Nieper, M.D., a West German physician. Patients from many countries, including the United States, reportedly have sought his treatment. Nieper specializes in the treatment of cancer, multiple sclerosis, and heart disease (77). For cancer, Nieper prescribes a combination of conventional and unconventional agents (including pharmaceutical drugs, vitamins, minerals, and animal and plant extracts), and recommends that patients follow a special diet and avoid particular physical agents, foods, and physical locations ("geopathogenic zones' that he believes are damaging.

Since 1964, Nieper has been affiliated with the Paracelsus Silbersee Hospital in Hannover, West Germany. He received his M.D. from the University of Hamburg in 1953 (77). In addition to his medical practice and clinical research, Nieper hypothesizes about some aspects of theoretical physics. His writings cover subjects such as the "shielding theory of gravity" and the potential for harnessing useful energy from space, which he refers to as the "tachyon field. Some of his ideas about problems in medicine, including some aspects of cancer etiology and treatment, are based on his theories of energy fields (677).

Nieper has published a large number of papers and books on medical subjects, in several languages, according to information from a private library in Wisconsin[11] that collects and distributes some of Nieper's papers in the United States. These papers, some of which are translated from German, are

[11]The Admiral Ruge Archives, A. Keith Brewer Science Library, Richland Center, Wisconsin.

distributed by that library as mimeographed typescripts, with a title, Nieper's name as author, and a date; although in all but a few papers, no source or citation is given to indicate whether they correspond to published articles. Using indexes to the open medical literature accessible in the United States (e.g., Index Medicus and Science Citation Index), OTA found citations to a small number of articles by Nieper, only a few in English (675).

In 1985, an English translation of his book Revolution in Technology, Medicine and Society *was published (677). This book contains discussions (often difficult to follow) of his theories and research interests (titled, e.g., "On the Subject of Medicine and the Tachyon Era," "The Symposium on Energy Technology in Hannover," "Congress on Gravity Field Energy in Toronto, " "Epilog for the Hannover and Toronto Energy Conferences,' and 'Encouraging Signs in Politics, Economy, and Intellectual Leadership"). Within the context of these subjects, Nieper discusses approaches to the treatment of cancer, multiple sclerosis, thrombosis, arteriosclerosis, lupus, asthma, heart disease, and a variety of other conditions.*

Nieper's book and mimeographed papers cover a range of issues in cancer prevention and treatment and also discuss particular treatments that he believes are important. Although he states that his ideas are based on clinical and laboratory data, he does not explain them in the context of other available medical literature. Rather, he discusses his approaches to treatment in the context of theories and conclusions derived from his general knowledge of medical research. The lack of straightforward descriptions of his treatment approaches and of citations to existing medical literature make it difficult, at best, to determine the components of his treatment regimens and the specific information (including his data and others') on which they are based.

Nieper offers additional information about his treatments in the course of occasional seminars and workshops in the United States, which are sponsored by the Hans Nieper Foundation, an information and support group based in California and directed by a former patient. At a 1987 full-day seminar for medical professionals, held in New York, Nieper discussed his protocols for the treatment of cancer and multiple sclerosis (453). There is virtually no other available information intended for a U.S. audience on Nieper's treatment regimens from Nieper or his supporters.

Thus far, government and private organizations in the United States have not provided synopses of Nieper's treatment, as has been done for a variety of other unconventional cancer treatments that U.S. cancer patients use. No written statements about Nieper are available from the Cancer Information Service (CIS) at NCI or the Committee on Unproven Methods (ACS). One aspect of Nieper's treatment was addressed in a 1986 FDA 'talk paper' (890) on the issue of importation of Nieper's treatment materials. In 1987, FDA issued an import alert (891), announcing that shipments of drugs prescribed by Nieper would be detained by U.S. Customs agents. FDA considers the shipment of these drugs into the United States to be in violation of the Food, Drug, and Cosmetic Act, since they lack U.S. approval for use and are not labeled according to standards set forth in that law.

Based on the book and mimeographed papers referred to above, some aspects of Nieper's treatment for cancer can be described. Nieper describes his approach to treatment as "eumetabolic,' a term he coined to refer to the use of substances derived from plants or animals that he considers not to be "foreign" in the human body. The regimen for cancer includes "subtoxic doses of chemotherapy,' "hormone therapy," and "gene-repair therapy;" the components and rationale for them are only indirectly and partially described. The overall aim of the cancer treatment regimen is to activate the "internal defense system,' which Nieper believes is the body's own mechanism for fighting cancer. He uses low-dose chemotherapy, radiation, and surgery to kill or remove tumor cells directly, but cautions that chemotherapy "must never be so extensive that valuable mechanisms of the body's own defenses are thoughtlessly damaged" (677). Nieper believes that internal mechanisms control the healing process in cancer; "exogenous factors and procedures have, therefore, little effect on. . . the incidence. . . and the curing rate" (676). Nieper believes that cancer is caused by suppression of natural host defenses, by overeating the wrong types of food, and by exposure to certain environmental factors. He refers to particular environmental factors that he believes lead to "gene instabilities" and to the activation of oncogenes: X-rays, ultraviolet radiation, alternating current electrical fields, and the "tachyon field turbulence of the geopathic zone. "

In Nieper's view, geopathic zones "play a decisive role in the development of cancer cells and cancerous tumors" (677), in that he believes there is a higher incidence of cancer in areas of high levels of earth radiation and in areas situated over subterranean water veins. He believes that geopathic zones cause disturbances in the magnetic or electrostatic properties of tissues in the body, which disrupt the genetic material. Nieper claims that 92 percent of cancer cases he has examined are associated with long-term occupancy (particularly where the individuals sleep) of geopathic zones. He believes that "removal of cancer-stricken patients from geopathic zones absolutely belongs to the conscientious duties of an oncologist" (677).

Nieper states that his treatment regimen is "more or less the same in all conditions of malignancy whatever the finding" (673). A wide range of substances used to treat cancer patients is discussed in his writings, including dehydroepiandrosterone, magnesium, selenium, beta carotene, bromelaine (papain), cod liver oil capsules, vitamin C, photons, BCG, gamma globulin, magnesium orotate, tumosterone, mistletoe, amygdalin and mandelonitriles (laetrile), benzaldehyde, urea, glutathione, Didrouvaltrate, carnivora (an extract of the Dioneaea muscipula *plant), pau d'arco, "adrenal whole extract,' and squalene (derived from shark's liver oil) (676).*

In addition to prescribing some or all of these agents, Nieper cautions patients to avoid alternating current fields, such as electric blankets and heating pads, and to avoid all cigarette smoke. He recommends that they follow a special diet—a low-salt, low-carbohydrate, 'Kirlian-positive vegetarian diet," including whole grain cereals and breads, carrot juice with heavy cream, vegetable and fruit juices, low-fat milk, all types of vegetables and fruits, moderate amounts of coffee, tea, eggs, and butter, and limited amounts of fish. Patients are cautioned to avoid most types of meat, sausage, chicken, veal, shellfish, sugar, alcohol (except "sour" wine), white bread, cheese, vitamin B12, and iron (167).

The information available about Nieper's treatment regimen contains very little clinical data on outcomes in cancer patients following treatment. A mimeographed paper dated 1977 and a 1980 paper with the same information show a table listing 23 general tumor types found in 214 patients, along with the number of patients with each tumor type and the number of "positive responses' to his treatment. A "positive response" was defined as "18-month survival with considerably improved health." Nieper claims that "the percentage of patients whose disease gets under control within an 18-month period of observation is close to 40 percent" but he restricts this to "mobile, so-calld incurable patients, ' because "the results with hospitalized patients are less than half as good since hospitalization indicates that the disease has progressed too far" (674,675). Since no data are given on tumor stage, prior treatment, specific treatments given to patients under his regimen, or how these particular patients were chosen for inclusion in the analysis, the information provided is insufficient to draw any conclusions about efficacy.

OXYGEN TREATMENTS

Various types of oxidizing agents are discussed in the popular literature on unconventional cancer treatments and at meetings sponsored by advocacy and information groups such as the Cancer Control Society (162). Although not apparently widespread in the United States, the use of oxidizing agents has been reported at clinics in Mexico and West Germany where U.S. cancer patients are treated (289,588). The most commonly mentioned treatments of this type are ozone (a gas), hydrogen peroxide (a liquid), antioxidant enzymes, and related products (853). Oxidizing agents such as ozone and hydrogen peroxide are commonly available and have a variety of mainstream uses: as antiseptic, disinfectant, and cleansing agents, as laboratory chemical reagents, and in the food packaging industry. In addition to their use in unconventional cancer treatments, oxidizing agents are also proposed as components of unconventional treatments for AIDS, cardiovascular disease, multiple sclerosis, arthritis, and a variety of other conditions (96,297).

The late Otto Warburg, a German chemist twice awarded the Nobel Prize, was one of the first to discuss an association between oxygen levels in the body and the etiology of cancer, and to suggest that the growth of cancer cells is favored by an intracellular environment low in oxygen (936). Many others have since expanded on Warburg's ideas, and much has been written about oxygen treatments in general. Not only is there no accepted rationale for the proposed effects of oxidizing agents in cancer treatment among current proponents, but disputes among oxygen proponents are found in descriptions of these treatments in the unconventional literature

(80,217). The role of oxygen compounds in the initiation and progression of cancer has long been a subject of mainstream scientific study. In general, active oxygen is thought to contribute in a variety of ways to the development of malignant cells (180).

Ozone can be administered by direct infusion of the gaseous mixture into the rectum or into muscle, but it is usually given by unconventional practitioners in blood infusion, a process whereby blood is removed, treated with oxygen, and returned to the body, as explained in a recent review by an unconventional medicine advocate:

> *The ozone is produced by forcing oxygen through a metal tube carrying a 300-volt charge. A pint of blood is drawn from the patient and placed in an infusion bottle. The ozone is then forced into the bottle and mixed in by shaking gently, whereupon the blood turns bright cardinal red. As the ozone molecules dissolve into the blood they give up their third oxygen atom, releasing considerable energy which destroys all lipid-envelope virus, and apparently most other disease organisms as well, while leaving blood cells unharmed (297).*

Medizone International, a company that manufactures a device used to deliver ozone by infusion in the blood system, has filed an investigational new drug application with FDA to study the possible use of ozone as an antiviral agent. Before phase I studies in humans can proceed under the IND, however, the company is required to submit data, probably involving tests in animals using a range of doses, showing that ozone can be administered safely. Little information in the published, peer-reviewed literature is available on the use of ozone in general in the treatment of cancer, or on the recommended doses and regimen for treatment. Claims for the efficacy of ozone are based on a number of papers and case reports of its use on cancer patients (926,929), in animal studies (52,586), and in cell culture (940). One paper by Sweet and colleagues, published in Science, presents indirect evidence that atmospheric ozone selectively inhibits the growth of human tumor cells in cell culture (in vitro) (846).

Hydrogen peroxide is given in dilute form by various routes--oral, rectal, intravenous, vaginal, and in bathing. Proponents state that hydrogen peroxide oxidizes toxins, kills bacteria and viruses, and stimulates immunity (364). One unconventional practitioner, Kurt Donsbach, who treats cancer patients in Tijuana, formulated a line of products using hydrogen peroxide, including ear drops, nasal spray, and tooth gel. Donsbach states that every cancer patient at his clinic in Tijuana receives dilute "infusions of the 35% food grade hydrogen peroxide throughout their entire stay" (262). In 1988, the U.S. Postal Service issued Donsbach a cease and desist order to stop him from claiming that the hydrogen peroxide used orally or intravenously is effective against cancer or arthritis, or that it is fit for human consumption (69). Another clinic, the Gerson clinic in Tijuana, has recently added ozone therapy to their regimen, partly on the basis of the laboratory study by Sweet and colleagues referred to above (401). Patients at the Gerson clinic are commonly given ozone enemas, consisting of 500 to 1,000 cc of ozone given rectally in less than 1 minute (318).

Another form of oxygen treatment, superoxide dismutase, is an antioxidant enzyme believed to play a role in aerobic metabolism (689), Several unconventional treatment facilities in Tijuana (e.g., the Manner Clinic and American Biologics Hospital and Medical Center), reported using this enzyme in their regimens for cancer patients (22,574).

Oxidizing agents, such as ozone and hydrogen peroxide, can destroy cells, including those of the blood-forming organs, and at some doses, can be seriously damaging or even lethal (860). The doses at which these agents can be administered safely have not yet been determined. Although advocates of ozone and hydrogen peroxide maintain that these substances can be used safely, other unconventional practitioners have noted possible adverse effects (98).

EMANUEL REVICI AND "BIOLOGICALLY GUIDED CHEMOTHERAPY"

Emanuel Revici, M.D., is a physician in his nineties who currently practices in New York City. During a career spanning seven decades and four countries, Revici has developed an apparently unique approach to the treatment of cancer and a wide range of other disorders, including AIDS, Alzheimer's disease, arthritis, chronic pain, radiation injury, Sshizophrenia drug addiction and others (597,747,748). Revici proposes that the clinical manifestations of cancer are associated with an imbalance of two general classes of lipids (fatty acids and sterols) in the body and in some cases also with the presence of particular lipid constituents (conjugated fatty acids).

Using a test system he developed to measure certain physiologic changes that he believes reflect these lipid imbalances, Revici treats patients he identifies as having a predominance of one or the other class of lipid with one or more lipid-based pharmacologic agents intended to counteract the imbalance (741). Revici characterizes his regimen as a "dualistic" approach to cancer chemotherapy (747), referring to his proposal that different and opposing groups of agents, rather than a single type operating by one mode of action, may be required to treat cancer.

Revici received his medical degree in 1920 from the University of Bucharest, Romania, where he later worked as assistant professor in internal medicine. He practiced medicine and conducted clinical research in Paris (1936-41) and in Mexico City (1941-46) before settling in New York, where in 1946 he established the Institute of Applied Biology. Since 1947, Revici has maintained a private practice in New York. He also served as chief of oncology (1955-65) and as consultant (1965-78) at Trafalgar Hospital, formerly the Beth David Hospital, a New York facility purchased by Revici's fundraising organization (212,213). A recent review of Revici's career characterized that hospital as a general care facility employing over 200 resident and visiting physicians, and noted that it contained animal research laboratories staffed by 35 scientists and technicians, "all involved in projects inspired by or related to Revici's theories and therapeutic method" (212). Trafalgar Hospital closed in 1978, reportedly because of financial difficulties (21 1).

In 1949, the AMA Council on Pharmacy and Chemistry published an article in the *Journal of the American Medical Association (J.AM.A.)* warning against Revici's treatment, among other unconventional treatments (39). In a letter to the editor, the AMA article was criticized for disparaging Revici with unwarranted accusations about his work (738). The *J.A.M.A.* article was reportedly reprinted and distributed by the ACS's Brooklyn Cancer Committee, which Revici later sued for libel. The case was eventually settled out of court through mediation by the Medical Society of the State of New York (740). The ACS Committee on Unproven Methods of Cancer Management published its first statement on Revici's treatment in 1961 (22a). Since 1984, Revici has faced legal challenge regarding his license to practice medicine in New York State; he is currently on probation for a 5-year period that began in October 1988. Two malpractice suits charging medical negligence have also been filed against him in Federal court since 1983 (see ch. 11 for details).

The main source of information available about Revici's treatment is his book, published in 1%1, entitled *Research in Physiopathology as a Basis of Guided Chemotherapy With Special Application to Cancer (747),* which focuses on the theoretical basis for his approach. In it, he argues that "cancer-as well as other conditions-can be integrated into a hierarchic concept of organization which applies throughout nature." According to his theory, that organization is determined by certain laws, among them the law of dualism, or opposing forces, at every level. He discusses his views of the activity of organic and inorganic substances in relation to: the level of organization in the body at which they act (nuclear, cellular, organ, etc.); their "dualistic nature' other substances in the body (particularly lipids); and how they affect the body's defense mechanism (747). Revici believes that this dualism affects one's physiologic state and is key to understanding how disease may develop and how it may be treated.

Revici deseribes his treatment for cancer-which he refers to as "biologically guided chemotherapy" — as nontoxic, individually guided chemotherapy using lipid and lipid-based substances (210). He believes that tumor cells, as well as other types of abnorma1 cells, share a common biochemical characteristic— an imbalance in the normal distribution of lipids-which he views not as the primary cause of cancer, but as the direct cause of its impact on the body's metabolism. He categorizes two general patterns of local and systemic effects of lipid imbalances reportedly found by him in patients with cancer, one pattern resulting from an excess of fatty acids and the other pattern resulting from an excess of sterols.

According to Revici's analysis, a relative predominance of fatty acids leads to an electrolyte imbalance, specifically an increase in sodium in the extracellular fluids, and an alkaline environment in tumor tissues; Revici refers to this as a "catabolic" condition. In the opposite case, a predominance of sterols reportedly leads to a reduction in cell membrane permeability and an inhibition of the cells' oxidative processes, which in turn reduces the availability of intracellular oxygen, interferes with the breakdown of carbohydrates, and results in excess lactic acid in the extracellular fluids; Revici

refers to this outcome as an 'anabolic' condition.[12] Patients determined by Revici to have a predominance of fatty acids are treated with sterols and other agents with positive electrical charges that can counteract the negatively charged fatty acids. Those determined to have a predominance of sterols are treated with fatty acids and other agents that increase the metabolic activity of fatty acids (513,741,749).

A physician who worked closely with Revici from 1946 until 1957 noted in a summary of Revici's approach that "since the lipid imbalances appear to play an important role in determininggg the metabolic, local and systemic features of the disease," the treatment regimen is intended to modify those features by administering substances that influence the lipid imbalance. Some of Revici's research efforts focused on developing chemical agents capable of modifying lipid imbalances and on developing tests to identify and measure the balance of lipid in individual patients (741).

Revici has some support for various aspects of his theoretical approach among a small group of researchers. In a recently published paper, Harold Ladas reviewed Revici's work with selenium compounds in the treatment of cancer (513). In a recent unpublished manuscript, Leonard Kunst, Harold Ladas, and Frederick van Kampen reviewed some aspects of Revici's theory in the context of current knowledge about the role of lipids in the cancer process, and suggested that lipid substances such as those Revici uses may act by targeting and potentiating the action of antitumor agents at the tumor site (494). In another unpublished manuscript, Kunst and Ladas reviewed Revici's proposal regarding biochemical changes in lipids associated with radiation exposure and the use of n-butanol to treat radiation injury (492). A third unpublished paper by Kunst and Ladas examined Revici's ideas concerning correlations between the molecular charge and biological activity of certain types of molecules (493). In a 1985 Institute of Applied Biology publication, one of Revici's medical associates, Dwight McKee, described many aspects of Revici's current theoretical approach to treating a wide variety of conditions (597). There has been no comprehensive review in the mainstream medical literature of Revici's theory and its application to cancer treatment, however.

Revici's treatment regimen has apparently not been adopted or continued by other practitioners outside of his institute, either in the context of conventional clinical studies or unconventional practice, so at present, Revici's New York office is the only site where the treatment is used. For several years in the 1960s, however, some of Revici's treatment agents were reportedly used in Belgium by the late Joseph Maisin, who at that time was Director of the Cancer Institute of the University of Louvain and President of the International Union Against Cancer. According to several letters written to Revici between 1965 and 1970 (573), Maisin obtained a number of compounds from Revici (including fluoroheptanol, selenium diethylthiocarbamate, and others referred to as "PCA," "CMS," "MHS," "MHSe5,' and "anti-MHSe") and treated patients generally described as those with advanced metastatic cancer who had failed previous treatment. Some patients were treated with a combination of Revici's agents and radiotherapy, while others were given Revici's agents alone. These letters do not describe the conditions under which the patients were treated (e.g., as part of a formal evaluation or on an informal basis), or how particular agents were chosen for particular patients. The letters were apparently written to inform Revici of Maisin's clinical observations, and included brief summaries of some cases considered to have responded well to the treatment. Maisin noted that some patients experienced tumor regressions, disappearance of metastasis, and improved fictional status following treatment. Maisin died in 1970 and no further information about Maisin's experience with Revici's treatment is available.

Earlier in his career, Revici published papers in South American and European scientific journals (31). Since the 1950s (751,961), however, Revici has not published updated descriptions or studies of his cancer treatment in the peer-reviewed scientific literature (although attempts were reportedly made to do so (739,836)). The most recent openly available description of his cancer treatment regimen written by Revici is his 1961 book, referred to above, which provides some information from laboratory experiments and clinical experience (including case histories of patients treated with his method) supporting his theoretical approach. The book does not,

[12] Anabolic and catabolic are terms referring to the body's metabolism. In usual usage, anabolic metabolism corresponds to the constructive synthesis of macromolecules, whereas catabolic refers to the breakdown of complex materials in the body and the release of energy.

however, provide details of the empirical basis for classifying cancer patients' metabolic conditions or for choosing specific treatment agents according to that system of classification. At present, Revici and his associates appear to be the only ones who know how to interpret and apply his diagnostic and treatment protocols, since the protocols are, at least to some extent, proprietary and cannot be deduced from his book. In the absence of up-to-date descriptions of the rationale and process of his treatment regimen, it maybe impossible for Revici's treatment to be continued in the future without his personal involvement.

Revici's Cancer Treatment Regimen

In order to determine whether a patient's condition is anabolic or catabolic, Revici-tests for certain characteristics (specific gravity, pH, and surface tension) of the patient's urine before treatment is initiated. Revici believes that these indices, while not diagnostic of cancer, reflect systemic changes in the body produced by lipid imbalances (513,741). As treatment progresses, the urine is reexamined periodically to determine whether and by how much these indices change. A sterol predominant or anabolic condition is considered to be indicated by urine that is alkaline (pH greater than 6.0 to 6.2), has a high surface tension (above 68 dynes/cm^2), and has a low specific gravity. Patients whose urine measures below 6.0 to 6.2 in pH and below 68 dynes/cm^2 in surface tension are considered to be catabolic, or fatty acid predominant (741).

Revici reportedly believes that, in healthy individuals, these urine indices tend to fluctuate up and down over a narrow range around median values—pH of 6.0 to 6.2 and surface tension of 68 dynes/cm^2—while cancer patients tend to show values fixed at either higher or lower levels (741). Progress of treatment is measured by the degree to which it alters these urine indices toward normal values. Revici asks his patients to monitor these changes at home using a colorimeter to indicate urine pH. Urinary surface tension is measured using a glass "urotensiometer" (747), a device designed for Revici's use. Other urine indices reportedly used in Revici's classification method include specific gravity and a chloride index (the ratio between specific gravity and chloride concentration) (748).

The urine indices that Revici uses as diagnostic and treatment tools are not used in this way in mainstream medicine; they are not diagnostic of the presence of cancer or its systemic effects and have wide natural variations depending, for example, on fluid intake and ingestion of acid or alkaline foods or other substances. Revici's 1961 book and some of his articles discuss the use of these urine indices, but do not offer evidence validating their reliable use in identifying metabolic abnormalities, or confirming that such metabolic abnormalities actually exist among patients. In support of his conclusions about these tests and their clinical significance, Revici refers to laboratory experiments and clinical studies conducted under his direction at the Institute of Applied Biology over many years, the bulk of which have apparently not been reported, critiqued, or confirmed externally.

Revici uses the Periodic Table of Elements as one of several guides to deciding on treatment regimens for his patients. Based on his study of the organization of elements in the Periodic Table, he believes that the periods (horizontal rows) indicate at which level of biological organization in the body a particular element acts—at the level of subnuclear particles, the nucleus, the cell, the tissue, or the whole body. He also believes that the placement of elements in particular series (columns) determines whether they act anabolically or catabolically in the body (749). For example, he considers elements in group VIA-oxygen, sulfur, selenium, and tellurium-active against a chronically anabolic state (513).

According to Revici and several others writing about Revici's treatment, a wide variety of chemical agents has been used in his regimen. Revici recently stated that most of the substances he uses as treatments for cancer are either "twin formations" (reportedly defined as two adjacent carbon atoms having the same induced electrical charge (493)) or inorganic elements (e.g., iron, magnesium, copper, or selenium) incorporated in or bound to lipids (749), but he did not say which specific substances are in current use in his practice.

Since the 1940s, one of the agents Revici has frequently used to treat patients classified as having a sterol predominance is lipid-bound selenium. Revici reportedly has used many different prepmations of selenium, such as "T Sel' (selenium bound to "eleostearic acid," "Rel" ("a mixture of a 7-carbon diselenide and 3-heptanone") (513), and

hexyldiselenide (741). Other substances used to treat this classification of patients include: fatty acids (including some isolated from human and animal sources), sulfur compounds (e.g., colloidal sulfur, sodium thiosulfate), hydrines (e.g., epichlorohydrin), aldehydes, male hormones (testosterone), and mustard compounds (513).

Substances Revici has reported using to treat patients classified as catabolic or fatty acid predominant include: sterols (e.g., cholesterol), alcohols (e.g., butanol, glycerol, heptanol, octanol), female hormones (estrogens), amines (e.g., aminobutanol), nicotinic acid derivatives, metals (mercury, iron, bismuth), and halogens (e.g., iodine) (747).

The treatment agents are given orally or by injection (210). Revici's technicians prepare the treatment agents according to Revici's formulas and instructions (213). To OTA's knowledge, these treatment agents have not been analyzed independently. According to a 1989 statement on Revici by the American Cancer Society, Revici was issued 17 U.S. patents between 1981 and 1988 for chemical formulations described for use against cancer, viral diseases, and substance abuse, and for termination of pregnancy (31).

While selenium compounds can generally be toxic (197), Revici reportedly believes that he has identified a form of selenium that is nontoxic to patients (the "negative bivalent form") (213). He believes that treatment can cause inflammation around the area of the tumor, causing it to become more painful and to become larger and softer, before causing it to shrink and disappear (513). No adverse effects from Revici's treatment have been reported in the medical literature.

Claims

Revici states in his book that his treatment 'when correctly applied. . . can, in many cases, bring under control even far-advanced malignancies" (747). In support of this, he presents many case histories of cancer patients with partial or complete remissions following his treatment. The recent transcripts of a congressional hearing held in New York also contain numerous presentations by and on behalf of Revici's cancer patients claiming remissions as a result of his treatment (749). Revici concludes his 1961 book by noting:

> The results obtained and especially their high proportion, even in far advanced cases, permits a fair judgment of the place of the present form of application of this method in the fight against cancer. Based on these results, we are fully entitled to consider it, not only a highly beneficial treatment which can be offered now for this disease, but even a major step nearer to the solution of the problem of the therapy of cancer (747).

Attempts at Evaluating the Revici Treatment Regimen

In 1978, two compounds containing selenium that Revici has used—amyl selenide and selenium diethyldithiocarbamate ("Secar")-were submitted on Revici's behalf to the Drug Therapeutics Program, NCI, for testing of antitumor activity in an animal tumor screening test (l). One of the compounds, amyl selenide, showed antitumor activity in the mouse P388 Leukemia test system (905). The other compound, selenium diethyldithiocarbamate, showed no antitumor activity in this test (905). Although agents that test positive in prescreen are usually tested further in NCI'S tumor panel, amyl selenide was not submitted for further testing. Another compound, trithioformaldehyde, was said by Revici supporters to have been tested in experimental animals at Roswell Park Memorial Institute in the late 1970s (212,652), but the Institute has no records to confirm such tests or their results (754).

More recently, another selenium compound that Revici reportedly uses was tested in several other animal tumor systems. According to a letter from a British company (Advisory Services, Ltd., London), the diheptyl diselenide was reportedly tested at the Imperial Cancer Research Fund and Westminster Hospital, London, on a variety of tumor systems, and was found to be active in four of them (L1210 leukemia, Lewis lung metastasis, M5076 liver metastasis, and early S 180 tumor growth). Acute and chronic toxicity of the compound was also studied, and it was found that the dose at which antitumor activity was found was 'fairly close to the toxic dose" (484). Further studies on the compound were recommended "to determine more precisely the nature of the activity and to see if we can obtain significant anti-tumor activity without, at the same time, inducing undue toxic reactions" (484).

As a means of presenting Revici's overall clinical experience in cancer treatment, a descriptive study of clinical outcomes in all the cancer patients treated

with the Revici regimen between 1946 and 1955 was summarized in an unpublished paper (741). The paper was written by Robert Ravich, M. D., who worked closely with Revici at the Institute of Applied Biology and who, with Revici, treated the patients described in the report. Most of the patients were reported as "far advanced" or "terminal" and had had previous treatment (e.g., surgery, radiation, hormones, and nitrogen mustard). Cases included in the report were limited to those whose diagnosis of cancer was 'clearly established by the best available means, by qualified physicians, surgeons and pathologists not connected with the Institute of Applied Biology" but otherwise were not selectively included or excluded, since the report was intended to describe the entire population of patients treated by Revici during that time.

The 1,047 patients were classified as either fatty acid or sterol predominant, according to Revici's diagnostic testing (based mainly on urine analyses of pH and surface tension, as described above). Of the patients found to have a sterol predominance, 152 were treated with sodium thiosulfate and sulfurized oil; 95 with sulfhydryl containing compounds (e.g., ethyl, hexyl, heptyl and dodecyl mercaptan, methylthioglycholate, and dimercaprol); 78 with fatty acid mixtures extracted from various natural sources including human placenta, and animal and fish organs; 64 with conjugated or alpha-hydroxy fatty acids; and 53 with hexyldiselenide. Of the patients found to have a fatty acid predominance, 106 were treated with n-butanol; 77 with glycerin, 51 with cholesterol or other non-saponifiable lipids extracted from unspecified organs; and 10 with octanol. Treatment agents given to the remaining 361 patients were not specified. Individual determinations of dose were made on the basis of each patient's urine analyses and it was noted that no toxic reactions were observed. Treatments were given orally and by injection.

Both objective and subjective outcomes were recorded. A favorable objective response was defined as measurable "reductions in size and extent of the disease as visualized either directly by the eye or by X-ray, or by palpation" that were "sustained for a significant period of time and in the direction of improvement over several successive observation intervals.' However, in some cases, stabilization of disease "over long intervals" was also considered an objective response. A favorable subjective response was defined as "satisfactory improvement for a sustained period as reported by the patient," usually referring to relief from pain, a sense of well-being, and increased energy, strength, and appetite.

Of the 1,047 cases reviewed, 100 were judged to have had favorable objective and subjective responses; 11 had objective responses only; and 95 had subjective responses only. These cases included 23 different types of primary cancers. Two hundred ninety-six patients were judged to have had no response, subjective or objective, and 545 patients had equivocal or undetermined responses (380 of this latter group were treated less than 3 months). Details of the individual cases were not given in the report.

To date, the only published clinical study of Revici's treatment for cancer is a paper that appeared in J.A.MA. in 1965 written by the "Clinical Appraisal Group" (CAG), a group of nine New York physicians assembled specifically for that study (571). According to the report, the study was done at the request of the Board of Trustees of Revici's Trafalgar Hospital. It evaluated the clinical course and outcomes of selected cancer patients who were referred to Revici for treatment. The authors reported that they did not influence or modify the treatment Revici offered to these patients during the study. All of these patients were considered refractory to conventional treatment. Other criteria were that only hormone-independent (571), solid tumors, certified by tissue diagnosis, were included. Excluded from the study were tumor types that were not expected to progress in a short period of time and patients who had recently undergone conventional therapy. Thirty-three cancer patients were ultimately included in the study.

The authors reported that 22 of the 33 patients died of cancer or its complications while on the Revici treatment. Eight other patients left the study group "in unimproved condition" after some time on the regimen. Four of these eight patients later died of cancer, two of them went elsewhere for palliative treatment, and two were lost to followup. The three remaining patients were under Revici's care at the close of the study period and all of these were reported to have shown signs of tumor progression. The study group concluded that none of these 33 patients Revici treated showed signs of objective tumor regression. The group concluded that "the

Revici method of treatment of cancer is without value" (571).

Apparently responding to a full version of the report (a two-page summary of which became the published J.A.M.A. version), Revici wrote a detailed statement sharply criticizing the CAG'S methods, conduct, and interpretations (750). He also presented summaries of patient records that he claimed showed objective responses to treatment, contradicting the CAG's interpretation of the same data. He noted, among other things, that several patients in the study had tumor remissions that the study group allegedly failed to recognize. Revici also noted that it was he, rather than the Board of Directors of the Trafalgar Hospital, who requested the study in the "hope that the demonstration of positive results in even a few of these advanced cases would excite sufficient interest to lead to a large scale study of our approach.' He particularly criticized the overall conclusion stated in the full version of the report (that "the Revici method of treatment of cancer . . . should be abandoned."), he wrote:

> *In the event that this method should have proven ineffective in the types of cancer accepted (in the analysis), and not a single reduction in the size of any tumor noted, these should have been the only conclusions that could have been rightfully drawn. To conclude from a limited study, such as this, that the method should be discontinued, in all cancers, is to say that since surgery and radiation have failed in these same terminal patients, these "recognized" methods should also be discontinued, not only in these types of cancer but in all cancers in general. (emphasis in original)*

Recently, Seymour Brenner, M.D., a radiologist in private practice in New York, took initial steps toward documenting and verifying the medical records of 10 patients treated by Revici. In presenting summaries of these cases at the March 1990 meeting of the Advisory Panel for the present OTA study, Brenner stated that he believed these 10 patients to be examples of successful treatment with Revici's method, citing evidence of tumor regression, improved quality of life, and enhanced survival. These case histories have not yet been subjected to critical review. No prospective controlled clinical trial to evaluate the safety and efficacy of Revici's treatment has been conducted.

VITAMIN C

Vitamin C (ascorbic acid or ascorbate) may be discussed more frequently in connection with the common cold, but its use in the treatment and palliation of cancer has also been promoted and widely adopted; thousands of U.S. cancer patients are believed to take large doses of vitamin C (756). The proponents most closely associated with the study and use of vitamin C for cancer treatment are the Nobel laureate Linus Pauling, Ph.D., whose advocacy, expressed in books, articles, and personal appearances publicized by the media, has been primarily responsible for popularizing vitamin C for cancer, and his colleague Ewan Cameron, M. B., Ch.B., a Scottish surgeon. Treatment with vitamin C is generally promoted as an adjunct to conventional cancer treatment, with the aim, according to Cameron and Pauling, of supporting the patient's natural defenses against the disease--e.g., to support encapsulation of the tumor, to resist the formation of metastasis, to enhance immunologic competence, to reduce cachexia, and to improve general health Status (158).

Although it is an essential nutrient, vitamin C cannot be synthesized by the human body and must be derived from the diet or from supplements, which can be prepared synthetically or extracted from fruits and vegetables. Relatively small amounts of vitamin C in the diet are needed to avoid overt deficiency diseases such as scurvy. The recommended daily allowance (RDA) for vitamin C is 45 milligrams (0.045 grams) per day (661a). Its use in unconventional cancer treatment usually involves megadoses (usually 10 grams per day or more) of vitamin C, administered intravenously or orally (dissolved in water or juice or as capsules). Dosages are adjusted to each patient, but in general, they usually begin with 1 to 2 grams daily and increase gradually to 10 grams or more per day. The tolerance level is reached when the patient experiences the vitamin's laxative effects (when taken orally), and dosage is then reduced and maintained at a slightly lower level (557). Proponents state that they do not know the best dose in cancer patients, but generally assume it to be about 10 grams per day, which is "as much ascorbate as the patient can tolerate without gastrointestinal side effects" (158).

The idea of using vitamin C in cancer treatment was first proposed in the early 1970s by Cameron. Cameron examined the process of uncontrolled

invasiveness in tumor growth, and looked for ways to inhibit cancer cells from infiltrating and damaging surrounding normal tissue and from metastasizing to distant organs. He focused on the possible role of an enzyme, hyaluronidase, in supporting tumor invasiveness, and suggested that manipulation of an inhibitor of this enzyme, which existed in the blood, could be used to control the process (151). In the early 1970s, Cameron and his colleague Douglas Rotman noted that the inhibitor molecule they were examining contained an ascorbate component. They hypothesized that increasing the supply of ascorbate in the blood might increase the production or action of the hyaluronidase inhibitor, and thereby restrain the invasion of tumor cells into normal tissue (160).

Linus Pauling, working in California, considered a possible role for vitamin C in cancer treatment. He focused on the role of collagen in the process of tumor invasiveness, and noted that vitamin C was required for the synthesis of collagen (158). Cameron and Pauling, collaborating in their research, suggested that increasing the intake of vitamin C would stimulate the synthesis of more collagen fibrils and thereby strengthen it, which in turn would help restrain malignant cells from invading surrounding tissue and increase the body's natural resistance to cancer (155). They later reported that a deficiency of vitamin C was associated with a weaker intercellular matrix, and suggested that malignant cells could more easily infiltrate local tissue and metastasize to distant sites as a result (159).

Cameron began administering high-dose vitamin C intravenously to some of his most advanced cancer patients at the Vale of Leven Hospital, Loch Lomonside, Scotland, in 1971. He reported that "the majority had gained a respite period of relative well-being, comfort, and dignity" despite eventually succumbing to their disease (153). In 1974, Cameron and a colleague reported tumorregressions and subjective benefits in cancer patients treated with high-dose vitamin C (154). He and Pauling reported enhanced survival and improved well-being (improved appetite, increased mental alertness, decreased need for pain relievers, etc.) among patients who took high-dose vitamin C (156,157) (see discussion below for details of these studies).

Cameron and Pauling's advocacy of the use of vitamin C in cancer patients sets them apart from mainstream medicine, but they are by no means alone in research into the biochemical and physiologic effects of ascorbate in experimental systems. During the 1980s in particular, a wide range of experimental studies supporting a biological rationale for considering the role of ascorbate in cancer processes was conducted and reported in the literature. Many of the studies focus on the role of vitamin C in preventing the development of cancer (e.g., epidemiologic studies examining associations between consumption of foods containing vitamin C with cancer incidence), reviewed and summarized in the recent National Research Council (NRC) document Diet and Health (661). *That document also reviewed experimental evidence concerning the role of ascorbic acid in preventing the formation of certain carcinogens in the body and in enhancing cellular immunity. In addition, studies have examined the effect of ascorbate in animal tumor models, which have produced positive, though somewhat variable, results (342).*

Claims

Cameron and Pauling state that high doses of vitamin C are "helpful to virtually every cancer patient and can be dramatically beneficial to a fortunate few" (558). They claim that vitamin C "not only increases the time of survival of the patient but also leads to improvement in general health and the feeling of well-being" (158). They note in their 1979 book that:

> *Giving vitamin C in large dosage to patients with advanced cancer produces subjective benefit in almost every patient by about the fifth day. The patient will claim to feel better, stronger, and mentally more alert. Distressing symptoms such as bone pain from skeletal metastasis diminish and may even disappear completely . . . the patient becomes more lively and shows more interest and also eats more food, indicating that he has a better appetite and is no longer feeling nauseated and miserable. (158)*

Vitamin C is generally advocated as a supportive measure, not a replacement for mainstream treatment. "With the possible exception of during intense chemotherapy,' Cameron and Pauling write, "we strongly advocate the use of supplemental ascorbate in the management of all cancer patients from as early in the illness as possible . . ." (158) to make patients more resistant to their illness and to reduce toxic side-effects of mainstream treatment.

Cameron and Pauling's 1979 book, *Cancer and Vitamin C (158),* **contains brief case histories of patients who had reportedly exhausted all mainstream treatment options. Responses to vitamin C treatment are categorized as: no response (20 percent of patients), minimal response (25 percent), retardation of tumor growth (25 percent), cytostasis (the "standstill effect") (20 percent), tumor regression (9 percent), and tumor hemorrhage and necrosis (1 percent). The authors speculate that better results would be seen with earlier adjunctive use of vitamin C with surgery, radiotherapy, or hormonal treatment, although possibly not with chemotherapy (even though vitamin C is stated to protect against unpleasant side-effects of the chemotherapy).**

Pauling states that "a large body of scientific work clearly shows that vitamin C plays a central and most important role in developing and maintaining the immune system' and that it is "a key material necessary to this defense system' (556). He believes it acts by "strengthening the natural protective mechanisms of the body and making them more effective" (158).

Potential Adverse Effects

Pauling states that large doses of vitamin C can be given over long periods of time without serious side-effects. No large case series or placebo controlled studies have revealed any adverse effects of megadoses of vitamin C other than looseness of the bowels. In the two studies conducted by the Mayo Clinic (discussed later in this chapter), vitamin C megadoses were found to be relatively nontoxic (236,622). Mild nausea and vomiting, the most frequent toxic reactions, which affected 40 percent of patients in the earlier study (236), were seen in identical proportions of treatment and placebo groups.

The medical literature contains a few case reports of toxicities that might have been associated with taking large doses of vitamin C. One report suggested a risk of kidney failure in patients with preexisting renal insufficiency (587,696). Vitamin C ingestion may also increase the risk of kidney stones (812), although no cases have been reported. It has also been argued that vitamin C may increase the risk of other types of kidney stone (e.g., mate stones), and Stein and colleagues (833) noted that a single 4 gram dose of vitamin C could increase urinary excretion of uric acid, which might increase the risk of developing urate stones. No cases of urate stones have been reported in the literature, however.

Several additional side-effects noted in a small number of patients have been attributed to high doses of vitamin C, although the clinical significance of these problems is unclear. These side-effects include "rebound scurvy" (a scurvy-like syndrome) resulting from sudden cessation of high-dose vitamin C intake (8 18), gastritis (inflammation of the lining of the stomach due to the acidity of vitamin C) (821), hemolysis (breakdown of red blood cells) (161), reduction of serum ceruloplasmin activity (which suggests interference with copper metabolism) (290), and iron overload.

Attempts at Evaluating High-Dose Vitamin C in Cancer Treatment

The first major study reporting clinical results of vitamin C treatment in patients with advanced cancer was published in 1974 by Cameron and Campbell (154). They studied a series of 50 consecutive patients with advanced cancer who were under Cameron's care at the Vale of Leven Hospital in Scotland and who, at the time, had no viable mainstream treatment options. Most patients were treated with 10 g/day of oral ascorbic acid (a liquid formulation), and some began with intravenous ascorbic acid for up to 10 days, at a usual dose of 10 g/day (some received higher doses), then switching to the liquid oral formulation.

The authors categorized the responses of patients' tumors into the following categories: no response, 17 patients; minimal response, 10 patients; growth retardation, 11 patients; cytostasis (stopping of growth), 3 patients; tumor regression, 5 patients; and tumor hemorrhage and necrosis, 4 patients. In addition, the majority of patients reported improvements in well-being. Other benefits included: relief of pain from bone metastasis; in one patient, relief of headache from a cranial tumor; reduction in malignant ascites and pleural effusions; reduction in hematuria (blood in the urine) in patients with urinary tract cancers; reduced malignant hepatomegaly (liver enlargement) and reduced malignant jaundice in some patients; and halting or reversal of rising erythrocyte sedimentation rates. The authors also claimed that these patients lived longer than expected, an outcome that cannot be reliably measured in this type of study, which lacked a comparable control group.

In a 1976 study (156), Cameron collaborated with Linus Pauling, reporting on the 50 patients from the Cameron and Campbell study described above plus 50 additional ascorbate-treated patients. The patients were matched for certain characteristics (age, sex, and site and histologic features of the primary tumor) in a 1 to I0 ratio with patients not treated with vitamin C whose records were pulled from the files of the Vale of Leven Hospital. All patients in both groups had been labeled as "untreatable" with mainstream treatment. A follow-up to this study was published in 1978 (157) in which 10 of the original 100 ascorbate-treated patients who had rare cancers were replaced with 10 patients with more common cancers, for whom 10 good control "matches" could be made. A new control group was chosen from the same pool of hospital cases as for the earlier study (about half of the earlier control group was also in this group). In the 1976 and 1978 papers, comparisons of survival from: 1) frost "hospital attendance,' and 2) "date of untreatability" were presented. In the later results, which were somewhat more extreme than the earlier ones, a survival time from date of untreatability for vitamin C patients of 293 days was reported, compared with 38 days for the control patients. The survival times from first hospital attendance were 681 days for treated and 360 for control patients. Cameron knew that these studies were "less than perfect" methodologically, but he hoped that they would stimulate interest among investigators with experience in clinical trial design to carry out randomized trials (153).

The experience of 99 Japanese cancer patients, classified as "terminal," who received vitamin C during the period 1973 through 1977 has been reported by Morishige and Murata (640), researchers affiliated with the Linus Pauling Institute. The most prevalent cancers were of the stomach, lung, and uterus, accounting for more than half the total. Patients were divided into two groups for analysis: "low-ascorbate,' defined as zero to four g of vitamin C per day (44 patients), and "high-ascorbate," defined as 4 or more g/day (14 patients had 5 to 9 g/day, 13 had 10 to 29 g/day, and 28 had 30 to 60 g/day). The practice in the hospital where they were treated had evolved toward larger doses, over the time period of this retrospective review, so the low-ascorbate group was treated generally in the earlier years and the high-ascorbate group in later years.

Patients in the low- and high-ascorbate groups were compared according to "survival times after being pronounced terminal." The low-ascorbate group survived an average of 43 days and the high-ascorbate group, 201+ days (some patients were still alive at the time the paper was written). The authors concluded that this report "may be considered to substantiate the observations reported by Cameron and Pauling." They further concluded that "vitamin C seems to improve the state of well being, as indicated by better appetite, increased mental alertness, and desire to return to ordinary life." No information is given on how these characteristics were assessed.

This study has similar drawbacks to Cameron and Pauling's, mainly that the groups compared were not comparable on factors other than vitamin C. In this study, the two groups were treated at different (though overlapping) time periods, making the comparison more tenuous. The suggestive results of this study, however, reinforced the need for randomized studies.

The First Mayo Clinic Study

Cameron and Pauling's clinical studies, which generated widespread interest among cancer patients, prompted a series of three NCI-funded randomized trials of vitamin C. The first trial, conducted at the Mayo Clinic, enrolled 150 advanced cancer patients; most (93 percent) had progressive disease after prior radiotherapy or chemotherapy and the rest were considered too ill to undergo mainstream treatment (236). About 40 percent of the patients had colorectal cancer, which was also a prevalent type in Cameron's studies. About 20 percent had pancreatic cancer, 10 percent had lung cancer, and the rest had various other types.

Of the 150 patients randomized to receive vitamin C or placebo, 27 chose not to participate immediately following randomization, before they had taken any of their assigned medication. The 63 patients in the control group were given a' 'comparably flavored lactose placebo. ' The vitamin C dose was 10 g/day, as recommended by Cameron and Pauling, taken as 20 500-milligram capsules; those taking the placebo were also given 20 capsules per day. Treatment was continued until death or until the patient was no longer able to take the oral treatment. Median survival for all patients in the study was about 7 weeks.

The survival curves for the vitamin C-treated and placebo-treated groups were nearly identical. In the entire study population, there was one long-term survivor, a patient with metastatic pancreatic cancer, who had a massively enlarged liver, and jaundice. He had not responded to "many previous attempts at chemotherapy,' but had symptomatic improvement and some reduction of the jaundice, and was alive 63 weeks after entering the study. This patient was in the placebo group.

The two groups of patients taking vitamin C or placebo were found to be similar in the percentages of patients experiencing symptomatic relief and side-effects. About a quarter in each group reported improved appetite, and about 40 percent, improved activity levels. Improvements in strength and pain control were slightly greater in the vitamin C group (63 percent of patients) compared to controls (58 percent), but this difference was not statistically significant. More than 40 percent of both vitamin C and placebo groups reported nausea and leg swelling, and between 20 and 40 percent reported vomiting, heartburn, and diarrhea.

The authors concluded that vitamin C conferred no significant survival or symptomatic benefit on the patients in the study. Noting that the patients in this study differed, however, from those in Cameron and Pauling's studies in at least one respect-prior treatment with immunosuppressive chemotherapy --Creagan stated that it was impossible to draw any conclusions about the possible effectiveness of vitamin C in previously untreated patients. The immune systems of the patients in Creagan's study may have been more compromised (though not considered entirely unable of mounting an immune response) than Cameron's patients, few of whom had received prior cytotoxic chemotherapy. Creagan and colleagues noted that their patients' "earlier immunosuppressive treatment might have obscured any benefit" resulting from vitamin C.

The Second Mayo Clinic Study

The postulated interference of previous chemotherapy on the action of vitamin C prompted the Mayo Clinic investigators to undertake another randomized trial, this time including only patients with no previous chemotherapy (622). All patients had advanced colorectal cancer, a type claimed by Cameron and Pauling to respond well to vitamin C, and one for which no chemotherapy was recommended at the time of the study. These patients were not considered eligible for surgery or radiation. The doses of vitamin C and placebo were the same as for the first Mayo Clinic trial and were administered orally in the form of 20 tablets per day. No intravenous or oral liquid doses were used.

The endpoints in this trial were: survival after randomization, time to disease progression, objective regression, toxicity, and changes in pre-trial symptoms. One hundred and one patients were randomized, one dropping out before taking any of the capsules, so the analysis is based on the 100 patients who participated. Eight patients stopped taking the capsules or reduced their dosage for a variety of reasons. Three of these cases were known to be related to adverse effects of treatment: one taking placebo stopped because of intolerable side-effects, and the other two, who were taking vitamin C, reduced dosages because of gastrointestinal upset. All treatment was stopped at progression of disease, worsening of symptoms or performance status, or loss of body weight. As in the first Mayo Clinic study, side-effects were similar among the two groups, and not generally severe.

The study found no difference in time to progression of disease and no increase in survival time in patients treated with vitamin C; through the frost year of followup, 49 percent of patients taking vitamin C and 47 percent of patients taking placebo were alive, and there was a substantially larger proportion of long-term survivors in the placebo group. No patients in the study had measurable tumor regression. Eleven vitamin C-treated and 17 placebo-treated patients had some cancer symptoms at the beginning of the trial; 7 and 11, respectively (about equal proportions), reported symptomatic relief during the trial.

The Third Mayo Clinic Study

According to one of the investigators in the first two studies, a third, multi-center randomized trial, with similar treatment regimens to the first two trials, was undertaken to address criticism that the earlier trials may have been inherently biased because they were single-center trials (234). The only published report of this trial gives preliminary results in abstract form (859). The authors report no survival benefit, but "a possible but not significant trend of improved appetite, strength and pain control in the vitamin C group but no change in disability.' The median survival of all patients in the study was 6.5 weeks. Little other information is given.

According to one of the investigators (235), analysis of this study was never completed because the early results were unpromising, consistent with the results of the two previous studies. He believed that the vitamin C question had been laid to rest and did not consider it important to complete and publish full details of this study.

Australian Study

A clinical trial of the effect of megadoses of vitamin C on survival in cancer patients was begun in 1982 at the Royal North Shore Hospital in Sydney, Australia (152,540). The results of the study have not yet been published, so only the design can be described here (541). Using a double-blind, randomized prospective format, the study focused on survival time among 99 patients with Dukes D colorectal cancer who had not undergone major surgery, radiotherapy, or chemotherapy for at least 4 weeks prior to entry in the trial. Asymptomatic patients were randomized to receive either vitamin C (10 g in liquid oral doses) or placebo (liquid oral citric acid), while symptomatic patients were randomized to receive mainstream chemotherapy plus vitamin C or chemotherapy plus placebo. The vitamin C or placebo mixtures were to be continued in each patient regardless of changes in their clinical status. The study protocol did not indicate whether patients were tested for compliance to the regimen by performing urine or blood analyses for ascorbate. According to one researcher who interviewed the principal investigator of the study, no survival benefit of vitamin C over placebo was found in the study (757). OTA was unable to obtain further details about the results of this study.

Methodologic Issues in Evaluations of Vitamin C

The explicit aim of the frost two Mayo Clinic studies was to confirm or refute Cameron and Pauling's assertion that patients treated with megadoses of vitamin C would live longer than expected and would benefit from an improved quality of life during their illness. The Mayo Clinic studies attempted to test Cameron's treatment regimen in prospective, randomized, placebo-controlled studies designed to generate unbiased conclusions about effects of the treatment. As discussed above, Moertel and colleagues found that patients who were randomly assigned to vitamin C had no survival advantage over patients assigned to placebo. A major consideration in interpreting Cameron and Pauling's positive results is the possibility that "selection bias,' a problem often encountered in retrospective, uncontrolled studies, was responsible for the apparent success of the treatment.

Cameron does not deny the existence of inherent flaws in his studies, but he argues that the Mayo Clinic trials did not adequately test his premise or reproduce his procedure, and therefore do not refute his conclusions. Several important methodologic issues raised by the Mayo Clinic studies, some of which have been debated in a number of published letters and articles (621,708,710,755,756), are summarized below.

Types of Patient Enrolled-In Cameron's study, few patients were previously treated with chemotherapy, whereas in the first Mayo Clinic study, the majority had previous chemotherapy or radiotherapy. Pauling argued that vitamin C acted by strengthening patients' immune systems and that those who were previously exposed to cytotoxic chemotherapy were less capable of responding to the immune-enhancing effects of vitamin C than were patients who had not had chemotherapy. Creagan and colleagues argued that, although the patients were irnmunosuppressed, they were not totally incapable of generating an immune response. They noted, however, that their results in pretreated patients did not allow them to draw conclusions about the possible effectiveness of vitamin C in previously untreated patients. The second Mayo Clinic study addressed this issue by enrolling patients who more closely resembled Cameron's patients-patients with advanced cancer of the large bowel who were previously unexposed to cytotoxic drugs.

Method of Administration of Ascorbate—Cameron administered ascorbic acid either by intravenous solution or by oral liquid doses. In Moertel's studies, patients were instructed to take 20 tablets orally per day. It has been argued that higher blood levels of ascorbate could have been achieved using intravenous administration compared with either oral form, but this was not measured in any of the studies reported here. Also, since oral doses given in liquid form are generally easier to take than are 20 pills a day, patient compliance with the oral tablet regimen could have been lower than with an oral liquid regimen.

Testing for Compliance to the Regimen—It is possible that some patients in the Mayo Clinic trials may have taken fewer than the assigned 20 pills a day (which could result in lower vitamin C doses in

the treatment group) and that some patients may have self-medicated with commonly available vitamin C supplements outside of the trial (which could result in higher vitamin C levels in the placebo group). One or both of these possibilities could reduce the difference observed between treatment and control groups and thereby make the detection of treatment effects more unlikely.

Ascorbate concentrations in the body can be measured in samples of urine or blood. Such testing by urinalysis was not conducted in the frost Mayo Clinic trial, but was done to a limited extent in the second trial, where 11 patients were tested at one point: 5 patients assigned to the vitamin C group showed high urine ascorbate levels, and 5 patients assigned to the placebo group had "negligible" levels within the range of normal controls for the assay. The other patient assigned to the placebo group had an intermediate level, but the result was attributed to problems with the assay in that case.

Cameron and Pauling argued that the levels of ascorbate measured in patients assigned to the placebo group were higher than would be expected for cancer patients and that the testing was incomplete and inadequate to verify compliance with the regimen, since only about 10 percent of the patients were tested and then only once during the study. Moertel argued that their data, based on patient compliance records' and urinalyses, indicated that patient compliance with the regimen was very high and that self-medication among the patients assigned to the placebo group did not occur. Testing for ascorbate in blood, rather than urine, may have provided more meaningful data, particularly if such testing were done periodically during the study.

Duration of Treatment-It is common in clinical trials of cytotoxic agents for treatment to be withdrawn when patients show signs of tumor progression. In Cameron's studies, vitamin C was administered to patients in most cases until the time of death, since it was believed that vitamin C acts not by direct cytotoxic action, but by strengthening patients' resistance to the disease, slowing the rate of tumor progression, or increasing the patient's ability to forestall death even in the presence of the disease. In the second Mayo Clinic trial, vitamin C or placebo was withdrawn when patients showed signs of significant tumor progression or deterioration in general or symptomatic status, since such signs were taken to indicate treatment failure. Cameron and Pauling argue that normal procedures for dealing with cytotoxic drugs in clinical trials should not have been applied to vitamin C.

In addition, Pauling believes that patients could have been harmed by the sudden cessation of high doses of vitamin C, and that gradual reduction in dose is a safer approach to stopping treatment. Pauling states that high blood levels of vitamin C can drop to below normal levels when intake is stopped abruptly (described as the "rebound effect") and that for a period of a week or two, very low ascorbate levels can cause greater susceptibility to infection, decreased resistance to the disease, or worsening of an existing condition (158,555). Experimental evidence exists for a biochemical effect in the body of sudden cessation of high doses of vitamin C, but it has not yet been shown that these biochemical changes lead to overt changes in physical condition among cancer patients. In Moertel's study, patients treated with and then withdrawn from vitamin C showed similar survival times compared to patients in the placebo group, but other possible adverse effects of ascorbate withdrawal were not specifically reported.

Although the Mayo Clinic trials addressed some of the relevant questions pertaining to the effects of vitamin C, they do not appear to have settled the controversy surrounding its efficacy in cancer treatment. In addition to the issues discussed above, the Mayo Clinic trials did not fully address Cameron and Pauling's claims that vitamin C improves the quality of life of advanced cancer patients in helping to control pain and improving general well-being. Cameron and Pauling found easing of pain particularly in patients with bone metastasis; few patients in the Mayo Clinic trials had bone metastasis. Among the issues noted above, only the issue of testing patients not previously treated with chemotherapy was addressed in subsequent evaluations. The other issues remain unresolved and lead to difficulties in interpreting the results of the two Mayo Clinic studies.

Cameron reported that he and Pauling submitted a collection of "best cases" to NCI for review in December 1989. According to Cameron, NCI is sponsoring a symposium at NIH in September 1990, on experimental research concerning biological functions of ascorbate in relation to cancer (153).

Chapter 6

Immuno-Augmentative Therapy

CONTENTS

Chapter 6
Immuno-Augmentative Therapy

INTRODUCTION

This chapter is devoted to a single treatment, Immuno-Augmentative Therapy (IAT). IAT is covered more extensively than other treatments in this report because, in addition to being asked to produce an overall report on the topic of unconventional cancer treatments, OTA was asked to seek a way to gather valid information on the effectiveness and safety of IAT. The request concerning IAT was initiated by then-Congressman Guy Molinari of New York, and cosigned by about 40 other Members of Congress. The request arose because the IAT Clinic, located in the Bahamas, had been closed by the Bahamian Government at the recommendation of the Pan American Health Organization (PAHO), after contamination of IAT treatment materials with hepatitis B and the AIDS virus was reported. Congressman Molinari acted in the interest of constituents who were patients at the clinic. In response to the request, OTA attempted to develop a clinical trial protocol for IAT as a case study under the umbrella of the larger study. IAT is popular among unconventional treatments, but no evidence existed when OTA began this study in 1987, nor does it exist 3 years later, to suggest that IAT is more or less "promising" than many of the other treatments discussed in this report.

The development and current use of IAT and background on its developer and practitioner, Lawrence Burton, Ph.D., are covered in the first part of this chapter. OTA's unsuccessful attempt to develop a clinical trial protocol in agreement with Burton is discussed in the latter part.

BACKGROUND ON IAT

IAT is one of the most widely known unconventional cancer treatments. Treatment consists of daily self-injections of processed blood products, continuing for the life of the patient. IAT patient literature states that IAT acts as an immunologic control that causes most types of cancer to either stabilize or regress (430). Biologist Lawrence Burton, Ph. D., developed IAT and first offered it to cancer patients in the 1970s at an office in New York State. Burton left there in 1977 to start the Immunology Researching Centre, Inc. (IRC) in the Bahamas. A second clinic under his direction was opened in 1987 in West Germany, and a third opened in Mexico in 1989.

Various State and Federal legislators have, in recent years, sought to broaden the availability of IAT. In 1980, a bill was introduced in Congress (though not passed) to exempt the "blood fractions" used in IAT from the requirements of the Federal Food, Drug, and Cosmetic Act (FDCA) for 5 years.[1] The Florida and Oklahoma Legislatures enacted laws (since repealed) in the early 1980s to permit the prescribing and administering of IAT in those States (32). In 1986, U.S. Congressman Guy Molinari of New York held a special public hearing on IAT. Subsequently, he and 41 other Congressmen and Senators signed letters to OTA requesting an evaluation of IAT.

In July 1986, the Food and Drug Administration (FDA) imposed an import ban, prohibiting bringing IAT into the United States, "due to the direct hazards that have been associated with IAT agents" (888). Although the circumstances under which IAT is manufactured and offered have reportedly been improved (115,553), the ban remains in effect and IAT products may be confiscated by U.S. Customs or Postal officials. The ban is generally not enforced, however, and there have been no reports of IAT seizures or of IAT patients without access to treatment materials (426).

Burton's cancer treatment, his controversial career, and the circumstances under which he manufactures and offers IAT have intrigued the press and public for many years. IAT has been described in several books that are widely read by U.S. cancer patients (341,510,531,648) and was the subject of a 1980 segment of the television program 60 Miinutes *(782). Magazines such as* Penthouse *(685) and New York (49), and journals that advocate unconventional medical treatments (20,496) have also carried stories on IAT.*

[1]House of Representatives Bills 7936 (Aug. 18, 1980) and 8341 (Nov. 13, 1980), introduced by Representative McDonald.

Several organizations, including the American Cancer Society (ACS) (27), the National Cancer Institute (NCI) (246,901), FDA (679,888), and the Centers for Disease Control (CDC) (882,883), have published statements warning U.S. cancer patients against using IAT. Some of these statements are based on possible viral contamination of IAT. Since IAT materials are not tested regularly by any independent laboratory, it is not known whether the claimed improvement in manufacturing and viral testing procedures since 1986 effectively mitigates the risk of biologic contamination identified at that time.

Burton's Theory of Cancer Control Through Augmentation of the Immune System

The IAT patient brochure describes a specific anti-cancer immune system in mammals and states that "it works optimally when a balanced proportion of activated components are present. Burton adopted this theory early in his career and he continues to cite it (114). However, despite the fact that laboratory technology to do so has existed for many years, Burton has never directly demonstrated that the factors he describes actually exist in IAT, nor shown that IAT has activity to alter the course of human cancers.

Burton asserts that IAT is based on restoring optimal function to the native immune system, one function of which "is to recognize and destroy neoplastic cells and thus to serve as a natural mechanism for the control of carcinogenesis' (430). Burton maintains that "an immune defense against cancer antigens is at least initiated in most, if not all, persons who contract cancer." The IAT brochure states that "some patients' immune systems are initially impaired by cancer itself, or were previously impaired to allow the disease, and are then further weakened in patients treated by radiation or chemotherapy." This allows "mutant cells that otherwise would have been neutralized or destroyed . . . to proliferate, invade nearby tissues, and migrate to other parts of the body' (430). Burton claims that "immune augmentation' with IAT will "destroy the cells and metastatic or local recurrence of cancer" (430).

John Clement, M. D., a physician at the IRC, describes the theory behind IAT as follows:

> ***In the normal healthy person any mutant cancer cells are recognized and antibodies attempt to destroy them; this reaction is promoted by Tumour Complement (TC), which is produced by cancer cells, and is the effective signal to the antibodies to destroy that cell. These necrotic tumour cells are then passed to the liver to be "sanitized." If tumour cell necrosis occurs too rapidly the liver can be overloaded, leading to production of Blocking Proteins which shield tumour cells and slows down the antibody reaction to those cells. Patients with cancer may have very high levels of this Blocking Protein. Deblocking Proteins neutralize this blocking action and so enable antibodies to access the tumour cells. Patients with cancer tend to have a deficiency of Deblocking Protein.***
>
> ***. . . in order to effect this control you need Tumor Complement produced by the cancer cell to alert and activate the Antibodies and you also need sufficient Deblocking Protein to neutralize the Blocking Protein and allow the antibodies access to the cancer cells. (200)***

At least four IAT products maybe prescribed to treat human cancer patients. The IAT brochure states that some of these are manufactured from the pooled blood of cancer patients and others from the pooled blood of human donors who do not have cancer. The brochure (430) describes IAT products as:

> *Deblocking Protein* ***(DP)—an alpha 2 macroglobulin[2] derived from the pooled sera of healthy donors.***
>
> *Tumor Antibody 1 (TA1)-a* ***combination of alpha 2 macroglobulin, IgG, IgM, and IgA[3] derived from the pooled sera of healthy donors.***
>
> *Tumor Antibody 2* ***(TA2)-differs from TA1 in potency and possibly composition of immunoglobulins; also derived from pooled sera of healthy donors.***
>
> *Tumor Complement (TC)-a* ***substance isolated from blood clots of IRC patients with many types of cancer. Described as complement C3[4] that is uniquely active in activating TA1 and TM.***

---

[2]In usual scientific use, alpha 2 macroglobulin would refer to anantibodybelonging to one of the five major classes of bloodborne immunoglobulin, the Ig M group. Although Burton describes DP as an alpha 2 macroglobulin, to OTA's knowledge he has produced no analytical results to confirm that. No alpha 2 macroglobulin that has been identified by mainstream researchers has the properties Burton ascribes to DP.

31@, IgM, and IgA are three of the five classes of bloodborne immunoglobulins. IgM molecules are also called macroglobulins.

[4]In usual scientific use, C3 refers t. one of a group of plasma proteins that are activated to various immunologic functions by antibody-antigen complexes.

There is no record of Burton's carrying out biochemical analyses of these materials to identify their components, and his patents describing their manufacture prescribe no tests for verifying identity. Nor has independent analysis of IAT materials been reported from samples provided directly by Burton. Reference to analysis is made in a popular article (982) on IAT, which says that it has not been classified "down to the last molecule," but that there were "some limited chemical and immunochemical analyses run by an outside chemist several years ago." The article goes on to say that Burton and his former partner Friedman were told that the substances contained " alpha^{2}macroglobulin, "immunoglobulin A" and traces of "complement C'3." There is no indication of who did these analyses and no actual record of the results.

NCI analyzed IAT treatment materials provided by the family of a deceased IAT patient in 1984. According to the NCI analysis, all the treatment materials were dilute blood proteins, in which the major component was albumin, and all were reported to be devoid of the components described in the IRC brochure (246).

The IAT Cancer Treatment Regimen

Burton states that treatment regimens are based on his determination of the patient's initial immunocompetence and the responses of past patients with similar status, which have been compiled in a computer program. As treatment proceeds, Burton tests patients' blood daily or twice-daily for the relative concentrations of four basic factors: Tumor Antibody (TA1 and TA2), Tumor Complement (TC), Blocking Protein Factor (BPF), and Deblocking Protein Factor (DPF). BPF "blocks" the claimed antitumor effects of TA1 and TA2, and is not administered as part of the IAT regimen. Burton adjusts the daily prescription of TA1, TA2, TC, and DPF in light of his blood tests during patients' initial 6-to 8-week course (430). Patients inject themselves subcutaneously or intramuscularly with the prescribed amounts. Other medications (e.g., prednisone, a corticosteroid) are also prescribed for many patients (199).

After the initial treatment period at the IAT clinic, patients generally return home with supplies of IAT to continue self-injections according to a schedule provided by Burton, based on his proprietary computer program (115). At regular several-month intervals, or if patients have acute illnesses unrelated to their cancer or the treatment, they are encouraged to return to the IAT clinic for further assessment and adjustment of their treatment regimens (199). Burton advocates surgical removal of cancerous tissue before beginning IAT, to the extent possible, but discourages chemotherapy or radiotherapy (1 15).

Burton's Pre-Clinical Research

Burton asserts that the basis for IAT, as it is currently offered, is the pre-clinical research that he and his colleagues conducted at U.S. research institutions (114,430). Burton and various colleagues published about 20 papers dealing with biological factors affecting turners in fruitflies and mice in scientific journals between 1954 and 1963, and brief abstracts of additional work with mice and humans through 1969. One or two articles on human research were reportedly submitted for publication through 1972 but were never published.

Research on Fruitflies

As graduate students in biology at New York University, Burton and his colleague Frank Friedman studied the inheritance of various traits in fruitflies. Though many researchers were studying fruitflies at the time, Burton and Friedman were apparently alone in postulating that tumor-bearing fiuitflies contained a transmissible, biologic factor that could be isolated, injected into, and cause tumors in other fruitflies (113,117,123,380).

Burton and Friedman received their doctoral degrees from New York University in 1955 and, in 1957, went to the California Institute of Technology (Caltech) for post-doctoral training. In the course of their research at Caltech, Professor Herschel Mitchell advised Burton and Friedman on developing a method to purify the tumor factor they had reportedly identified in fruitflies (618). They later reported that purified tumor induction factor, "TIF," had interspecies activity (between fruitflies and mice), while the crude extract did not (315). After a series of experiments (122,312,313), Burton and his coinvestigators concluded that TIF, the presumed active component in the purified fruitfly extracts, contained protein, nucleic acid, and lipid (312), and was most likely a tumor-inducing virus (122).

Burton and his colleagues hypothesized that the variable tumor-inducing potential of TIF that they observed in different stages of its purification was explained by other substances that motified its

activity or had independent tumor-inducing or inhibiting properties (121,309,310,312,313). However, these conclusions are also consistent with an assumption that the fruitfly bioassay was valid, and neglecting to consider the inherent variability of the test as an alternative explanation for their results.

Burton and Friedman's research was questioned at Caltech when it was noted that the control fruitflies in their experiments had no injection scars while their experimental animals did, although the research protocol called for injecting controls with an inert material (618a). After this was reported, Renato Dulbecco, Ph. D., then Professor of Virology (later a Nobel laureate), became skeptical about the results already published, and Burton and Friedman were asked to participate in a validation of their assay. Mitchell reported on this experiment and his own attempt to reproduce Burton and Friedman's findings in *Science (618).* Using Burton and Friedman's own materials and reported purification methods, George Beadle (another advisor) and Dulbecco presented Burton and Friedman with "coded samples containing only buffer solution or buffer plus various concentrations of 'purified TIF.' " Mitchell reported that, "using their own fruitfly assay, Burton and Friedman could not distinguish buffer solution from TIF solution."

To rule out possible explanations for the failure of the blind experiment, Mitchell himself repeated Burton's tumor transmission experiments on more than 2,000 fruitflies. The percentage developing melanotic inclusions (which Burton and Friedman identified as "tumors") varied from experiment to experiment (from 2 to 80 percent), but the percentage of controls with these inclusions was always similar to the percentage of experimental, when injected at the same time, suggesting no effect of TIF. Burton and Friedman left Caltech shortly after this series of events.

In his report in *Science,* Mitchell stated that he "would be pleased to be forgotten as a collaborator' in Burton and Friedman's work (618). In a letter to OTA, Mitchell concluded that 'none of the work on the so-called tumor factor in Drosophila is valid and this fact raises serious doubts about the validity of subsequent claims. '

Research on Mice

In 1958, Burton and Friedman began work as Research Assistants in the Department of Pathology at St. Vincent's Hospital in New York. Later they were promoted to Associates, and then Senior Associates in Oncology in St. Vincent Hospital's Hodgkins Laboratories. As members of a small research staff, Burton and Friedman worked with Robert Kassel, Ph.D., and Antonio Rottino, M.D., a pathologist and Director of St. Vincent's Laboratories. They began to investigate biologic substances that might affect tumors in mammals.

They injected purified extracts from leukemic mice into both fruitflies and newborn mice with a low natural incidence of cancer and reported the surprising induction of cancers other than leukemias in the mice (469), and speculated that the substance was similar or identical to the TIF previously discovered in fruitflies. Burton and colleagues asserted that identification of the factor was less important than defining its mode of action (120), and assumed that similar activity correlates with similar identity. Biochemical tests of identity were never carried out to confirm the similarity to the fruitfly material.

Burton and his colleagues subsequently reported that they had isolated substances similar to TIF from several other species of animal, including a human patient with lymphoma (120,311). They stated that since TIF from human sources induced tumors in test mice, this suggested that TIF was not species-specific and that "the purification procedure apparently removed substances responsible for the maintenance of the. species specificity barrier."

Burton's published work in the early 1960s concerned TIF's interaction with various modifying agents in mammalian cancer. A brief abstract by Burton and Friedman on tumor remission in mice (injected with extracts of mouse and human origin) stated that tissues of leukemic mice contain two oncolytic (anticancer) substances, "V' and "I" (118). While "I" was stated to produce a 50 to 100 percent reduction in mouse lymph node and spleen size within 24 hours, "deleterious side effects' were produced. Lesser amounts of "I" were needed to reduce organ size when given with "V," and in this situation, the side effects did not occur. The abstract also stated that daily administration of combined "I" and "V" to mice with early leukemia for 4 weeks eliminated palpable disease in 26 of 50

treated animals, and that the treated group survived longer than did the untreated controls. What appears to be the same experiment was included in the 1963 presentation and paper discussed below.

Burton and his colleagues presented three papers about tumor induction and inhibition in mice at the New York Academy of Sciences in 1%2 (119,311,470). They described an elaborate system of bloodborne tumor-inducing and inhibiting factors that was stated to exist in mammals. The effects of injecting different combinations of purified extracts were described, some of which reportedly reduced measurable tumors in mice. In these presentations, Burton's group first speculated that injection of carefully balanced doses of these factors could be used therapeutically to control mammalian cancers. They reported on six experiments with leukemic mice, including the results that, in five of the experiments:

> *. . . 37 of 68 experimental animals survived for an average of 131 days without any evidence of leukemia. The leukemia had gradually regressed, as evidenced by reduction of palpable nodes and spleen, until it was eliminated by the end of the fourth week of treatment.*

They reported that average survival of untreated mice was 12 days.

In 1963, the team presented a summary of their research on tumor-inducing complexes in mammals to the New York Academy of Sciences (subsequently published in the Annals of the New York Academy of Sciences (468)) *describing the response of cancerous mice to various combinations of purified fractions. In leukemic mice, they reported that the untreated controls died after an average of about 13 days. About half of the treated mice died after an average of about 37 days, and the other survived much longer. In mice with mammary tumors, they reported significant decreases in tumor volume in the treated groups and significantly increased volume in the controls.*

The authors concluded:

> *The study of the biological action and interaction of these components in mice bearing spontaneous neoplasms has suggested the existence of an inhibitory system involved in the genesis of tumors and capable of causing specific tumor cell breakdown.*

This talk met with a mixed reception among researchers in attendance. Of particular concern was the fruitfly assay that they were still using as part of the mouse experiments. During the discussion, Kassel indicated that they were in fact using a new assay, based on blackening and death of fruitflies, that was "much less complicated than identifying a tumor and also bypasses this question. " Burton stated that the new assay correlated completely with their old assays and they had given them up.

At about this time, Kassel left St. Vincent's to pursue research elsewhere and was involved in the discovery of tumor necrosis factor (170). In 1966, Burton and Friedman presented a demonstration of their extracts' ability to shrink tumors in mice to the Science Writers Seminar sponsored by the American Cancer Society. They injected four mice with hard mammary tumors with their serum fractions, and, one observer wrote, within 45 minutes the tumors had become soft and shrunk by half their original size (982).

Some observers were amazed and others were skeptical. Some journalists quickly sensationalized Burton and Friedman's demonstration. One newspaper headline read, "15 Minute Cancer Cure for Mice: Humans Next?" (565). An oncologist who examined the mice following the demonstration later stated that "it was obvious that he had massaged the tumors until they had become fluid and then aspirated out the tumor and necrotic material. ' He stated further that a "fresh puncture wound was found at each tumor site' (638). Although his colleagues apparently took this mixed response in stride, Burton was reportedly infuriated (982). After the science writers' seminar, the ACS offered to fund Burton and Friedman's research, on the condition that it proceed in collaboration with a team of clinical research oncologists. The ACS offer was refused. The mouse demonstration was repeated before oncologists and pathologists at the New York Academy of Medicine in September 1965, but there was apparently skepticism and little interest in pursuing their research.

A brief abstract in 1965 reported an experiment in which 48 tumor-bearing mice were injected with "I" and "V" extracts derived from leukemic mice and from cows with lymphosarcoma (314). The abstract states in part:

Small tumors disappeared in 2 hours. Larger ones softened-liquefied in 24 hours and in many instances, resorbed in 2 to 4 days. Many of the mice died, the cause of death being associated with *massive hemorrhage into the tumor.... Conditions necessary to obtain survival after tumor liquefaction included a precise ratio mixture of V and I and the precise dose.*

Treatment of Human Cancer Patients With IAT

Burton described the use of IAT in cancer patients at the hearing held by Congressman Molinari in 1986 (see above) (114). Burton recounted that Antonio Rottino, M.D., then Director of Laboratories at St. Vincent's Hospital, administered some of the purified blood fractions prepared by Burton and Friedman to a few terminal cancer patients during the mid to late 1960s. Burton recalls some encouraging results in this undocumented initial human trial.

An early goal of Burton and Friedman's human research was to develop a blood test to measure the effects of their injections. Burton testified that a paper submitted in 1972 to the Society for Experimental Biology and Medicine reported the isolation of "Blocking Protein" (BP), which Burton described as a titratible substance that reflected tumor status and could be used to monitor changes. Burton stated at the Molinari hearing that this paper was rejected for publication because it included insufficient information on the substance's identity. This was one of his last attempts to publish his work in the scientific literature.

Burton and Friedman left St. Vincent's in the mid 1970s. With the support of clergy, businessmen, and several physicians, the Immunology Research Foundation (IRF) of Great Neck, New York was established on their behalf in 1973. It was there that significant numbers of cancer patients were first treated with IA" By the late 1970s, more than 100 cancer patients had been treated at IRF. Also during that period, Burton and Friedman obtained five U.S. patents for four IAT-like products and the methods by which they are produced (432,433,434,435,436). They also took initial steps with FDA toward obtaining Investigational New Drug (IND) status for MT. The FDA did not allow the IND to proceed because it lacked specific information that they required (889), and eventually, Burton and Friedman withdrew the IND. The Great Neck facility closed in 1977, and Friedman ended his affiliation with both Burton and IAT (308).

Later in 1977, Burton's New York sponsors helped him to establish the Immunology Researching Centre, Ltd. (IRC) in Freeport, Grand Bahamas (958). It was intended by the sponsors as a research institute, with investigational treatment to be provided to cancer patients. The initial plan was to treat 3,000 to 5,000 cancer patients according to a specific study protocol submitted by IRF to the Bahamian Ministry of Health (957). In practice, IAT has not been provided according to a formal study protocol, and clinical data have not been collected systematically, beyond patient history and encounter records.

In 1978, the Bahamian Ministry of Health asked the Pan American Health Organization (PAHO) to participate with them in a joint site visit to IRC after its first year of operation (852). Based on this visit, PAHO recommended to the Ministry that IRC be closed in large part on grounds that IRC was not carrying out its stated intent, part of its agreement with the Government of the Bahamas to operate there, to evaluate IAT as a cancer treatment. The site visit report concluded that "the present procedures of the Center do not permit any meaningful evaluation,' and further that "it is highly unlikely that any change in procedures will make the treatment evaluable. They observed in addition that "no consistent treatment effect has been achieved when assessed by objective criteria. "

Commenting on IAT treatment materials, the report states:

> *The material being used to treat patients is similarly a totally unknown quantity. Although the various fractions are referred to by Dr. Burton as "antibody fractions' and 'complement fractions,' there is in fact no evidence that any of these fractions do contain antibody of any relevance to the tumor involved or that in fact there are any active or even inactive complement components.*

The Bahamian Government did not close the clinic after the PAHO report was issued.

As scientific knowledge about the human immunodeficiency virus (HIV, the AIDS virus) and technologies for detecting it emerged in the mid-1980s, the safety of all biologics derived from human blood and blood products, including IAT, began to be questioned. In 1985, two patients in Washington State brought vials of various IAT products to the health

department for testing. Using ELISA (enzyme-linked immunosorbent assay) screening tests, all tested vials were reportedly positive for hepatitis B surface antigen, and 8 of the 18 were reported positive for HIV antibody (diagnostic for the presence of the viruses themselves) (883).

The set of IAT vials and accumulated test data were then sent from Washington State to CDC for additional testing. At CDC, repeat testing by ELISA identified 6 vials positive for HIV antibody, and all 18 positive for hepatitis B surface antigen. Results of more definitive Western Blot testing on all 18 vials were uninterpretable. The final test, the "gold standard' for establishing the presence of HIV, is to grow it in lymphocyte culture in the laboratory. A sample from one of the IAT vials did contain live HIV which was grown and isolated by this method. Thirteen of the vials were also positive for hepatitis B antigen (883).

As a result of these tests (all had been completed except the HIV culture), the Bahamian Ministry of Health asked CDC and PAHO to send a scientific team to IRC, to determine whether a public health hazard existed. On July 2, 1985, the scientists toured the facility and met with Burton and his staff concerning sterility practices and precautions.

Burton told the site visitors that he did not acknowledge the association of hepatitis B surface antigen with the potential for infection, nor the association of HIV (then called HTLV-III or LAV) or HIV antibody with AIDS. Burton said he relied on micropore filtration and heating during processing of the products to eliminate biological contaminants and product infectivity. He stated also that the sterility of the serum is checked by injecting it into laboratory mice and monitoring for sickness (89). In his trip report, the PAHO Chief of Epidemiology, who led the site visit, concluded that the clinic should be closed for several reasons, beginning with:

> *First and foremost, the clinic is producing an unsafe biological product with procedures and methods which appear to be unsafe for the staff involved. There are no indications of real interest in establishing accepted quality control measures. (830)*

Later that month, the Bahamian Government closed the IRC.

During the period the clinic was closed, Congressman Guy Molinari visited IRC, and in January 1986 in New York, held a "congressional public hearing on the Immuno-Augmentative Therapy of Lawrence Burton" (114). At that time, the patients formed the IAT Patients' Association (LATPA), and reportedly shared the IAT treatment materials that they had among them.

The clinic reopened in March 1986, after IRC agreed to conditions set forth by the Bahamian Government, including the acquisition of equipment to screen blood sources for HIV and hepatitis B; regular reporting of all viral test results to the Ministry of Health; compliance with standard blood donor screening and collection practices; treating only non-Bahamian cancer patients; requiring that patients who begin IAT have a confirmed outside diagnosis of cancer; and requiring review by the Ministry of full medical records for all new patients.

Scientific Review of Burton's Patents

The IAT patient brochure states that the methods of isolation and extraction for the IAT fractions given to patients at IRC and for blocking protein are described in five U.S. patents (two patents pertain to "Blocking Protein' issued to Burton between 1978 and 1980 (430). The findings reported here come largely from a contract report to OTA (725) and comments on it by outside reviewers.

The patents describe substantially different substances and processes than those described in Burton's pre-clinical research. The relationship to his previous work is not direct. The extent to which the patents describe the process actually used at the clinic also is unknown, as there are no available eyewitness accounts of its preparation.[5]

The patents are confusing and complicated, without being particularly complex or sophisticated scientifically, and all contain directions that would make it impossible to assure that the end products would be similar from batch to batch. These directions include ranges of settings on analytic instruments, ranges of processing times, and the necessity of taking precise readings that go well beyond the reliability of the laboratory equipment specified. In addition, the methods described to

[5]OTA has been criticized, in review comments by Robert Houston, for assuming that the patented procedures accurately represent the production of IAT at the Clinic, as is stated in the brochure. Mr. Houston asserts that "patents often omit key elements and blur important details as a safeguard against infringement."

establish the identity and potency of the products are often convoluted; many steps are repeated with no clear purpose, after which the process returns to a previous step.

The essential method of isolating the specified fraction in each of the patents is by differential centrifugation-spinning at high speeds—many different times. Centrifugation alone is an ineffectual technique for isolating specific proteins, contrary to what is claimed in the patents (725). For example, "Prol A Fraction" (corresponding to Tumor Antibody in the IAT patient brochure) is described as an antibody, meaning that it belongs to a particular class of protein with distinct immunologic activity. Using the patented Prol A Fraction recovery technique, however, it would not be possible to isolate an active antibody.

In the Tumor Complement Fraction patent, ammonium hydroxide (a strong base in the acid-base system) is used to adjust the pH of the material. This will damage or inactivate most components of the immune system, including all elements currently thought by mainstream researchers to be active against cancer. The procedures for Blocking Protein Fractions I and II could not specifically produce anything except clarified blood serum. While substances present in the original donor serum (except the active immunologic molecules which would be inactivated by a heating step) might remain in the final product, these would vary from batch to batch, depending on what was initially present.

It is possible that immunologically active substances, such as lymphokines, tumor necrosis factor (TNF), etc., could be present at various stages of the IAT manufacturing process, but it appears likely that they would be inactivated by the process, and if present at all, could be in only trace amounts.

The "MetPath contract"

60 Minutes, in its May 1980 episode about Lawrence Burton (782), Glassman's book, *The Cancer Survivors* (341), and Lerner's *Integral Cancer Therapy* (531) (citing Glassman) all report that a major U.S. manufacturer of diagnostic technology, MetPath, had been interested in Burton's blood test for detecting cancer. According to *60 Minutes*, MetPath entered into a contract with Dr. Burton in July 1979, in the frost phase, to "verify the existence and determine the measurability of the substance in serum said by Dr. Burton to be related to the presence or absence of cancer.' They reported further that MetPath setup a laboratory in Freeport to "see if there really was a protein in the blood of patients who have malignant disease," and to ascertain if their scientists could measure "what Dr. Burton said he was measuring." MetPath was reportedly able to find a "strange protein in the blood of certain of the specimens." According to a 1981 letter from Paul Brown, M.D., Chairman of the Board of MetPath at the time of the interaction with Burton (105a), MetPath was unable to develop a reliable test based on Burton's information and "extensive laboratory testing." There were 25 percent false positives in patients without cancer, and 25 percent false negatives in patients with cancer.

Glassman reported that MetPath sent 193 coded vials of blood samples, four from cancer patients, to Burton for testing. She states that Burton identified the cancer patients correctly, but also identified six other samples as positive. While MetPath initially considered them 'false positives,' Glassman states that within a year, all six had been diagnosed with cancer. Brown stated:

> MetPath did, in fact, send a certain number of vials of blood samples to Dr. Burton in the Bahamas for testing. The results obtained by Dr. Burton were substantially delayed and were not received by MetPath until well after the original specimens had been destroyed. Accordingly, no conclusion can be drawn from the results of this testing trial. We are not aware of the basis for the assertion that the results were "spectacular" or that the "tests proved to be 100% accurate and identfied the blood specimens of patients known to have cancer."
>
> We are quite distressed at the assertions being made by Dr. Burton and hope that this letter will put any misconceptions to rest. (105a)

OTA could find no other documentation of the relationship between Burton and MetPath, and no specific references were given in the books cited or by *60 Minutes*. We contacted MetPath to see if the original test results were available for independent analysis. They replied that they no longer have the records. The medical personnel with a memory of this event hold the general view that the assay did not work (486), as reported in 1981 by Paul Brown.

Information on Safety

No formal studies have been done to identify possible adverse effects of treatment with IAT. The information presented here includes past reports of safety problems (documented and suspected) and indicates potential areas of concern.

Risk of Inherent Treatment Toxicities[6]-The IAT patient brochure states that earlier animal research has shown IAT to be non-toxic; however, no systematically collected data are available to support this statement, particularly as it applies to human beings. Early publications suggested that the materials Burton was studying in mice may have had some liver toxicity, however, these papers did not contain detailed physiologic data. In support of Burton's application to open the Bahamas facility in 1977, the Immunology Research Foundation of New York reportedly submitted unpublished data on 100 human beings injected with one IAT product, among whom no toxicity was noted (852); but OTA was unable to obtain these data.

Potential Side-Effects—Based on the anecdotal reports of patients, in most cases the short-term side-effects of IAT appear minor (426). John Clement, an IRC physician, states that IAT is generally non-toxic, and the few side-effects reported have been minor (e.g., fatigue, malaise, pain at the site of injection or at bony metastasis, flu-like symptoms, somnolence) (199).

Risk of Exposure to Infectious Agents—As with any treatment material produced from human blood, IAT poses some risk of infection to patients, which could be minimized with appropriate manufacturing practices and product testing. Donor screening practices, the exact precautions taken during manufacture, whether standard "good laboratory and manufacturing practices' are followed, and the infection rate in IAT patients all are unknown.

The most serious safety concern is the possible contamination of IAT with viruses, including HIV and hepatitis B. Equipment to test for hepatitis B antibody, which has been required of U.S. blood centers since 1972, and for HIV antibody, which has been used voluntarily by manufacturers of biologics and by blood banks since 1985, was brought to IRC as a condition set by the Bahamian Government for the clinic to reopen in 1986. The IAT production processes themselves, as judged from Burton's patents and statements he has made about the processes, are not likely to be sufficient to inactivate these viruses.

Contamination of IAT products with Nocardia, a bacterium, was reported in the early 1980s, and was linked to nocardial skin infections and abscesses in IAT patients (850). By 1984, CDC had reports of 16 IAT patients with abscesses at injection sites, most of those cultured due to Nocardia, but other organisms (Staphylococcus aureus, Escherichia coli, an Actinomyces-like organism) were cultured from some patients. Four vials of IAT serum analyzed by CDC at that time were contaminated with a number of disease-producing organisms (882). NCI also studied treatment materials provided by five IAT patients in 1984, and reported that all were contaminated with bacteria (246). Burton has attributed the Nocardia problem to an air-conditioning vent from an adjacent animal laboratory, a problem he states was corrected by separating animal laboratories and manufacturing laboratories in a new IRC building (199). The poor laboratory practices and the potential for transmission of bloodborne infectious agents was the main reason PAHO gave for recommending that the clinic be closed in 1985, as discussed earlier (830).

Cassileth and colleagues surveyed IAT patients by telephone to find out the results of any tests for HIV or hepatitis B that they had. Fifty-four IAT patients and 25 next-of-kin of deceased patients were interviewed. Of 23 who had been tested for hepatitis B antibody, 4 tested positive, and 1 of 24 patients tested for HIV antibody reported a positive result. Although these data provide no information about the source of infection, the authors conclude that the findings suggest a need for "more careful, controlled testing of the immune serums and their preparation by its proponent." They noted also that the patients were convinced of IAT's medical safety and were generally unwilling to be tested for infection with viruses (178).

The IAT Patients' Association (IATPA), formed shortly after the clinic was closed in 1985, sent questionaires to about 500 IAT patients, in which they asked about possible infection with hepatitis B

[6]Toxicities are defined as unintended or adverse physiological effects of treatment, such as decline in cardiac, renal, or hepatic function. "Sterility" is defined as the absence of biological contaminants or infectious agents (e.g., viruses, bacteria, fungi, mycoplasma).

and HTLV-III (now called HIV). About 50 of the 150 IAT patients who responded reported negative blood tests for HTLV-III antibody or virus, and none reported a positive test. About 6.5 percent indicated that they had confirmed diagnoses of hepatitis B, though the questionaire did not ask how the diagnosis had been made or when it occurred in relation to the timing of IAT treatment (552).

U.S. oncologists responding to a 1987 survey by NCI and the American Society of Clinical Oncology (ASCO) reported their observations of 95 IAT patients seen in the course of their practices. These reports included 1 patient positive for HIV antibody; 1 case of adenopathy (enlarged lymph nodes); 3 cases of fever of unknown origin; 7 cases of hepatitis; 13 cases of infection (abscesses or sepsis, mainly Nocardia); and 1 case of rash or arthralgia. The Nocardia infections were acknowledged by Burton as originating at the Clinic (see above). For the other problems, it cannot be concluded that IAT was or was not the source (898).

Because some IAT products are made from the pooled blood of cancer patients, there is an additional theoretical concern about transmission of cancer-causing viruses (111), however no data exist on which to judge the likelihood of this happening with IAT. The potential infectious and oncogenic risks posed by IAT increase with the number of donors used in product manufacture.

Recently, the AMA's Diagnostic and Therapeutic Technology Assessment (DATTA) program attempted an assessment of the safety and efficacy of IAT. DATTA provided a panel of medical experts with published and unpublished information on IAT and asked for their evaluation of the treatment. Of 26 panelists, none rated IAT safetyas"established"; 6 rated it as "investigational"; 19 rated it as "unacceptable"; and 1 rated IAT safety as "indeterminate" (467).

Information About Effectiveness

There are currently no reliable data about IAT's efficacy as a cancer treatment. A number of anecdotal reports exist, however. One hundred forty-two testimonials of cancer patients treated at IRC were submitted to the Florida State Legislature in the early 1980s. Despite discrepancies noted later, an analysis of these submissions showed patient reports of subjective improvement (986). A few oncologists have reported on terminal cancer patients who benefited psychologically from seeking and undergoing IAT. During the 1978 PAHO site visit, 49 charts, selected by IRC staff, of patients who had "encouraging results,' were reviewed. The site visit report concluded that, "In the majority of cases, the best thing that could be said is that there was insufficient information to reach any kind of judgment" (852).

The IAT Patient Brochure contains a detailed two-page table that lists a large number of human malignancies for which "at least 50% of patients have responded to immuno-augmentative therapy with long-term regression of tumors and/or remission of symptoms" (428). The major types are: cancers of the breast, colon, lung, ovary, pancreas, prostate, head and neck, stomach, cervix, liver, bladder, and kidney; Hodgkins disease; leukemias; mesotheliomas; lymphomas; melanomas; and brain tumors. These include patients with metastatic disease. A few subgroups are identified for which fewer than 50 percent of patients have responded. OTA requested the data or calculations on which this table is based, but IRC was unable to provide them or to support the claims with other data (199).

In the 1987 survey of IAT patients by Cassileth and colleagues referred to above (178), an attempt was made to look at two standard measures of treatment efficacy. The study was designed originally to compare survival and quality of life between matched pairs of patients with metastatic cancer (a patient from the Pennsylvania Cancer Center files was to be matched to each IAT patient), but because too few IAT patients met the eligibility requirements (only 29 had available biopsy reports and metastatic disease at diagnosis), the authors did not carry out a matched analysis. In addition, the authors found that at the time they first went to the IRC, the IAT patients in the survey were more likely to be ambulatory, were younger, better educated, and of higher socioeconomic status than are cancer patients in general.

About a third of the patients reported improvement in appetite following the first visit to the clinic, and about a third reported becoming more ambulatory (although 86 percent reported being ambulatory before starting treatment). About half the patients reported no change in their performance status.

Cassileth and colleagues also reported on the survival of the 79 IAT patients. The patients in the study began IAT an average of 17 months after

diagnosis, and 50 patients were alive an average of 65 months after diagnosis. The 29 deceased patients survived an average of 59 months. The authors cautioned against inappropriate interpretation of these data, later writing that "it is not possible to determine the extent to which patient sampling biases contributed to these results, especially the observed survival distribution' (175). In a review of Cassileth's study done at OTA's request, John Bailar (a biostatistician) agreed with Cassileth's conclusion, adding that the quality of life questionnaire used may have been seriously flawed and inadequate for obtaining accurate information from these patients. Bailar emphasized that the information Cassileth reported on survival time is unusable in the absence of some appropriate comparison (64). Accordingly, valid inferences about the efficacy of IAT in controlling cancer cannot be drawn from this study. Nonetheless, IAT supporters continue to point to this study as strong evidence of the efficacy of IAT (see, e.g., (416)).

Clement, Burton, and Lampe compiled the records of 11 peritoneal mesothelioma patients treated with IAT between May 1980 and February 1987 (202). They reported the following survival information:

> *The total subject population represents a mean survival of 35 months and a median survival of 30 months; with a range for all cases from seven months to 80 months.*

Comparing survival to average survival of mesothelioma patients reported in other published series, the authors conclude that survival in these IAT-treated patients is two to three times greater than that reported for mesothelioma patients otherwise treated. They apparently did not consider the IAT patients' prior treatment regimens, however, nor the selection factors that rendered patients well enough to go to the Bahamas clinic even before IAT treatment began. The authors also failed to note that the ranges of survival times observed are actually quite similar to the ranges of survival times noted in other reported series of mesothelioma patients. They reported a survival range of 7 to 80 months for IAT-treated mesothelioma patients, while the literature reports they cite give survival times ranging from 1 to 60 months.

No valid statistical analysis can be performed on such a group of cases. They are not analogous to the usual case series presented in the literature, which comprises all patients who present at diagnosis in some identifiable catchment area (though this cannot always be defined precisely, on a population basis). The experience of the series, if large enough, should approximate the survival experience of the larger population of patients with that type of cancer. If some patients, in particular those who die in the first few months after diagnosis, are excluded, the statistics of the group would be skewed toward longer survival times. During a site visit to IRC in September 1987, OTA staff were asked to examine the IRC medical charts of the 11 peritoneal mesothelioma patients included in this study. The mean survival of the 11 patients was 9 months before they began treatment with IAT. One of the comparisons made in the paper by Clement, Burton, and Lampe *is with a series of 45 patients whose mean survival was 6 months. It is clear that many patients with this type of cancer die very soon after diagnosis. For the most part, Burton's patients had already survived a critical period before beginning IAT"*

As described above, a survey was conducted by NCI and ASCO in 1987 to ask U.S. oncologists about their experiences with IAT patients. Responding to a series of questions concerning IAT's potential efficacy, oncologists treating 78 cancer patients reported: 2 patients alive with objective response; 9 alive with no objective response; 12 alive with evidence of disease progression; 1 dead despite objective evidence of response; 63 dead with objective evidence of progression; 4 dead with evidence of IAT-related toxicities; and 3 unevaluable patients. The researchers concluded that this survey cannot be used to draw valid inferences about the effectiveness of IAT (898).

The AMA's recent DATTA report on IAT included a rating of efficacy (in addition to safety, discussed earlier). Of the 27 DATTA panelists, none rated the efficacy of IAT as "established"; 6 rated it as "investigational," 16 rated it as "unacceptable' and 5 rated it as ''indeterminate. ' The DATTA report concluded that IAT is "of no proved value as a treatment for cancer' (467). Because the information base on which to judge efficacy is inadequate, this DATTA opinion cannot be regarded as evidence that IAT is or is not efficacious.

After more than 10 years of IAT use in human cancer patients, and despite several attempts to plan a prospective clinical trial, no reliable data are available on which to base a determination of IAT's

efficacy as a cancer treatment. IRF and various New York physicians attempted unsuccessfully to arrange a clinical trial for IAT in the 1970s. NCI directly attempted to arrange a clinical trial again in the early 1980s, but negotiations finally broke down with Burton's representative. The process was aborted due to poor communication between NCI and Burton, complicated by reported findings of product contamination (244). In all of these attempts, as with OTA's, Burton himself was, for the most part, involved only indirectly; the people he designated as representatives, who were devoted patients or other supporters, did not have authority to speak for him, nor did they have intimate knowledge of the details of IAT treatment. OTA's attempt to develop a clinical trial protocol in collaboration with Burton, described below, also ended in failure.

DESIGN OF A CLINICAL TRIAL FOR IAT

Congressman Molinari and his cosigners asked OTA to develop "the first comprehensive protocol to be used in an evaluation of IAT," and to perform a "statistical analysis on IAT's efficacy, utilizing existing clinical data. ' OTA enlisted the assistance of academically based experts in clinical trials, an oncologist from NCI and one from FDA, and asked Burton for his participation. Burton appointed a resident patient who was active in the IATPA, to represent him on this "IAT Working Group." Burton himself would not participate except at interim and final decision points. As is turned out, this was a significant handicap.

There were pluses and minuses to having IAT as the object of this task. On the plus side, IAT presented many of the challenges likely to arise in attempting to evaluate other unconventional treatments for cancer+. g., "secret' components to the treatment, significant concerns about safety, treatment taking place outside the country. Another advantage was that the claimed effects of IAT were no different from those made for most mainstream cancer pharmaceuticals, and should, therefore, have been amenable to testing and measurement using standard study designs. On the minus side, it was not Burton but Congress, speaking for Burton's patients, who initiated the request for evaluation; and previous attempts on the part of NCI to work with Burton on an evaluation of IAT had ended in failure, with Burton finally refusing to provide what NCI considered crucial information about IAT, and then claiming bad faith on NCI's part (762).

The First IAT Working Group Meeting

OTA's IAT Working Group first met on March 31,1987, to discuss possible approaches to a fair and competent evaluation of IAT. A specific proposal prepared by IRC was considered as were other approaches. At the meeting, three major issues were discussed at length: 1) the potential for obtaining information from IRC patient records that might be useful in an overall evaluation of IAT; 2) the patient safety issues raised by a clinical trial of IAT; and 3) possible approaches to clinical trials of IAT.

Obtaining Information From IRC Patient Records

A proposal by IRC and suggestions from the Working Group for use of existing patient records were considered. The IRC proposal asked for a "statistical analysis" of the records of 11 patients with peritoneal mesothelioma who had been treated at the clinic. These 11 patients are discussed in the paper by Clement, Burton, and Lampe (201), which was reviewed earlier in this chapter. For the reasons given earlier, there appears to be no valid means to analyze this group of patients for the possible effect of IAT on length of survival, which was the suggestion made in the IRC proposal.

The Working Group considered two other approaches to using existing patient records. A "best case' approach similar to that carried out by NCI for laetrile (discussed in ch. 5), relying on documented evidence of tumor regression, was considered. OTA considers the best case approach potentially useful as a formal way to present evidence that could be useful to support carrying out appropriate clinical trials of unconventional treatments. In the case of IAT, however, the goals of such an exercise were unclear. Since the decision to evaluate IAT had already been made on political grounds, it did not appear that presenting best cases would accomplish anything, except to delay the beginning of a clinical trial, if it were to take place.[7] This is somewhat analogous to the laetrile review, which ended with

[7]The mesothelioma cases did not meet the standards of a best case review; because the analysis was based only on length of survival and nOt tumor regression it did not appear that those eases would be appropriate for a best case review.

very little evidence in support of the treatment. With laetrile, a decision was made to proceed with a clinical trial anyway, because of the public health importance of doing so. (At the time, laetrile had been legalized in more than 20 States, and was in widespread use, which was not the case with IAT.)

An "informal" examination of patient records was also considered by the Working Group. It was thought that there might be some value in simply looking at typical patient records to get an idea of the type of patient treated at IRC and to see how records were generally kept. This activity would have no specific endpoint. It was decided that the time and money needed to carry out such a review, given the lack of clear goals, would not have been justified.

Issues Related to Patient Safety in a Trial of IAT

IAT materials are made from pooled blood samples from people with and without cancer. As such, the potential for infection must be assessed and minimized before such mater-ids are given to patients in a clinical trial. At the time of the first Working Group meeting, it was assumed that treatment with IAT would take place in the Bahamas, so the treatment materials would be made there. What was contemplated was that quality assurance procedures would be developed to be put in place at the clinic and that testing of fmished materials would take place on some regular schedule at an independent laboratory in the United States. At the time of the meeting, it was left that OTA would ask IRC for information about the processing of IAT materials and would gather information from FDA and elsewhere concerning probable testing requirements. This issue was left in an unfinished state at the first meeting.

Planning a Clinical Trial

The IRC proposed a clinical trial in patients with peritoneal mesothelioma who did not have advanced disease. According to the proposal, patients would have to be diagnosed in the United States and "given a definitive prognosis by the evaluating oncologist." Patients would be treated at IRC under Burton's direction. After treatment, 'Patients would be re-examined at a period after their prognosis date thought to have statistical significance and possibly again near the end of the study period. " Serious problems with this proposal, discussed below, relate to the patient population and the basic study design.

Peritoneal mesothelioma is an exceedingly rare cancer; about 200 cases per year are diagnosed in the United States (894). This may be contrasted with 149,000 cancers of the lung, 98,000 cancers of the colon, 42,000 cancers of the rectum, and 90,000 cancers of the prostate (25). Under the best of circumstances, even if patients with more advanced disease were included, it would take years to accrue sufficient numbers of patients for even a modest clinical trial in this disease. If IAT were a treatment used exclusively on patients with peritoneal mesothelioma, then there would be no choice, but since it is used widely, and is reported successful by Burton for patients with a wide range of cancers, the preferable choice is a commonly occurring cancer.

A more fundamental concern with the IRC proposal is the concept of comparing actual survival with a "definitive prognosis' given to the patient on entering the study. Except in rare circumstances, prognosis for individual cancer patients cannot be determined accurately enough to form the basis for such analysis, which is why it is necessary in attempting to determine effects of treatment on survival to have a randomized control group. Based on the 11 cases presented by Clement, Burton, and Lampe, if IAT is effective, its effect is not so extreme as to be evaluable in this way.

Regression of disease was the other major endpoint proposed by IRC, and it would be possible to measure this in a clinical trial without a control group. "Phase II" clinical trials in cancer, designed to detect tumor regression, are often of this type. According to members of the Working Group, however, mesothelioma can be a difficult disease to follow in terms of disease progression or regression. Other solid turners are more easily followed and assessed.

The Working Group went on to consider other approaches to an IAT clinical trial and cancers other than mesothelioma. According to IRC literature, patients with virtually all types of cancer are treated and for most types, IRC reports that more than 50 percent benefit from treatment (430). The Working Group stressed the need to study patients with common cancers who have measurable and followable disease (e.g., primary or metastatic lung cancer, colon cancer with followable lung, liver, or intra-abdominal masses, or primary renal carcinoma).

Two possible phase II clinical trial designs were discussed: uncontrolled (all patients treated with IAT), similar in some ways to the IRC proposal, and a trial with randomized controls (one group treated with IAT and the other receiving other standard or supportive treatment, whichever is appropriate). OTA and the Working Group assumed at the time that IAT-treated patients, regardless of the study design, would have to be treated at the IRC in the Bahamas.

In an uncontrolled phase II study, patients who met study criteria (type and stage of disease, previous treatment, general condition or "performance status," etc.) would be offered participation. Those who agreed would be evaluated for tumor status and other possible outcome measures (e.g., "quality of life" measures) and sent to IRC for treatment. The number of patients needed for the study would be determined in part on the basis of the predicted effectiveness of the treatment (this would have to be supplied by Burton). Patients would be reevaluated at specified intervals (determined on the basis of how quickly Burton predicted the treatment would work), the number of responses (complete and partial remissions) counted, and the proportion responding compared with prespecified measures of success. For instance, a sample size of 20 to 30 would give a good chance to detect a benefit in 20 to 30 percent of patients (399).

It was envisioned that, in a randomized study of IAT, a principal investigator in the United States would share overall responsibility for the clinical trial with Burton. Physicians agreeing to collaborate at various institutions would offer enrollment to patients meeting specified entry criteria. The design would be explained to patients, so that they understood that they had an equal chance of getting IAT or supportive treatment. As each patient agreed to participate, random assignment would be made to one or the other arm (this could be done by an independent center). After patients were fully evaluated, those randomized to receive IAT would go to the Bahamas for treatment. Patients in the control group would receive their specified care. All patients would be reevaluated at appropriate intervals. The endpoints would be standard, objective measures of disease regression or progression. The results would be analyzed by comparing the percentage of patients with positive responses who had been randomized to the IAT arm with the percentage responding in the control arm. In addition, measures of the quality of life of the two groups would be compared.

A reasonable size for a study of this type assuming, for instance, that about 25 percent of patients would benefit (a more modest goal than what is claimed for IAT), would be a total of about 80 patients, 40 in each arm.

The advantages and disadvantages of each study design were discussed at length. The main advantages of a small uncontrolled study, compared with the randomized design, would be its lower cost, somewhat shorter duration, and the fact that it is a standard design. As used in mainstream research, small phase II studies are often used to help identify which specific cancers should be included in further phase II studies. With IAT, however, Burton would specify, based on his experience, which cancers would and would not be appropriate.

The main disadvantage of the small uncontrolled study would be the difficulty in interpreting the results. A "patient selection bias," which would not affect trials of new mainstream treatments to the same degree, could work either for or against finding an effect. On one side, for instance, physicians enrolling patients in the study may have a conscious or unconscious bias for or against the treatment, and may choose to offer enrollment in the trial as an alternative selectively, based on a preconceived notion of IAT's value and on the patient's prognosis. Patients themselves may also have preconceptions about IAT and may "select themselves" into the study differentially on that basis. With no control group, there is no way to assess the effects of this possible "enrollment bias," which could be large, on the outcome. This would not be a concern in a randomized design.

Other factors may also show some variability that would be impossible to account for adequately without a randomized control group. These include variations in tumor size due to measurement variability, real short-term fluctuations (but not long-term shrinkage) in tumor size, and other influences on the size of the tumor (e.g., effects of previous treatment). Any small or moderate response in an uncontrolled study would be inconclusive and likely to lead to controversy. While this could happen in a randomized study as well, it is much less likely, given the direct comparison with controls. Another advantage of the randomized design is that evaluation of serial tumor images would be conducted by individuals

blinded as to which treatment group patients were in, eliminating a potential source of bias.

overall, a clear-cut result would be much more likely in a randomized trial than in an uncontrolled one. Even a negative result in the proposed randomized study would be more informative and would allow better estimation of the upper limit of potential effectiveness of IAT than would the uncontrolled design, should further studies be planned. Of the options considered, OTA adopted the randomized phase 11 trial as the best first step toward the fair and unbiased evaluation of IAT called for by Members of Congress.

A summary of the meeting was circulated to all participants afterward, and some important points emerged in their comments. Some of these, particularly concerns of NCI and FDA, had to do with whether Burton would be willing to supply Suffi cient information about the treatment materials for their safety to be assessed and assured, to the degree possible. NCI stated that the study should take place at a research institution in the United States. Other comments expanded on the types of cancer that might be considered. In general, the Working Group members were supportive of proceeding in the direction spelled out in the draft summary paper.

The response from Burton's representative (425), who had offered little guidance during the meeting, was received 2 months after the draft was sent. It was a long and legalistic discourse on the OTA process for the study, with general discussion about evaluating unconventional treatments and the need for "innovative evaluative techniques," but with no comments specifically on the plan set out for consideration. The response also said that Burton himself had been advised by his representative not to read the draft.

OTA responded to Burton's representative in detail, and wrote to Burton (397) to inform him that his "lack of representation by an appropriately skilled person' on the Working Group appeared to be making progress difficult. In the letter, Burton was asked to replace his representative with someone with technical experience in appropriate areas, and to become more involved himself in the process.

Burton responded that he believed the situation would improve with the participation of his attorney, who was very familiar with IAT and with Burton's views. Contact was made between OTA and the attorney, and subsequently the attorney, acting on Burton's behalf, asked that OTA staff visit the clinic in the Bahamas. Specifically, Burton wanted OTA staff to tour the clinic, examine the records of his patients with peritoneal mesothelioma, and meet some patients. OTA agreed to travel to the clinic and to follow an agenda set by Burton, with the understanding that progress on the protocol, as reported in the draft OTA report, would be discussed as well. An OTA Assistant Director (Herdman), Project Director (Gelband), and Analyst (Solan) planned a 3-day trip to Freeport in early September 1987, in accord with Burton's proposed agenda.

The First Bahamas Meeting

In addition to OTA staff and Burton, Burton's original representative, his lawyer, a consultant statistician, and a member of then-Congressman Molinari's staff were present. The outcome of the meeting, which actually ended after 2 days, was a review by OTA of the peritoneal mesothelioma records (discussed earlier in this chapter) and a "memorandum of understanding" (see Addendum to this chapter), signed by Burton and Herdman, covering some key points in the design of a clinical trial. OTA staff were present on the second morning to observe the process of drawing and testing patients' blood according to Burton's specifications. There was no preparation of the treatment materials going on, however, and OTA requests for more information about how the products were made were not fulfilled.

Burton's participation in the discussion was limited mainly to the first morning. At that time, he characterized the OTA draft as "childish and inane. At the conclusion of the meeting, OTA agreed to continue exploring the feasibility of studying peritoneal mesothelioma and to try to further develop a protocol based on the memorandum of understanding.

Key provisions of the memorandum of understanding included: that the design would be a randomized trial; that the trial would be conducted in the United States; that recruitment of patients should be possible within a span of about 1 year; and that appropriate measures would be taken to assure the safety and sterility of materials that would be given to patients.

Further Development by OTA

The two issues requiring the greatest attention after the first meeting in Freeport were: 1) whether peritoneal mesothelioma was a feasible choice for tumor type, and if not, what types of cancer could be studied; and 2) further development of information relating to assuring the biological safety of IAT for patients in a clinical trial. OTA looked into these areas and began planning another meeting with the IAT Working Group.

Burton and his attorney agreed, based on further documentation gathered by OTA, that it would not be possible to accrue sufficient patients within 1 year for a trial of peritoneal mesothelioma, because it is such a rare cancer. Burton subsequently requested that various types of non-Hodgkin's lymphoma (NHL) be considered (116). OTA gathered information about the incidence, current treatment and prognosis for the types and stages of NHL, and about current clinical trials enrolling patients with these cancers. In addition, two NHL experts, one in the pathology of NHL and the other in clinical management, were consulted and asked to attend the planned second meeting of the Working Group.

The issue of the biological safety of IAT continued to be difficult to deal with satisfactorily. OTA consulted with biologics experts within and outside the government, and developed some general guidelines and some minimum testing requirements. However, because the preparation methods for IAT fractions were not known to OTA and would not be divulged at that time by Burton, it was impossible to develop any specific recommendations. (Testing and preparation requirement for biologics are determined very much on a case-by-case basis, because the compounds in the class are so varied and requirements not amenable to complete standardization.) OTA also arranged for an expert in biologics from the FDA to be present at the second Working Group meeting.

The Second IAT Working Group Meeting

The Working Group met in May 1988, supplemented by two experts in NHL, a biologics expert from FDA, and an oncologist who had looked into methods that might be used to gather information about possible toxicities associated with IAT before a clinical trial began. Burton was represented by his attorney only, as his patient representative was unable to attend at the last minute.

It was concluded that it might be possible to study NHL patients with particular types of tumor (i.e., tumors consisting of predominantly certain cell types) and particular stages. There was little enthusiasm for this, however, as these can be difficult cancers to follow and patients often receive considerable palliative treatment during the course of their illness, which would complicate following them over the relatively long period of time (on the order of 6 months to 1 year) needed on treatment with IAT for a fair evaluation of its effect. The Working Group expressed the strong opinion that a solid tumor (e.g., colon cancer) be included in the study as well, if a trial in patients with NHL were to be planned.

Further consultation after the meeting led OTA to the conclusion that NHL would actually be a poor choice because, although not as rare as mesothelioma, the number of eligible patients would probably be too small for the trial to be conducted within a reasonable time period. A common type of cancer, one of the many treated with reported success at IRC, still appeared to be a more appropriate target.

The issue of biologic safety of IAT was again discussed at length at the meeting, but with little real progress because of the lack of detail concerning how the products are made. The Working Group considered several mechanisms for gathering information about possible IAT toxicities before a trial would begin. The information would serve two main purposes: first, to anticipate testing requirements for possible adverse effects during the actual clinical trial, and to inform potential trial participants of what they might expect were they to take IAT. Unless dire problems arose, the information would not be used to attempt to cancel plans for the clinical trial.

One pre-trial mechanism emerged as the best possibility for determining short-term effects. Under this plan, patients just beginning IAT treatment in the Bahamas would be asked to have blood drawn in the United States before going to the clinic, to establish baseline measurements, after returning from their initial course of treatment (usually 6 to 8 weeks), and at intervals thereafter (e.g., monthly). Standard measurements (e.g., liver function tests, hematologic profiles) would be recorded. Patients could also be interviewed to gather information about subjective effects.

The most significant issue relating to patient safety, however, was whether the clinical trial would be carried with official Investigational New Drug (IND) status from FDA. For all practical purposes, if the trial were to be carried out as envisioned in the United States, an IND would be necessary. The IND application would entail Burton's disclosing the details of how IAT treatment materials are made and how much of each material patients generally receive. This information would allow FDA to consider possible risks, ways of reducing them without interfering with the basic IAT regimen, and appropriate quality control tests to be carried out during the clinical trial. (Information provided to FDA in an IND or a Drug Master File (DMF), on which an IND may be based, remains entirely confidential with FDA.)

It was possible that Burton could maintain as confidential the algorithm used to determine the exact dosages, which is the one part of the treatment that he maintains exclusively proprietary, but it was not assured that FDA could agree to this. The materials themselves are prepared in both the Mexican and German IAT clinics, but Burton provides dosage information for all clinics based on transmitted laboratory values. Burton would have the same relationship to the U.S. trial as to his clinics in other locations.

All of this information was communicated to Burton in a letter in June 1989 (397). In concluding, the letter stated:

> At this point in our process, I now need your assurance that we all understand where we are. We still must select a type of tumor that will make for a feasible, meaningful trial of IAT. We need to know any conditions you would place on NCI as a trial sponsor, the role you expect to play in the trial, and we especially need to know that you can provide the type of information that I've described [regarding an IND], which is absolutely essential to getting a trial going.

OTA proposed a meeting with Burtor$_A$ to discuss these issues, with the added participation of an expert in biologics and an oncologist of Burton's choice, or suggested by OTA. In further telephone conversations, OTA requested also that the visit include an opportunity to observe IAT materials being produced.

The Second Bahamas Meeting

OTA representatives (Herdman and Gelband), accompanied by an FDA oncologist who is an expert in biologics, traveled to the clinic in August 1989. The objectives for the meeting were to come to agreement on an appropriate type of cancer to be studied, and to allow Burton and his representatives to begin a dialog with FDA so that the IND process could be started.

It was OTA's belief that the first of these objectives was met: an agreement was reached that patients with advanced colon cancer with measurable disease would be studied. The entire meeting with Burton, planned for 2 days, lasted only a few hours. There was no opportunity to observe the IAT production process. The FDA biologics expert discussed the general requirements for an IND and explained what is done with the information fried with FDA. Burton and his then-current representative (the original representative to the IAT Working Group had died by this time) did not pursue this discussion in detail.

Burton expressed his wish to have a "pre-test," in which patients with advanced colon cancer with measurable disease (the same criteria as for the clinical trial) would be treated at the clinic in the Bahamas and their progress monitored in the United States. Burton stated that this would require patients to be recruited in the United States by NCI or another clinical trial sponsor and sent to the clinic. OTA made it clear that this would not be considered part of the clinical trial and that NCI was unlikely to cooperate in such a venture.

OTA prepared a draft summary of the second Bahamas meeting, covering mainly the choice of cancer type to be studied, the requirements for an ~-D, and-Burton's responsibilities during the trial. It reiterated OTA's position that a pre-test in the Bahamas, as described by Burton, could not be the basis for an acceptable evaluation of IAT, and therefore the idea could not be supported by OTA. The draft report was sent to the IAT Working Group and Burton for comments.

The Clinical Trial Described by OTA

The clinical trial design developed by OTA, in consultation with the IAT Working Group, expert consultants, and Burton and his representatives, would be a test primarily of whether treatment with IAT leads to shrinkage of tumors, as reported by

Burton. It would also gather information on quality of life, adverse effects, and survival (though it probably would not be large enough to definitively detect possible improved survival due to IAT).

The clinical trial would take place at an accredited U.S. medical center acceptable to both the trial sponsor (possibly NCI) and Burton, in accordance with the current regulations of the Department of Health and Human Services concerning IND and Institutional Review Board requirements. All patients would be treated in the United States. Patients agreeing to participate after giving informed consent would be allocated by random assignment to IAT or supportive treatment.

Patients with metastatic cancer of the colon with measurable disease would be eligible, specifically a diagnosis of "Dukes' D colorectal carcinoma.' This is a relatively common cancer, and one for which treatment options are limited. To the extent possible, patients would have had no previous chemotherapy or radiotherapy, a condition set by Burton to preclude the possibility that responses during the trial could be attributed to the previous treatment rather than IAT. However, response to prior treatment would not be a problem because the control group would provide a check on late responders to previous treatment.

Patients would spend the necessary 6 to 8 weeks initially at the treatment center, having blood drawn each day and receiving IAT. They would return home with treatment materials and a schedule for self-administering them for periods of time specified by Burton (about every 3 months, according to treatment regimens at the clinic in the Bahamas).

Burton (personally or through a representative) would be responsible for providing instructions for making the various IAT fractions and for carrying out necessary laboratory measurements at the U.S. treatment site. He would be asked to test materials made at the site to ensure that they met his standards. Measurements would be transmitted to Burton daily during initial treatment and thereafter at intervals specified by Burton, and he would transmit back the dosage schedules for each patient.

All patients would be examined at regular intervals, including appropriate scans and tumor measurements, and aspects of quality of life assessed. All review of patient data to assess response would be done in a blinded fashion, that is, the reviewers would not know which treatment group patients were in. Blinding is used to assure that the groups are assessed without bias. In this trial, the assessment would involve review of initial pathology and assessing the regression or progression of tumors.

Standard, accepted, statistical techniques would be applied in the analysis. Whatever the result of the study, Burton and the trial investigators would agree to publish the results for scrutiny by the scientific community.

Burton's Response to OTA's Clinical Trial Description

Burton responded to the OTA draft (116) stating that he had "not agreed to much of what you have chosen to include in your report,' and that the report ''reflects little more than an outline to obtain negative results. ' The letter goes on to state that "the pre-trial was a nonnegotiable prerequisite to the clinical trial of IAT in the U.S.,' and points out that, in an earlier letter to him, OTA had stated that "NCI had suggested just such a 'small non-randomized pilot phase.'" He terms it "strange" that the draft states his pre-trial would not be considered part of OTA's plan.

Burton had misinterpreted NCI'S proposed "pilot phase," which they clearly stated would be a small study preceding the randomized study in the United States, for the purpose of assuring the feasibility of the full trial and collecting information about potential toxic effects. These were not Burton's goals, and a pre-trial at his clinic would not have provided the information desired by NCI.

In his letter and in a telephone conversation with OTA, Burton signaled his wish to deal directly with NCI. Herdman responded (397) that he believed the OTA draft report was an accurate representation of the discussions and agreements that had been made and that 'the trial described in the draft would be the fairest, most expeditious initial evaluation of IAT." However, OTA accepted Burton's decision to proceed with the NCI as final.

In several telephone calls following shortly, one of Burton's representatives (the same one who had several years earlier represented Burton in discussions with NCI) and the President of the IAT Patients Association both attempted to reopen discussion with OTA. OTA agreed that this would, of course, be possible, if Burton himself wished to do

so, but no word was ever received from Burton himself; nor has he initiated discussions with NCI.

ADDENDUM

Memorandum of Understanding Between OTA and Lawrence Burton Concerning a Clinical Trial of IAT

On September 9, 1987, the Office of Technology Assessment of the U.S. Congress (OTA) and the IAT, Ltd. (Centre) of Freeport, Bahamas have agreed in principle to the following points regarding the design of a clinical trial protocol to evaluate the efficacy of Imnmno-augmentative therapy (IAT).

1. *Peritoneal mesothelioma will be the tumor candidate of choice for the protocol, provided both parties are satisfied that enough patients can be recruited for such a study within approximately 1 year of commencing recruitment efforts.*
2. *The study will be a randomized clinical trial in which patients will be assigned to treatment with IAT or some standard treatment.*
3. *The endpoints that will be considered for use in this protocol shall include survival time, quality of life, and tumor status.*
4. *Both the Centre and OTA agree that no interim data or study results will be published before the clinical trial is completed.*
5. *Patients will be eligible for the trial only if they have a confirmed pathological diagnosis of peritoneal mesothelioma, preferably confirmed by the Armed Forces Institute of Pathology or another medical institution to be mutually agreed upon. Efforts will be made to recruit patients with minimal or no prior chemotherapy or radiotherapy. Prior surgery will be acceptable. Patients with advanced disease (beyond the abdomen) will be excluded [referring specifically to peritoneal mesothelioma].*
6. *The trial will be conducted at a single site (to be mutually agreed upon at a later date) in the United States.*
7. *IAT blood analysis and preparation of IAT treatment materials will take place at the U.S. study site by personnel trained and supervised by Lawrence Burton, Ph.D., of the IAT or his designated representative. Data from IAT blood analysis will be transmitted to Dr. Burton, who will specify the daily IAT regimen for each patient. Information required for "standardization" of treatment material will be transmitted to Dr. Burton as he requires.*
8. *Methods of assessing the safety and sterility of all IAT materials to be given to patients will be included as part of the protocol. Such testing will be a pre-condition for beginning a clinical trial and will continue as appropriate throughout the trial. Such testing will be performed by an established clinical laboratory to be mutually agreed upon.*
9. *During the course of the trial, patient care, other than IAT treatments, will be provided by the patients' private physicians or licensed physicians at the agreed-upon study center.*
10. *As in all clinical trials, patients offered participation will be informed of all significant details relevant to both IAT and the other treatment before their consent is sought.*
11. *Interim studies (e.g. x-rays, ultrasound, CT scans, as specified in the final protocol) will be submitted to independent groups of qualified specialists in those particular disciplines. All such materials will be sent without revealing patient identifiers or, importantly, which treatment the patient is receiving.*
12. *OTA and the Centre will provide any and all non-proprietary materials (including articles, data, etc.) used to support recommendations or conclusions bearing on study design.*
13. *Lines of communication between OTA and the Centre will be kept open for the prompt exchange of pertinent information.*

Both the Centre and OTA will make a good faith effort to research these points and determine their feasibility in order to complete the design of a protocol as promptly as possible.

Office of Technology Assessment:

(signed by Roger C. Herdman, M.D.)

IAT Ltd:

(signed by Lawrence Burton, Ph.D., Director)

Chapter 7

Patients Who Use Unconventional Cancer Treatments and How They Find Out About Them

CONTENTS

Chapter 7

Patients Who Use Unconventional Cancer Treatments and How They Find Out About Them

INTRODUCTION

Whether or not they have cancer, most people know that unconventional cancer treatments exist. Most have heard of one or another treatment-from friends, neighbors, relatives, or through the media. A subset of cancer patients, their health care providers, friends, and family, however, actively seek information about these treatments in order to decide whether to try one. Federal agencies, advocacy groups, specialized information services, professional associations, various private sector societies, libraries, hotlines, and others offer an array of information for patients.

Information from a given source is generally either quite encouraging or quite discouraging about unconventional treatments. Advocacy groups and treatment proponents are positive about the treatments. The American Cancer Society (ACS) and the National Cancer Institute (NCI) try to discourage patients from using untested and unproven treatments. A few sources attempt to provide information in a neutral way.

This chapter presents the limited demographic information available about U.S. patients who use unconventional cancer treatments, and examines the ways in which people find out about and decide whether to try an unconventional treatment. Chapter 8 discusses the organizations that provide information on unconventional cancer treatments.

PATIENTS WHO USE UNCONVENTIONAL CANCER TREATMENTS

Patient Characteristics

The published literature on unconventional cancer treatments has often depicted users of these treatments as deviant, poor, marginal persons, hostile to mainstream medicine, mentally unstable, ignorant, gullible, "straw-graspers," or as uninformed "miracle-seekers" (see, e.g., (104)). These stereotypes generally reflect the opinions of the writers and society, and are not backed by systematic observation. Though scanty, the studies that have been carried out suggest that the stereotype should be discarded.

In the largest study to date of patients using unconventional cancer treatments, Cassileth and her colleagues at the University of Pennsylvania Cancer Center interviewed more than 600 cancer patients, approximately half of whom were selected because they used unconventional treatments; the other half were patients at the University of Pennsylvania Cancer Center. The patients using unconventional treatments were identified in a variety of ways: through lists of patients associated with clinics or practitioners across the country, direct contact by patients whose practitioners suggested they contact the researchers, referrals by other patients, and publicly available lists of patients associated with a national organization that supports alternative medicine.

In analyzing the results of the survey, Cassileth found that respondents could be sorted into three groups: those receiving conventional treatments exclusively, those who used both conventional and unconventional treatments, and a small group that used unconventional treatments only. Cassileth found that the majority of patients in the study who used unconventional treatments, either exclusively or in addition to conventional treatment, were well educated, and had accepted mainstream medical care before getting cancer (177). In another survey of 79 cancer patients who used a particular unconventional cancer treatment, Immuno-Augmentative Therapy (IAT), Cassileth reported that the patients were younger, better educated, and of higher socioeconomic status than are cancer patients in general (178).

NCI's Cancer Information Service (CIS) runs a nationwide telephone hotline that provides information on the gamut of questions about cancer, including unconventional treatments. In an analysis of computerized data reporting on more than 10,000 CIS inquiries over a 4-year period, Freimuth found that callers inquiring about unconventional cancer treatments had a higher average level of education than the "average" of all CIS callers (306).

In 1986, Louis Harris & Associates, under contract to the Food and Drug Administration (FDA) and the Department of Health and Human Services (DHHS), surveyed attitudes toward "questionable treatments." Questions were asked of a national cross-sectional sample of 1,514 adults, including a sample of 297 people who reported a diagnosis of cancer at some time. The survey found that among the surveyed population, including the subgroup with cancer, "college graduates seem more likely than those without a degree to use treatments that are questionable." The researchers concluded that people who report using "questionable treatments' are generally similar demographically to the whole population of those seeking treatment for particular health reasons (566).

Users of unconventional cancer treatments in the United States cannot be characterized adequately because so little work has been done to find out about them. The few studies discussed here, however, suggest that patients interested in using unconventional cancer treatments are a heterogeneous group, not from one stratum of society.

Patient Attitudes and Motivations

Cancer patients may become interested in unconventional treatments for a variety of reasons. The available data suggest that patients most frequently add unconventional treatments to their mainstream treatment regimens well after their diagnosis and mainstream treatment, and then either continue both or continue only unconventional treatment (177).[1] *The experience of CIS suggests that disease progression or recurrence may precipitate or intensify a patient's interest in unconventional cancer treatments (174). One of the cancer patients who wrote to OTA described her family's anguish and growing interest in identifing unconventional treatment as her condition worsened on mainstream treatment (733). OTA received a number of similar letters and telephone calls during the course of this assessment. However, many patients seek unconventional treatments after completing mainstream treatment, when they have no evidence of cancer remaining but cannot know whether the treatment was successful for the long term. This section will present factors that may motivate patients at various stages of their disease to seek information about or use unconventional cancer treatments.*

Many patients are motivated to seek unconventional treatments by their desire to live and their fear of death from cancer (395,445). One cancer patient wrote to OTA that she began looking into unconventional cancer treatments in 'attempt to move beyond incapacitating fear and panic" (366). While these motivations may contribute significant.ly to decisions to seek treatment, there are no data to suggest that those who use unconventional cancer treatments are either more fearful or life-loving than other cancer patients. These two factors might equally motivate a cancer patient to seek out or accept mainstream treatment. The limited data available thus far suggest that overcoming fear of illness and death can be viewed as psychological challenges faced by most cancer patients (233,417,713). In this context, use of an unconventional cancer treatment is one of many possible responses.

The desire to mitigate feelings of helplessness and hopelessness may specifically motivate cancer patients to use unconventional treatments. Holland, a psychiatric oncologist, suggests that cancer patients may become vulnerable psychologically when they learn of metastasis or disease progression because it is so difficult to accept a worsened prognosis. She finds that many patients wrestle with the "uncontrollability" of their disease and may experience helplessness and hopelessness, manifested by symptoms of anxiety, depression, or both (408). In this context, Holland observes that exploring unconventional cancer treatments serves to both restore a degree of personal control and offer a perceived antidote to the cause of turmoil. Both the activity required to search for alternative treatments and the fact that most unconventional treatments represent some promise of cure may be irresistible (408).

Some cancer patients may be motivated to use unconventional treatments by their feelings of abandonment or rejection by mainstream physicians during the course of their cancer treatment (395). Both cancer patients and oncologists have commented on how poorly many physicians respond to the intense psychological needs of cancer patients and cope with their own limited success in this arena as healers. Some patients may begin to seek out

[1] In Cassileth's 1984 study of cancer patients, 60 percent of those using unconventional cancer treatments began their nse of these at an average of 24 months after beginning conventional treatment.

unconventional treatments when, in the course of their mainstream treatment, they are made to feel like treatment failures, of little interest, or abandoned (410,802).

Patients who use unconventional cancer treatments have cited an undeniable need to "do something' to assure continued survival (366,733). This need was dramatized in the 1988 television movie, "Leap of Faith,' in which lymphoma patient Deborah Ogg sought out several unconventional cancer treatments during a time when she was asymptomatic, her cancer was stable, and no mainstream treatment was recommended. A patient with metastatic lymphoma who wrote to OTA about his use of several unconventional cancer treatments stated, "I felt I had nothing to lose and I just might get some help" (265). Another cancer patient who uses an unconventional cancer treatment wrote to OTA that she began her dedicated search for these treatments at the point when, although her disease was stable, she realized "the limitations of traditional medicine in the treatment of [her] type of cancer' (366).

Little information exists about the attitudes towards mainstream medicine of patients using unconventional cancer treatments. An Australian study (which may or may not be generalizable to U.S. patients) reports that negative views of mainstream medicine are not key factors in most patients' decisions to use alternative forms of care (260). Another study suggests that a constellation of attitudes, including an opposition to mainstream medicine and acceptance of officially condemned health beliefs, was important to the widespread use of one unconventional cancer treatment, laetrile, in the 1950s and 1960s (931). Holland suggests that patients who have previously relied exclusively on mainstream care may be willing to suspend their usual pattern of disbelief and accept unproven or unconventional treatments when it becomes clear to them that mainstream medical treatment can no longer control the cancer (408).

The belief that unconventional cancer treatments may be useful even if they may not cure cancer is common among users. In one study, 190 cancer patients with metastatic disease were interviewed about their beliefs; only 25 percent indicated that they thought laetrile, vitamins, or special diets could cure cancer, yet 70 percent stated that they would try these forms of treatment if they were available (272). Similarly, in the 1986 Harris Poll described above, although 90 percent of U.S. cancer patients using questionable treatment methods did not consider it likely that unconventional treatment would "cure" them, a substantial number found them 'effective.'

GATHERING INFORMATION ABOUT UNCONVENTIONAL CANCER TREATMENTS

Person-to-person contact—word of mouth-is an important way for cancer patients to find out about unconventional treatments, and is cited by many patients as the most persuasive source of information in treatment decisions (55,190,288,365). In an unpublished 1987 survey of cancer patients who use unconventional treatments, a sociology student working with an unconventional cancer treatment advocacy group (the International Association of Cancer Victors and Friends; IACVF) found that "friends" and "the media" were the two most frequent sources for learning about unconventional cancer treatments. Other sources included a large advocacy group (The Cancer Control Society; CCS), family members, physician referral, and incidental exposure to clinic advertisements or brochures (193).

Similarly, the Harris nationwide survey found "word of mouth' the most common method of introduction to unconventional treatments reported by U.S. adults. Although not asked specifically about unconventional cancer treatments, 3 out of 10 users of "questionable products" of all kinds reported that they learned of these from friends or neighbors, and 45 percent of users reported telling others of their experience ***(566).*** Cancer patients are likely to feel socially isolated and to some extent unique when they begin to consider alternatives to conventional treatment (365). Person-to-person con***tact appears to be especially compelling and persuasive in this situation, gaining camaraderie in what was previously seen as a unique problem.***

Once the surface is scratched, there is a great deal of supportive information that would encourage patients looking into unconventional cancer treatments. Patients find specific leads from advertisements in the many journals and newsletters published by advocacy organizations (described in ch. 8); at conventions held by some of the larger advocacy groups; and through the anecdotes of clergy, fiends, family members, nurses, physicians, physical therapists, social workers, etc. Others may

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get treatment advice and referrals from diverse sources such as fellow cancer patients at mutual aid group meetings, health food store workers (see below), or even wig store personnel. Information referrals may sometimes be obtained through social organizations, e.g., the Singles Club for Live Fooders, based in Hollywood. Some popular books on specific unconventional cancer treatments are available at commercial bookstores, health food stores, and specialized libraries, and these are often suggested to cancer patients.

Some patients take an analytical approach to researching unconventional cancer treatments. Many locate and interview patients already using unconventional treatments. Others may read widely, consult a professional research service, or take a special bus trip to visit unconventional cancer treatment facilities, and then compare features of available treatments.

Health Food Stores

Local health food stores are a major source of information about unconventional cancer treatment. In the 1970s and 1980s, health food stores became common fixtures in many communities. Having started as small businesses selling mostly vitamins and natural foods, health food stores gradually expanded in scope, variety, and number to become providers of a wide range of dietary, cosmetic, and household products. A common thread among many of the stores is an interest in "alternative" health care and its network of services and providers. They provide vitamins and natural foods promoted for general health maintenance, prevention of disease, and often treatment of disease; herbal products and homeopathic preparations for a variety of common ailments; and an array of written materials, including books, pamphlets, and popular health magazines. Health food stores also provide a link to unconventional health services by maintaining bulletin boards for notices about clinics, practitioners, and mail-order products and by referring customers directly to practitioners who use unconventional approaches, including physicians, herbalists, chiropractors, homeopaths, naturopaths, and acupuncturists.

Other than the most popular ones, books and articles about unconventional cancer treatments are relatively difficult to find in public places outside of health food stores. The selection of materials varies widely among different health food stores, however, depending in part on the nature of the store and local interest in particular treatments.

Health food stores and their employees are thought to be influential in cancer patients' decisions about unconventional treatment, but the evidence in support of this contention is largely anecdotal or conjectural. One exception is a 1983 survey sponsored by the American Council on Science and Health (839), a group that describes its purpose as protecting consumers by providing them with valid scientific information. In that survey, researchers visited or telephoned health food stores in the New York, New Jersey, and Connecticut areas and either asked specific questions about products or presented a set of symptoms and asked for advice. In the one scenario that might relate to cancer treatment, a researcher called 17 stores, stating that, for no apparent reason, she had lost 15 pounds in the past month (a symptom that could result from cancer) and was concerned about losing more. Employees in seven stores recommended that the caller see a physician. Five tried to diagnose the problem, and in nine stores, employees recommended dietary products plus a variety of mineral, vitamin, and other supplements. Two other store employees referred the caller to an herbalist and a naturopath, while a third employee discouraged her from seeing a physician.

In an effort to understand more about the role of health food stores in patients' decisions about unconventional cancer treatments, OTA commissioned a small survey in three cities: Philadelphia, Tucson, and Berkeley (420). In that survey, the graduate student researchers noted the types of available printed material related to cancer treatment and asked for advice about treatment, giving the details of a friend or relative's cancer with which they were familiar. Responses to the reserchers differed by store and by city, but in all three cities, health food stores provided links to the alternative cancer treatment network. A pro-alternative, rather than an anti-medicine, attitude prevailed. In general, salespeople were willing to give advice, which included do-it-yourself practices, specific clinics and practitioners, further sources of advice, including referral networks or organizations favorable to alternative medicine, and books, magazines, and pamphlets. No single book, product, or treatment was brought up consistently, however. In addition to literature and products for sale, and the advice of salespeople, informal contact with other patrons and

bulletin board postings offer health food store customers entry into the alternative network.

The OTA survey is in general agreement with the American Council on Science and Health study and the anecdotal information pointing to health food stores as relatively easy places of entry for seeking out alternative cancer treatments. The growth in numbers of health food stores over the past decade suggests that a large portion of the population has easy access to such stores, but we still do not know the number of cancer patients for whom health food stores play an important role.

Mass Media and Books

According to the 1987 Harris poll described previously, most American adults are generally aware that "questionable' or unconventional treatments for cancer and other chronic diseases exist. The media are important sources of information about cancer in general, as was found by a 1978 ACS survey in which the overwhelming majority of respondents described television, newspapers, and radio as their primary sources of information about cancer (548). The airing of a single 15-minute segment of the television show "20/20' in October 1987, entitled "Promise Them Anything," which examined the promotion of unconventional cancer treatments at conventions held by advocacy groups, undoubtedly increased general awareness of unconventional cancer treatments among the estimated viewing audience of 18 million people (670). An example of "unintended publicity" by the media was the press coverage of actor Steve McQueen's use of unconventional treatments before his death from cancer. The total number of inquiries to NCI's Cancer Information Service concerning unconventional treatments-which is a useful marker of public awareness of unconventional cancer treatments—increased substantially during that time (305).

Over the last 3 years, in addition to the "20/20" episode cited above, a major network aired several shows on this topic, concerning individual patients' search for unconventional cancer treatment options, nutritional approaches to cancer treatment, the role of positive thinking in curing cancer, and the phenomena of underground medical cults and health fraud. These shows reached estimated audiences of 7 million, 20 million, 24 million, and 16 million respectively (670).

Occasionally, popular books and movies, such as *Death Be Not Proud,* **may contribute to the public's general awareness of unconventional cancer treatments. In some cases, it is not the treatments, but rather the political issues surrounding the availability and evaluation of unconventional cancer treatments that have been the specific subject of both movies and television shows, such as in the AMA Department of Investigation's** *Medicine Man in 1958, the film Hoxsey: Quacks Who Cure Cancer?* **and various radio and television talk shows in 1988 and 1989 (e.g., Morton Downey, Oprah Winfiey, Sally Jesse Raphael, Robert Atkins). As described in the discussion on health food stores, a number of popular books publicize unconventional cancer treatments and are frequently cited by users as their initial source of information.**

Although mass media may be the most powerful conduit of cancer information to the public, there are few data to assess their impact or how they may differentially portray mainstream and unconventional cancer treatments. One review suggests media's general handling of cancer to be fairly accurate in content and neutral in tone (307), but others raise concerns about undue sensationalism in reporting on cancer treatments (642). For example, in a recent nationally broadcast television talk show, Stanislaw Burzynski, M. D., developer of "Antineoplastons," and his patient-advocates were both encouraged and applauded by the hostess, with little opportunity allowed for the hastily invited expert in mainstream oncology to discuss her concerns about the treatment's safety and efficacy (729).

Some popular books, such as Glassman's *The Cancer Survivors and How They Did It (341),* **and Kushner's** *Alternatives: New Developments in the War Against Breast Cancer (510)* **make mention of unconventional treatments though not focusing on them. A chapter on unconventional treatments is included in the Consumer Reports Book,** *Charting the Journey: The Cancer Survivors' Almanac of Resources (651).* **Others, such as Moss'** ***The Cancer Industry: Unraveling the Politics (648),*** **and Lerner's** *Integral Cancer Therapies (531),* **focus on unconventional treatments and place them in a positive light.**

DECIDING ABOUT UNCONVENTIONAL CANCER TREATMENTS

As patients obtain information and begin to identify one or more unconventional treatments or approaches with which they feel comfortable, a single, pivotal experience may serve to focus and intensify the decisionmaking process. Several IAT patients, for example, have cited viewing a 1980 television show, "The Establishment Versus Dr. Lawrence Burton" (782), (which reached an estimated audience of 30 million viewers) as pivotal in their decision to investigate and ultimately use IAT. At some point in each cancer patient's research on unconventional treatments, he or she determines that sufficient verbal or written information has been obtained to either accept or reject specific treatments. However, as discussed elsewhere in this report, it is impossible to find published, scientifically valid information on most unconventional cancer treatments.

A cancer patient's personal and financial resources, belief system, and personal style of seeking health care all help to determine which sources of information are used, how information is interpreted, and how treatment decisions are made. As one author points out, patients considering unconventional cancer treatments may use the same lay referral network and go through much the same process of selecting information sources to rely on as they have in their previous health care decisions (54).

In response to written or telephone inquiries, many clinics or proponents send free brochures, published or unpublished articles, newsletters, issues of advocacy journals, or lists of suggested readings, and may offer to send books or more detailed audio-visual materials for a fee. A few clinics also send free audio cassettes or videotapes, lists of treated patients available for contact, or printed patient testimonials. Some clinics do not reply substantively to written or telephone inquiries or may send vaguely worded materials. Some encourage patients to pursue supplemental readings or ask their primary physician to contact the clinic before treatment information is made available (365).

Upon arrival at treatment centers, patients may obtain additional information from their contacts with practitioners and sometimes through informed consent documents. Nonetheless, the written materials sent by proponents and clinics to potential patients early in the information gathering process remain an important source of primary treatment information, often relied upon by patients in assessing and selecting among treatments.

Some factors that patients may consider in deliberating about the use of unconventional cancer treatments are: the nature of the treatment, the testimonies of other patients, claimed benefits, possible risks, expenses, associated discomfort, potential side-effects, philosophy of the provider, required travel, and anticipated difficulties in complying with the regimen (365).

Chapter 8

Organized Efforts Related to Unconventional Cancer Treatments: Information, Advocacy, and Opposition

CONTENTS

Box

Tables

Chapter 8

Organized Efforts Related to Unconventional Cancer Treatments: Information, Advocacy, and Opposition

INTRODUCTION

There are organizations that exist solely to advocate "alternative medicine, ' or "freedom of choice' in medicine; and there are organizations whose sole goal is to eradicate "health fraud. ' Unconventional cancer treatments are major concerns of both types of group. Other organizations, including Federal agencies, engage in activities related to unconventional cancer treatments as part of a broader agenda. The strategies of all these groups vary, but most include some component of providing information to the public or to health professionals; some include lobbying or other political activity; others become involved with private legaI actions involving patients, practitioners, and clinics.

This chapter presents the activities of the Federal Government concerning unconventional cancer treatments, through the National Cancer Institute (NCI) and the Food and Drug Administration (FDA), and then discusses the activities of private sector organizations that have taken stands for or against unconventional cancer treatments. Following that, the chapter discusses examples of specialized information services.

FEDERAL GOVERNMENT INFORMATION ON UNCONVENTIONAL CANCER TREATMENTS

The National Cancer Institute (NCI)

NCI has a responsibility to inform the public about cancer. In 1986, NCI staff answered about 400,000 public requests for information (373). The Public Inquiries Office and the Cancer Information Service (CIS), two branches of NCI's Office of Cancer Communication, supply information to the public about cancer treatments. The Public Inquiries Office and CIS have provided some information on unconventional treatments for several years, and NCI is in the process of developing a more detailed data base on unconventional treatments.

Public Inquiries office

This office is responsible for NCI responses to written inquiries about cancer treatments, including foreign inquiries and legislative requests, and also questions originating within the National Institutes of Health (NIH). Difficult or complex questions from the public may be referred by CIS to the Public Inquiries Office for research and resolution. The staff work with other NCI staff in writing and distributing many treatment-related publications, including the standard response paragraphs used by CIS staff to answer inquiries about unconventional cancer treatments (174).

Cancer Information Service

NCI established the CIS in 1975, as part of a Federal initiative to meet the diverse informational needs of cancer patients. CIS is a telephone network consisting of a national office and 25 regional offices, each covering one or more States or large population areas. Calls coming in after hours or on weekends are transferred to a toll-free 24-hour number answered by the national CIS office, which is run by a private business under contract to NCI. Information on a wide range of cancer-related topics is available to callers through CIS staff, who are health educators and trained volunteers. In response to inquiries, CIS staff may consult a computerized database, their office's subject matter files (including newspaper and periodical articles), and their reference library. CIS staff also have access to the expertise of NCI physicians and researchers. Followup on telephone inquiries is done by mailing printed materials or a return phone call (306).

Inquiries to CIS about unconventional cancer treatments constitute about 1 percent of all inquiries, and people most frequently ask about these treatments in addition to other cancer-related questions (e.g., clinical trials, treatment in general, coping and counseling, chemotherapy), according to a recent review of 4 years of CIS experience (306). Data on the types of unconventional cancer treatment asked about are not uniformly recorded by CIS staff. However, the Florida regional office of CIS did record this information between September 1982

and February 1983, a period when staff answered 558 telephone inquiries about unconventional cancer treatments. They reported that most of their inquiries concerned Immuno-Augmentative Therapy (probably due at least in part to the proximity of Florida to the Bahamas), other types of "immunotherapy,' Macrobiotic diets, and the use of vitamin C; other inquiries concerned advocacy organizations, home remedies, dimethyl sulfoxide (DMSO), and the Burzynski cancer treatment (781).

According to a recent review of the limited data available, CIS responded to a total of 10,399 inquiries about unconventional cancer treatments during the 4-year period between January 1983 and December 1986. Friends and relatives of cancer patients accounted for just over half these inquiries; cancer patients, 18 percent; the general public, 12 percent; health care professionals, 6 percent; and the media, less than 1 percent. Over the last 4 years, all CIS offices, with the exception of Oklahoma, have recorded some inquiries about unconventional cancer treatments. The six offices reporting the highest percentage of inquiries about unconventional treatments were Tennessee, California, Washington State, New York City, Texas, and Wisconsin (306).

CIS staff read or paraphrase a standard response paragraph to all callers asking about unconventional cancer treatments. This paragraph: 1) urges patients to remain in the care of physicians who use "accepted and proven methods' 2) warns that use of unconventional cancer treatments may result in loss of time and reduce chances for cure or control of disease; 3) points out the availability of experimental forms of treatment for situations where standard therapy is not available or has not been effective; and 4) encourages patients to ask their doctor about their eligibility for clinical trials (306).

When inquiries come in, CIS staff may also read from or paraphrase standard response statements about specific unconventional cancer treatments (see table 8-l), and they may send copies of these statements to callers. These standard response statements are prepared by NCI staff, reviewed by the Office of Cancer Communication, revised as necessary, and then passed through a formal clearance process. In addition to these statements, CIS staff may read, paraphrase, or photocopy other materials collected by individual CIS offices (306).

Table 8-l—Unconventional Cancer Treatments and Practitioners for Which NCI/CIS Has Standard Response Paragraphs

Janker Clinic
Antineoplastons/Dr. Stanis.liaw Burzynski
Dr. Hariton Alivizatos/Greek Cancer Cure, Inc.
Dr. Albert Szent-Gyorgyi
Laetrile
Hydrazine sulfate
Dr. Harold Manner
Koch synthetic antitoxins
Hoxsey herbs
Krebiozen
Gerson therapy
Lawrence Burton, Ph. D./IAT
Holistic medicine
Macrobiotic diet

SOURCE: V. Friemuth, "The Public's Search for Information on Unorthodox Cancer Treatments: The CIS Experience," prepared for the Office of Technology Assessment, U.S. Congress, Washington, DC, Feb. 18, 1988.

Most CIS statements about unconventional cancer treatments are several pages long, varying in what they cover. They often identify a major proponent, describe the treatment, and briefly state the claims made. Almost every statement summarizes the evidence available to NCI and draws some conclusion about the treatment, the proponent, or both.

For some treatments (e.g., Antineoplastons, laetrile), the details of evaluation attempts by NCI and other bodies are presented, while for others (e.g., "non-toxic chemicals,' Manner therapy), the statements simply state that "no evidence exists that these are effective in cancer treatment." In two cases, the Gerson therapy and Krebiozen, the statements indicate that a record review was conducted by NCI. Although the findings of those reviews are not presented in detail, the statements conclude that these reviews neither established treatment efficacy nor elucidated promise warranting clinical trial investigation. In a few of the statements (e.g., Koch antitoxins, Hoxsey), very little information about the treatment is provided, but actions of FDA, Federal Trade Commission (FTC), State cancer councils, and other governmental agencies related to the treatment or practitioner are described.

In several cases, while the statements report that there is little evidence to support the treatment itself, they acknowledge the potential importance of relevant fields of research, and go on to describe research conducted by NCI or another mainstream medical institution in those fields. For example, the statement on hydrazine sulfate and the statement on

the Gerson therapy acknowledge the potential role of adequate nutrition in cancer treatment and describe the research on nutrients in cancer being conducted by NCI'S Diet, Nutrition, and Cancer program (DNCP). Though the statement on hydrazine sulfate criticizes early published research, it also describes it as "provocative," and goes on to detail current NCI-funded research efforts on this substance and its possible role as an adjuvant cancer treatment (899, 900).

Data Base on Unconventional Treatments

In an effort to provide practitioners with more information about unconventional cancer treatments, in 1987, NCI awarded a contract to Emprise, Inc., a private consulting firm, to prepare information on 26 unconventional cancer treatments. Each entry will include: 1) a statement reviewing the scientific data supporting the treatment, 2) a sample "patient and doctor dialogue' that physicians may find useful in discussing these treatments with patients, and 3) a summary overview and fact sheet about the treatment. NCI has not decided how it will use this information. It may become part of PDQ, an on-line, free, cancer treatment information system targeted to health professionals, in operation by NCI since 1982. Emprise also plans to make versions of the information available in scientific monographs that will be submitted to peer-reviewed journals (631).

The Food and Drug Administration

FDA has statutory authority to regulate the marketing of drugs, devices, and biologics in interstate commerce. Many of the best-known unconventional cancer treatments involve drugs, devices, or biologics unapproved by FDA, and these treatments become FDA's concern when interstate shipment occurs or reports suggest they pose a public health hazard (411). (See ch. 10 for a description of FDA's responsibilities in regulating drugs.) Because FDA's interest arises from these concerns, FDA may provide the public with almost exclusively negative information about unconventional cancer treatments.

To some extent, FDA's Office of Consumer Affairs both initiates public awareness and responds to occasional public inquiries on unconventional cancer treatments. In the last few years, FDA and the Pharmaceutical Advertising Council (PAC) developed a multi-media public service campaign to teach the public how to recognize, avoid, and help stop what they consider to be 'health fraud,' a term that, as used by the FDA, encompasses some of the treatments covered in this report.[1] In 1986, FDA worked with the National Association of Consumer Agency Administrators (NACAA) to establish an Information Exchange Network. In 1988, the Office of Consumer Affairs contracted with Harris Associates to conduct a national survey (discussed in ch. 7) documenting the extent and impact of what they defined as health fraud on the U.S. public, focusing on use in the treatment of chronic diseases, such as arthritis and cancer.

A few individuals within FDA are knowledgeable about unconventional cancer treatments and may answer specific inquiries or represent the agency on related matters. Staff from the Office of Health Affairs also respond to inquiries from health professionals and organizations regarding unconventional cancer treatments. An FDA historian may respond to public inquiries about unconventional cancer treatments with articles and reprints.

The Office of Regulatory Affairs imposes and publicizes sanctions that may involve unconventional cancer treatments. The office publishes narrative notices of Import Alerts, which have, on occasion, dealt with bans on the importation of unconventional cancer treatments (e.g., IAT, Nieper products). Under the Commissioner of Regulatory Affairs, staff at regional and district offices specifically monitor health fraud and make enforcement efforts. In this vein, the government has sought injunctions against Dr. Stanislaw Burzynski to prevent shipment of unapproved drugs across state lines, and seized some of his records. (See ch. 10 for a full description of this case.)

The Office of Public Affairs prepares "FDA Talk Papers, " which are intended to guide FDA personnel in answering questions posed by the public, and are also available to the public directly. A few recent FDA Talk Papers have discussed unconventional cancer treatments (e.g., live cell therapy, homeopathic remedies).

On the agency level, FDA has provided considerable information about some unconventional cancer treatments through sponsorship of health fraud conferences (61 1). In 1985, FDA, FTC, and the U.S. Postal Service cosponsored a National Health Fraud

[1]Throughout this section the term "health fraud" is used in the way it is used by FDA.

Conference in Washington, DC. This was the first national conference on health fraud since 1966, and was attended by approximately 250 representatives of Federal, State, and local agencies, independent public interest groups, and industry associations (866). The goal of the conference was to heighten awareness of health fraud in the United States and to facilitate the cooperation of various concerned agencies in the public and private sectors. As a followup to the 1985 national conference, FDA held regional health fraud conferences during 1986 in several cities across the country.

In March 1988, FDA sponsored another national Health Fraud Conference in Kansas City. This 2-day conference, cosponsored by two local hospitals, included speeches and workshops with general and specific information about, among other topics, unconventional cancer treatments and their practitioners. Specific unconventional cancer treatments were highlighted as examples of fraudulent treatments (e.g., laetrile and IAT). Legal, fiscal, and sociological aspects of health fraud were discussed (658,988).

PRIVATE SECTOR INFORMATION ABOUT UNCONVENTIONAL CANCER TREATMENTS: OPPOSITION

Most information about unconventional cancer treatments, positive and negative, is developed and disseminated through private sector organizations. The most influential of these on the negative side is the American Cancer Society (ACS), through its "Unproven Methods" activities, which are only a small part of the Society's broad agenda. Historically, the American Medical Association (AMA) played a role in fighting what it defined as quackery, which has included a number of specific unconventional cancer treatments, but it has been less active in recent years. The American Society for Clinical Oncology (ASCO), a professional society for oncologists, has had an ongoing interest in unconventional cancer treatments. Other smaller organizations, such as the National Council Against Health Fraud (NCAHF), the National Council on Nutritional Information, and the Quackery Action Council, investigate, sometimes litigate, and generally warn the public about the hazards they believe are posed by unconventional cancer treatments. Many of these organizations collaborate, sharing resources and personnel, and have sometimes worked with Federal agencies, such as FTC or FDA, acting against health fraud. These organizations have been termed collectively "quackbusters." Many share information among themselves; and prominent individual "quackbusters" often serve on the committees of several organizations.

This section discusses ACS, AMA, ASCO, and NCAHF and their activities.

The American Cancer Society (ACS)

ACS is headquartered in Atlanta and has 57 divisions throughout the United States. Originally founded in 1913 as the American Society for the Control of Cancer, ACS is a large, voluntary health organization, "dedicated to eliminating cancer as a major health problem by preventing cancer, saving lives from cancer, and diminishing suffering from cancer through research, education, and service" (90). While a strong emphasis is placed on supporting cancer research and training, public and professional education remain important program priorities for ACS (373). An early ACS slogan was "Fight Cancer with Knowledge" (409). The most prominent program relating to unconventional cancer treatments is the long-standing ACS Committee on Unproven Methods of Cancer Management. The Committee and its statements, as well as other relevant ACS activities, are described below.

Committee on Unproven Methods of Cancer Management

The majority of ACS public and professional education activities regarding unconventional cancer treatments originate with the Committee on Unproven Methods of Cancer Management.[2] Established in 1954, the Committee is administered by the professional staff of the national office, and serves as an information resource for all ACS divisions. The Committee shares information with ASCO, FDA, the U.S. Pharmacopoeia, AMA, and also, on an ad hoc basis, with the unproven methods committee of the European Association of Cancer Societies (373).

[2]At its Mar. 7 1990 meeting, the Committee on Unproven Methods of Cancer Management proposed a name change to the Committee on Questionable Methods of Cancer Management. This change awaits approval by the Society's House of Delegates in November 1990 (90).

Although the original intent of the Committee was to provide information to physicians on unconventional forms of cancer treatment, more members of the public than physicians currently approach ACS about unproven methods. The main activity of the Committee is "to initiate and approve the preparation of materials for the education of the medical profession and the public concerning unproven methods for treatment and/or diagnosis of cancer" (90). The Committee also funds small research projects, such as two current pilot projects to determine the extent of use of unproven methods of cancer management across the United States.

The Committee meets three times a year to *discuss unproven cancer treatments, advocacy organizations for unconventional treatments, and practitioners offering unproven cancer treatments, and to review related projects. Members may be assigned to small working groups for specific projects, such as revising the Unproven Methods statements. The Committee maintains more than 900 information and documentation reference files. ACS states that they gather information by conducting literature searches, reviewing existing files, and inviting proponents of unconventional cancer treatments to submit materials during the drafting and revision processes (287). Statements on unproven methods that appear in the ACS publication CA-A Cancer Journal for Clinicians are drafted by a technical writer or by a health professional with interest and knowledge in the topic, and reviewed and approved by the Committee before adoption and public distribution (90).*

In an ACS brochure titled 'Unproven Methods of Cancer Management,' ACS urges the public not to use "unproven methods," and to distinguish these from established and investigational mainstream treatments:

> *Methods of investigation in cancer management . research generally include some of the following: observations on the effects of the therapy under study in an adequate number of patients with biopsy-proven cancer; complete evaluation of all clinical and laboratory data including case histories, radiographs, and microscopic slides; reproducible findings; assessment of treatment results as compared with a control group or standard treatment; examination of survival outcome; and consultation with other research groups.*
>
> *Unproven methods of cancer management differ from standard accepted treatments which have been shown by scientific study to be effective. Standard methods of treatment have undergone study to prove that they are both effective and safe. If methods of therapy have not had careful review by scientists and/or clinicians to show that they are effective, then they are not deemed proven and should not be recommended. (28)*

A recent brochure lists 27 individual ACS statements on Unproven Methods of Cancer Management (table 8-2). Most statements describe treatments, but some profile practitioners or advocacy organizations. Some statements open with a standard section that indicates the purpose of the statement and why ACS recommends that unproven methods of cancer management not be used. Additional information varies from statement to statement but may include claimed benefits of treatments, citations from published literature, summary and criticism of available data, examples of legal action, plans for mainstream evaluation of treatments, and biographical information about proponents. All have a strongly negative tone and clearly attempt to dissuade use of unconventional cancer treatments. Some advocates for unconventional cancer treatments term this "the ACS black list."

In 1988, ACS began the process of updating all of the unproven methods statements. As they are completed and approved by the Committee, they appear in the ACS professional journal, CA-A Cancer Journal for Clinicians. In 1989, the new statements on the International Association of Cancer Victors and Friends, Inc. (29), the Revici method " (31), and macrobiotic diets (30) were published.

The ACS unproven methods statements are regarded as authoritative by many public and private sector organizations. In addition to their use by patients and their physicians, the statements are also used as reference documents in insurance coverage decisionmaking (577). A recent survey of the commercial health insurance industry by the Association of Community Cancer Centers (ACCC) revealed that ACS Statements on Unproven Methods are one of the five most frequently consulted sources of information used by major insurance companies in their deliberations regarding reimbursement for cancer treatment claims (577).

Table 8-2—Treatments and Proponents of Treatments Declared Unproven in ACS Statements on Unproven Methods of Cancer Management, 1987

- Hariton Alivizatos, M.D. (Greek cancer cure, inc.)
- Antonio Agpaoa, the "psychic surgeon"
- Antineoplastons
- Vlastimil (Milan) Brych
- Chaparral tea
- The Committee for Freedom of Choice in Cancer Therapy, Inc.
- Contreras methods
- Dimethyl sulfoxide (DMSO)
- Electronic devices
- Fresh cell therapy
- Gerson method of treatment for cancer
- Hoxsey method or Hoxsey chemotherapy
- Immuno-Augmentative therapy of Lawrence Burton, Ph. D., Bahamas
- Independent Citizens Research Foundation for the Study of Degenerative Diseases
- International Association of Cancer Victors and Friends, Inc.
- Iscador
- Issels combination therapy, proposed by Josef Issels, M.D.
- Kelley malignancy index and ecology therapy
- Koch antitoxins
- Laetrile
- VirginiaWuerthele-Caspe Livingston, M.D. and EleanorAlexander-Jackson, Ph.D.—PPLO vaccine and test
- Macrobiotic diets
- Metabolic cancer therapy of Harold W. Manner, Ph.D.
- National Health Federation
- Carey Reams
- Revici cancer control
- O. Carl Simonton, M.D.

SOURCE: American Cancer Society Inc., "Unproven Methods of Cancer Management," pamphlet, 87-25M-No. 3028, 1987.

Inquiries to ACS About Unproven Methods of Cancer Management

Depending on whether callers inquire during or after office hours and on the level of information requested, inquiries to ACS about unconventional cancer treatments may be handled by the National Office Professional Education Staff, local Cancer Response System (CRS) staff, or other individuals designated by divisions (373). The Delaware Division, for example, has designated one individual to handle all inquiries from health professionals about unconventional cancer treatments (33).

The ACS National Office received about 800 telephone or written inquiries about unproven methods over the 46-month period from November 1983 through September 1987. (There is no count of similar inquiries to regional ACS offices.) The inquiries were handled either by the CRS or Unproven Methods Committee staff. Of those inquiring, 415 were patients or their family members, 356 were health professionals, and 33 were from the media. The specific content of the calls is not recorded in sufficient detail to determine patterns of public interest in particular treatments.

Educational Programs

ACS sponsors public service advertisements, health fairs, conferences, and other special programs with, generally, only a minor focus on unconventional cancer treatments. The ACS divisions are independent, however, and some choose to be more active in this area than others (796).

Cancer Response System

Since 1984, ACS has operated the CRS, its telephone "hotline" information service, as a joint educational project between ACS headquarters and regional offices. CRS is operated by ACS volunteers and professional staff, using two toll-free telephone lines, according to prescribed procedures and guidelines (796). A minority of CRS inquiries involve unconventional treatments.[3]

Although regional ACS offices may handle inquiries somewhat differently than does the national office, the national office provides the regional offices with most of the information used to respond. Most ACS staff reaming CRS telephone lines read or send standard statements prepared by the Unproven Methods Committee to callers inquiring about specific unconventional cancer treatments. Personnel are asked to emphasize that it is not ACS policy to recommend any specific treatment and urge callers to maintain contact with their mainstream physicians (796). Other reference information may include ACS public education pamphlets; articles from the ACS practitioner journal, *CA-A Cancer Journal for Clinicians;*[4] ***FDA Talk Papers; the ACS publication for medical students,*** *Clinical Oncology; the Cancer Manual,* ***written for a general audience; and articles from other journals. ACS divisions may also develop their own reference materials.***

[3]In addition t. information on unconventional cancer treatments, CRS also maintains materials on more commonly requested information (e.g., causes of cancer, prevention strategies, specific malignancies, orthodox cancer treatments, clinical trials, rehabilitation resources, and other support services for cancer patients).

[4]For example, the May/June 1988 issue of *CA-A Cancer Journal for Clinicians* contains articles on self-help groups, psychosocial issues, and unconventional cancer treatments.

The American Medical Association

AMA is a large trade organization whose membership includes individual physicians, all State and county medical societies, and 70 medical specialty societies throughout the United States. AMA states that it seeks to "promote the art and science of medicine and the betterment of public health," by "representing the medical profession, providing information about medical matters, upholding professional conduct and performance, and advancing standards of medical education" (47,71). Under this banner, AMA has made efforts to prevent what it considers health fraud and to educate the profession and the public as to the advantages and disadvantages of controversial therapies. In the past, AMA crusaded actively against unconventional cancer treatments (see box 8-A), but in recent years their activity in this area has waned.

Currently, questions concerning unconventional treatments are generally referred to other organizations, such as ACS. AMA does maintain fries of published and unpublished literature on unconventional treatments, however, and will respond to questions about them. Responses are provided by staff of the Division of Library and Information Management. In 1989, AMA published a small annotated bibliography of the published, mainstream literature on a group of unconventional treatments, not limited to cancer. AMA itself, however, did not editorialize on the treatments (843). Another AMA activity, the Diagnostic and Therapeutic Technology Assessment (DATTA) Program in the Division of Basic Sciences, Group on Science and Technology, also has become involved, to a limited extent, with unconventional treatments.

Diagnostic and Therapeutic Technology Assessment Program

DATTA was created in 1982 to distill and publicize information for practicing physicians on the safety and clinical efficacy of emerging or controversial medical technologies. DATTA responds to approximately 600 information requests per year with letters, phone calls, and formal DATTA opinions published in the *Journal of the American Medical Association* (71,446,787). Most inquiries are from individual physicians, patients, and third-party payers. (See ch. 9 for a description of the insurance industry's use of DATTA opinions.)

Medical technologies may be proposed for DATTA review by the public or by several offices within AMA, but are selected for the formal review process based on the priorities of the Council on Scientific Affairs. In formulating an opinion, DATTA staff review literature from technical journals and then survey assembled panels of experts from relevant medical specialties about the technology's safety and efficacy. About 10 DATTA opinions are published each year in the *Journal of the American Medical Association*. All DATTA opinions are considered provisional, and may be reassessed upon new findings and information.

Three unconventional cancer treatments have been evaluated by the DATTA program. The first two were subjects of mainstream research, which were also promoted in the alternative medical community. The third, IAT, exists wholly outside of conventional medicine and research. DATTA assessed Bacillus Calmette-Guerin (BCG) vaccine for use in cancer therapy several years ago.[5] Whole-body hyperthermia was originally assessed in 1983 (466) and rated as "investigational" for use in cancer treatment. DATTA later reassessed whole-body hyperthermia for cancer in 1986 (46) after FDA approved a hyperthermia system for a specific palliative cancer treatment indication. The updated DATTA evaluation states that use of regional or local hyperthermia for the indication approved by FDA represents "established medical practice," while the use of whole-body hyperthermia, and other applications of local and regional hyperthermia remained "investigational."

IAT was the subject of a 1988 DATTA evaluation (467). In the published DATTA opinion, panelists had no data from clinical trials or other studies to review; only historical information, descriptive articles, and reports of health hazards were included. The overall opinion was negative (680). (See ch. 6 for a full discussion of the IAT DATTA evaluation.)

The American Society for Clinical Oncology (ASCO)

ASCO has been generally silent about unconventional cancer treatments. Its primary concern is with

[5]BCG is a biologic used in other countries for treatment of tuberculosis, and is sometimes used in the United States as an unconventional treatment for both cancer and AIDS.

Box 8-A—The American Medical Association: Historical View

From the early part of the 20th century through the 1970s, the American Medical Association (AMA) crusaded actively to protect the public from what it considered medical fraud and quackery. In 1906, AMA established a formal department, the Propaganda Department, to confront the issue of health fraud in proprietary medications (649). The Department experienced several name changes, becoming the Bureau of Investigation in 1924 and then the Department of Investigation in 1958, but it retained the same goal: to combat health fraud by evaluating existing medications and technologies and through educating physicians and the lay public about the deceptive practices of quacks. Three mechanisms were used to accomplish this goal: dissemination of information by means of speeches, books (including *Nostrums and Quackery*), school texts, films, and written responses to individual inquiries; distribution of information to State medical boards on the credentials and qualifications of applicants for medical licensing; and cooperation with various Federal agencies, including FDA, FTC, and the U.S. Postal Service, in order to regulate, prevent, and prosecute individuals responsible for health fraud schemes (38,649).

During the 1930s, the peak period for inquiries, 10,000 to 12,000 requests for information on proprietary medicines and cosmetics were submitted each year by physicians and the public. After the passage of the 1938 Food, Drug, and Cosmetic Act, the number of inquiries declined significantly. From 1942 to 1963, an average of 3,000 to 4,000 letters and phone calls were answered each year. During the 1950s and 1960s, questions concerning cancer treatments were the most popular, and a smaller staff in the Department of Investigation continued writing newspaper columns and producing films such as the *Medicine Man (1958)* on the dangers of "quack" treatments.

AMA owed its quackbusting reputation in large part to Morris Fishbein, M.D., editor of the *Journal of the American Medical Association* from the mid-1920s through the 1940s. Fishbein waged public campaigns against well-known unconventional treatments and their purveyors, the most famous being his battle against Harry Hoxsey. In a 1947 editorial called "Hoxsey-Cancer Charlatan," Fishbein wrote, " [o]f all the ghouls who feed on the bodies of the dead and the dying, the cancer quacks are most vicious and most heartless" (292). The invective that flew between Hoxsey and Fishbein was captured in a recent film, *Hoxsey: Quacks Who Cure Cancer? In 1949,* Hoxsey sued for libel and won a judgment—$2—against Fishbein, reportedly the only one of the many suits brought against Fishbein that was decided against him (58). Fishbein left the editorship of the journal that same year.

In 1961, AMA's Department of Investigation and FDA collaborated in sponsoring the first National Congress on Medical Quackery. In this and three subsequent congresses, representatives of AMA, Federal agencies such as FDA and FTC, the Better Business Bureau, State health departments, and private organizations such as ACS, pledged to eradicate "health quacks," largely through public education campaigns. In the 1960s, the Department of Investigation also participated in the Coordinating Conference on Health Information which met twice annually to "implement and augment various activities against quacks, faddists, cultists, and other aspects of pseudomedicine" (41).

During the 1960s, the Department of Investigation targeted its health fraud prevention efforts on chiropractors; in 1962, it formed the Committee on Quackery, which focused its activities on opposing chiropractors' efforts to become recognized as legitimate health care providers (40). That episode culminated in a 1987 ruling against AMA and several other professional societies after an n-year lawsuit brought by Chester Wilk and three other chiropractors, who charged that the organizations had engaged in a conspiracy to boycott chiropractors (614,960).

Both the Department of Investigation and the Committee on Quackery were eliminated in a 1975 restructuring of AMA. The Division of Archival Services and Public Affairs assumed some of their functions (42,44,649). Since the restructuring, AMA activities on health fraud and unconventional cancer treatments have greatly diminished (842).

clarifying scientific and political issues germane to the mainstream practice of oncology in the United States. It does, however, have a standing committee concerning unconventional treatments, and has made some efforts to discuss these treatments with their membership and the public. Efforts in this regard have included the 1983 publication of "Ineffective Cancer Therapy: A Guide for the Layperson" (48), and collaboration with NCI in 1980 on a survey of U.S. oncologists to document their experience with patients who had been treated with IAT.

Public inquiries to ASCO on unconventional cancer treatments are generally referred to ACS or NCI, and the few inquiries received from oncologists are handled by the chairman of the Unorthodox Practices Committee (963). ASCO's 1989 representative on the ACS Unproven Methods Committee and on AMA's Cancer Council is an oncologist

known for his negative stance on unconventional cancer treatments. As of 1988, the same individual also was serving on the Committee on Hematology and Oncology in the Scientific Information Section of the United States Pharmacopoeia, which is currently developing information on unproven cancer remedies.

ASCO, along with AMA and ACS, articulates what is considered standard or reasonable cancer treatment in the United States. ASCO is considered highly credible and while, as an organization, it does not do much to influence directly the use of unconventional cancer treatments, its representation on related committees within AMA, ACS, and the United States Pharmacopoeia, and its general lack of public discourse on unconventional cancer treatments conveys a view of these treatments as collectively lacking value. Lack of ASCO endorsement or serious consideration probably influences mainstream oncologists against incorporating these treatments into their practices and, in general, from referring patients to unconventional practitioners.

The National Council Against Health Fraud (NCAHF)

NCAHF describes itself as an organization of "health professionals, educators, researchers, attorneys and concerned citizens, wishing to actively oppose misinformation, fraud, and quackery in the health marketplace" (656). The group was founded in 1977 in California as a local consumer advocacy group for health matters, and became national in 1984. The council "conducts studies and investigations to evaluate claims made for health products and services' educates Americans about "health fraud, misinformation, and quackery"; promotes consumer health laws; and "encourage[s] and aid[s] in legal actions against consumer protection health laws violators." Its newsletter is NCAHF's main means of promoting its cause, but it also has a Resource Center that sells books and articles on health care fraud (656).

Affiliated with NCAHF, the Nutrition Information Center is a non-profit group, based in Arizona, that publicizes negative information about providers of unconventional cancer treatments and specifically discourages use of what is considered fraudulent or unproven nutritional treatments. It also maintains a speakers' bureau, and sells videotapes, manuals, books, and assorted reprints.

PRIVATE SECTOR INFORMATION ABOUT UNCONVENTIONAL CANCER TREATMENTS: ADVOCACY

Some of the most active organizations providing information to promote the use of unconventional cancer treatments or, more generally, freedom of choice in medicine include the Cancer Control Society (CCS), the International Association of Cancer Victors and Friends (IACVF), the National Health Federation (NHF), the Foundation for Advancement in Cancer Therapies (FACT), the Coalition for Alternatives in Nutrition and Healthcare (CANAH), and the American Quack Association (AQA). There are, in addition, groups formed in support of particular treatments and practitioners, e.g., the IAT Patients' Association (IATPA), the Friends of Dr. Revici, and the Hans Nieper Foundation. A few private information services also provide specialized information about and, in some cases, referrals to unconventional cancer treatments. Examples of these types of organizations are discussed later in this chapter.

The Cancer Control Society (CCS)

CCS, founded in 1973 by two former IACVF members, is currently one of the most active organizations advocating the use of unconventional cancer treatments. Based in California, it has approximately 5,000 members. In a spring 1988 mailing, CCS stated that its purpose is "public education in the prevention and control of cancer and other diseases through nutrition, tests, and non-toxic alternative therapies.' The same flier cites laetrile, Gerson therapy, Hoxsey treatment, Koch enzymes, wheat grass, immunology, mega-vitamins and minerals, detoxification, nutrition, dimethyl sulfoxide (DMSO), and chelation therapy as examples of the treatments considered "non-toxic" by CCS (166).

CCS members receive a journal, the *Cancer Control Journal,* and may be eligible for discounts at selected treatment-related supply houses (270). CCS provides free lists of practitioners and clinics offering unconventional treatments, in addition to selling books, informational pamphlets, cassette tapes, self-help materials, and spectific treatment-related products directly to the public. CCS holds an annual convention on unconventional cancer treatments, attended by approximately 1,000 people per year, at which 50 to 100 practitioners of unconventional cancer treatments, many of whom practice in Mexico, discuss and promote their services (764). Treated patients also participate in the CCS annual convention and may offer testimonials in support of practitioners.

In order to respond to public inquiries, CCS maintains a 24-hour telephone hotline and sends out information (including names and addresses) about unconventional practitioners and clinics; mailings also include names and addresses of patients who have used unconventional treatments (163,164,166). In at least some cases, CCS specifically recommends practitioners and types of unconventional cancer treatment based on the inquiring patient's diagnosis and any expressed preferences. Aside from periodic updating of their membership list and letters to members asking their permission to be contacted by other patients, no formal effort is made to follow up on patients referred by CCS to unconventional practitioners (764).

CCS assists cancer patients in looking into unconventional treatment options by providing prospective patients with a list of patients who have used various unconventional treatments and their telephone numbers. CCS also arranges "Cancer Clinic Tours," consisting of guided bus trips to Mexican clinics that offer unconventional treatments. Commentary by CCS bus tour guides about the clinics and practitioners may influence patient decisionmaking, as may the comments made by the practitioners and patients they meet at each clinic. Approximately 200 people per year take the CCS trip to Mexican cancer clinics (764).

The International Association of Cancer Victors and Friends (IACVF)

IACVF, founded in 1963 by a cancer patient, currently has approximately 4,000 members. Headquartered in California, IACVF has chapters in Florida, Illinois, New York, Texas, Washington State, and affiliates in Canada and Australia. One IACVF goal is "to continually collect, research, analyze, evaluate, and disseminate new information concerning alternative non-toxic treatments, therapeutic agents, vaccines, pharmaceuticals, nutritional aids and clinics in the United States and abroad" (29).

IACVF facilitates person-to-person networking by providing a list of "recovered patients" and encouraging contact by potential patients. IACVF's publication, *Cancer Victors Journal,* focuses on unconventional and occasionally conventional approaches to cancer prevention and treatment, nutrition, interviews with researchers and practitioners, and personal case histories of cancer "victors." IACVF runs an informational telephone hotline through its national and regional offices. Its national office reports an average of 5 to 10 calls per day concerning unconventional cancer treatments, with some regional offices receiving more (192). In response to inquiries, IACVF provides supportive telephone counseling and, at the volunteer's discretion, general discussion of available unconventional cancer treatments. As followup, callers may be sent written materials advocating a wide variety of unconventional cancer treatments. IACVF's National Office develops and distributes sample informational packets, also distributed by regional chapters, along with supplemental information relevant to each area of the country. Regional chapters also sponsor seminars on topics related to cancer and cancer treatment.

IACVF cooperates with CCS in developing and publishing listings of alternative cancer treatments, practitioners, treatment supplies, clinics, and support groups. The Association also participates in the CCS annual convention.

The National Health Federation (NHF)

NHF was established in 1955 and provides generally positive information about unconventional medical treatments (not limited to cancer) coupled with consistent criticism of mainstream medicine. NHF also acts politically, attempting to effect legislative change to deregulate practitioners and enhance "freedom of choice" in health care. It is based in California, with 82 chapters in 32 states (389).

NHF advocates the use of unconventional treatments through its journal, *Health Freedom News,* which contains articles and advertisements for treatment-related supply houses, clinics, and practitioners offering unconventional cancer treatments. NHF also sells books, reprints, and pamphlets that advocate specific unconventional cancer treatments. One of the most vocal advocacy organizations in the United States, NHF uses its journal to seek both financial and political support from its readership for "freedom of choice" causes.

The main issue around which NHF frames most of its goals is its belief that many government actions in the health area are invasions of personal freedom and civil liberties. The organization's role is to fight for an individual's right to choose their health care, a liberty they feel is restricted by the health industry as it exists presently.

Coalition for Alternatives in Nutrition and Healthcare (CANAH)

CANAH is a coalition, based in Pennsylvania, that has as its main goal the enactment of a Healthcare Rights Amendment to the U.S. Constitution and similar amendments to the constitution of each state, but the group involves itself in a wide variety of health issues, including access to unconventional cancer treatments. Like NHF, CANAH argues that conventional medicine controls health care in the United States, suppressing other types of care (such as homeopathic, naturopathic, etc.) to which people should have access. CANAH presents its stands on various issues through its newsletter, *Healthcare Rights Advocate,* and other publications (205).

The Foundation for Advancement in Cancer Therapies (FACT)

FACT is a New York-based educational organization, founded in 1977, with chapters in Detroit, Boston, and Philadelphia. It distributes information about cancer treatments it considers "nontoxic." Based on a belief that cancer is a sign of systemic dysfunction or imbalance in a person, FACT advocates cancer treatments that purport to enhance patients' resistance. The group focuses on "early non-invasive diagnosis, nutrition, detoxification, structural balance, and mind-body connection' (298). FACT only advocates cancer treatments that it deems "holistic," "host-oriented," and "nontoxic." Treatments meeting FACT's nontoxic criteria are fever therapy, immunotherapy, cellular therapy and botanicals (298). In addition to the many unconventional cancer treatments advocated in FACT literature, a few innovative cancer treatments from mainstream research institutions are also advocated.

In its effort to educate the public, FACT responds to requests by sending out books, article reprints, and cassette tapes. Their publication, *Cancer Forum,* has a circulation of approximately 5,000. FACT volunteers respond to telephone inquiries by "assessing patients' physical, financial, and geographic needs" (770). In addition, FACT's public education activities have included a conference in Philadelphia on nutritional and psychoneuroimmunologic cancer treatments, attended by patients and professionals.

The group makes treatment referrals almost exclusively to "metabolic" practitioners. Referred patients are asked to report back to FACT on their treatment experiences and their comments are considered by FACT staff in making future referrals. FACT had planned to undertake a structured evaluation of the treatment experiences of their callers in 1987, but the project has been delayed indefinitely (770).

American Quack Association (AQA)

AQA, a sma11 organization founded in 1985 and based in Florida, views both patient and practitioner use of unconventional health care treatments as "freedom of choice' prerogatives. Its membership includes both professionals in the health field and lay practitioners. The AQA publication, the *Journal of the American Quack Association,* which is published with *Health Consciousness,* contains articles and letters to the editor from practitioners and patients advocating the use of unconventional medical treatments. AQA invites its members and readers of its journal to share ''descriptions of their experiences with Quack Remedies which they have found effective' (498). There are currently more than 350 members of AQA (497).

AQA sponsors an annual "Quality Care With Kindness" conference at which the availability and practices of numerous unconventional practitioners are publicized (497).

Project Cure and the Center for Alternative Cancer Research

Project Cure, established in 1979 by a former cancer patient and businessman, describes itself as "the first citizens' lobby group acting on behalf of cancer patients and their non-toxic treatment alternatives" (280). According to its literature, Project Cure's primary goal is to "encourage Congress and the medical community to evaluate and employ nutritional, non-toxic cancer therapies" (731).

Toward its stated goals, Project Cure provides the public with petitions and postcards to express their sentiments directly to legislators. Topics of recent Project Cure write-in campaigns include: supporting legislation to prohibit food irradiation, advocating increased nutritional education in medical school curricula, opposing licensing of dietitians, advocating that NCI spend more of its research budget on nutritional treatments and prevention of cancer, and urging Congress to "protect OTA from biasing influences' in this assessment of unconventional cancer treatments. In addition to postcard campaigns, Project Cure personnel contact congressional staff directly, and have collaborated with other advocacy organizations in efforts to influence public opinion.

Project Cure also created a Center for Alternative Cancer Research (CACR) (732). CACR'S primary service is the provision of free packets of information in response to inquiries about unconventional cancer treatments. CACR reports sending out more than 300,000 such packets between 1987 and 1989 (280), each including a 1986 article from the *New England Journal of Medicine* (65), a 1987 study by the General Accounting Office (862), and a reprint of the Fitzgerald Congressional Hearings of 1953 (294)-three documents that question the degree of success of current conventional approaches to cancer treatment.

Although Project Cure literature disavows advocating "a specific therapy or practitioner" (731), CACR provides the public with information on various alternative cancer treatments, clinics, and practitioners, and also refers patients to specific support groups or information services that provide "additional counseling and direction.' Project Cure tries to educate the public about non-toxic alternative cancer treatments by distributing free copies of a recently published international guide to alternative cancer treatments (289), publishing a quarterly newsletter, *The Turning Point*, and publishing a brochure summarizing their view of state-of-the-art mainstream cancer treatments and "alternatives" (280).

Committee for Freedom of Choice in Medicine (CFCM)

Formerly known as the Committee for Freedom of Choice in Cancer Therapy, CFCM, a California-based organization, describes itself as "committed to freedom of choice with informed consent for physicians and patients in medicine' (365). CFCM sponsors informational seminars on alternative cancer treatments and distributes generally positive information about specific treatments. CFCM is one of the oldest politically-active advocacy organizations in this field, beginning in the 1970s with lobbying efforts to legalize laetrile (365). At one time, there were 500 CFCM chapters nationwide; now there are approximately 50, the decrease due apparently to changes in the legal status and waning popularity of laetrile (54).

In recent years, CFCM has begun to advocate "metabolic therapy and general freedom of choice in health care" and currently provides a referral service to more than 500 'holistic' doctors in North America and abroad. CFCM frequently collaborates with other advocacy organizations (280).

Through their magazine, *The Choice*, CFCM consistently criticizes new and established mainstream cancer treatments, oncologists, and cancer treatment institutions and encourages the exclusive use of unconventional metabolic treatments for cancer (and other diseases). This journal contains advertisements for mail-order "metabolic products,' ' and books advocating unconventional cancer treatments (sold by CFCM), as well as for the two treatment clinics run by CFCM leaders.

The Coalition, Alliance, and Foundation

Over the last few years, individuals from several advocacy organizations have collaborated to advance the interests of alternative medicine in the United States. The 'Coalition for Alternative Medicine' was formed in the spring of 1986 by individuals from IATPA, CCS, CFCM, IACVF, NHF, People Against Cancer, and Project Cure. The Coalition cited a short-term goal of winning a political support for a congressionally mandated OTA evalu-

ation of IAT and a long-range goal of establishing 'a permanent mechanism in government for the evaluation of alternative therapies that show promise" (206). The Coalition met again in November 1986 and January 1987, but eventually disbanded due to internal conflicts and financial problems (595).

A few individuals from the defunct Coalition regrouped in late 1987 to form two new allied organizations-the Alliance for Alternative Medicine (AAM) and the Foundation for Alternative Medicine (FAM). AAM's literature states that it is composed of "organizations, physicians, and other professionals in the medical field, as well as alternative therapy practitioners. Alternately, FAM, whose goals are the same as AAM, is an organization open to the public (456).

AAM's primary goal "is to assist government agencies in developing an efficient and cost-effective evaluation method for both orthodox and alternative cancer therapy" (17). AAM anticipates that, as one outcome, such a government organized evaluation program will ''serve to separate the 'quacks' and 'opportunists' from the genuine researchers and practitioners" ***(19). As one of their first major*** efforts, AAM sponsored a spring 1988 showing of the fiim Hoxsey: *Quacks Who Cure Cancer?* for congressional staff, intended to increase awareness of the politics surrounding alternative medicine (18). In contrast, FAM's role is ''to support the educational and research goals" ***(299).***

Patient Associations

Immuno-Augmentative Therapy Patients' Association

IATPA was founded in July 1985 with the single goal of reopening the Immunology Researching Centre (IRC), a clinic in the Bahamas at which Lawrence Burton offers IAT IRC had been closed by the Bahamian Ministry of Health following a site visit by representatives of the Centers for Disease Control (CDC) and other consultants, prompted by much-disputed reports that IAT treatment materials were contaminated with Human Immunodeficiency ***Virus (HIV, the AIDS virus) and hepatitis B virus. (See ch. 6*** for a complete discussion.) In order to facilitate the clinic's reopening, the IATPA offered to purchase laboratory equipment so that the IAT clinic could test for these two viruses (553) (the clinic itself actually purchased the equipment). The leadership of IATPA also persuaded then-Congressman Guy Molinari to hold public hearings on IAT. Although Burton's clinic was allowed to reopen, ***an IATPA member indicated, "in the course of these events, we [IATPA] became convinced that a conspiracy exists which suppresses evaluation of unconventional treatments and have*** become more broadly politically active in response to this" (455).

Since the reopening of the IAT clinic in March 1986, IATPA leaders and a member of then-Congressman Molinari's staff, acting as principal members of the Coalition (and later the Alliance for Alternative Medicine), helped to rally congressional interest, culminating in the request for OTA's case study of IAT. In addition to political activity, IATPA members share information, emotional support, and assistance (e.g., discount lodging, arrangement for meals and transportation, legal assistance, insurance advice, customs tips, storage, and long-term access to medications) through a periodic newsletter and person-to-person networking. The IATPA also publishes ***a Patient's Handbook*** and informally provides information and support to new and potential IAT patients.

Hans Nieper Foundation (HNF)

In 1985, HNF was established to advocate the unconventional cancer treatments developed and provided by Hans Nieper, a German physician practicing in Hannover, Germany, where some U.S. patients are treated. In addition to publishing a newsletter, providing informational support to potential patients, and selling books and written materials about Dr. Nieper's treatment, HNF arranges for Nieper to speak in the United States (376,378,379). FDA has imposed an import ban on Nieper products because of inadequate labeling or misbranding and seizures have intermittently been made (678,892). HNF expresses concern about this and the problems it creates for Nieper patients in the United States, though they have taken no formal actions to alter the ban (377).

Friends of Dr. Revici

The ***Friends of Dr. Revici is a network of individuals who support Dr. Emanuel Revici's unconventional cancer treatment. The group is based in New York, with local groups in several cities across the United States. It states that its goal is to share information with new and current patients concerning all aspects of Revici treatment. Members assist each other in obtaining necessary medical***

records; arranging for lodging, food, and transportation to Dr. Revici's office in New York; and in acquisition, storage, and appropriate use of the prescribed medications (9). Like the Hans Nieper Foundation, this organization also provides financial support to assist with Dr. Revici's legal expenses.

Specialized Commercial Information Services

A few commercial information services offer to act as personal treatment information "brokers" for cancer patients. They assist in identifying conventional and unconventional treatments and providers. Can Help, one such service, provides patients with customized literature on both mainstream and unconventional cancer treatment options, but will also review medical records, obtain second opinions from selected medical advisers, and provide cancer patients with an independent synthesis and interpretation of all the information (595).

Another commercial information service, the Health Resource, provides cancer patients with reports containing a literature review for both conventional and unconventional treatments, and offers patient vignettes and patient contacts, all based on the client's diagnosis and interests (365).

Chapter 9

Financial Access to Unconventional Cancer Treatments

CONTENTS

Tables

Chapter 9

Financial Access to Unconventional Cancer Treatments

INTRODUCTION

How much unconventional cancer treatments cost and whether health insurance policies cover these costs are important to patients, their families, proponents of unconventional treatments, and third-party payers.[1] Insurers tend to stipulate that coverage of medical treatments is dependent on the treatment's being 'reasonable and necessary,' or 'medically necessary." Generally, to fulfill these terms the treatment must be accepted as effective and safe. Medicare, for instance, reasons that if the treatment is not accepted (by the medical profession) as effective then it is not reasonable to use the treatment. Third-party payers treat most unconventional cancer treatments as not having been shown to be medically efficacious in the treatment of cancer and that some, such as laetrile, have been shown to be ineffective. Insurers will not willingly pay for treatments that are not generally accepted as effective. On the other hand, patients and proponents often contend that unconventional treatments do have a beneficial medical effect on the patient, and therefore should be covered by the patient's health insurance.

At the core of this dispute is the issue of the safety and efficacy of the various unconventional cancer treatments. Patients and advocates of unconventional cancer treatments typically rely on subjective evidence, often the patients' perceptions of their post-treatment physiologic state, to determine treatment efficacy. Even if the size of the tumor has not decreased, patients may feel that the treatment has arrested further growth of the tumor, or has enabled them to enjoy a better quality of life. Patients previously treated with conventional therapies may believe the unconventional cancer treatment was more successful in restoring their health. Many individuals who believe they have benefited from unconventional treatments do not seethe charges for their treatment as excessive or unfair, and often expect that their health insurance will reimburse them for all expenses.

Third-party payers, however, rely on the opinions of physicians and scientists from the mainstream medical community regarding the safety and efficacy of medical treatments. If the physician reviewer is not already familiar with the treatment, the third-party payer will look for information from clinical trials, peer-reviewed medical literature, and duplication of results by other investigators. As shown in chapters 2 through 6, little of this sort of information currently exists for unconventional treatments. Although proponents of unconventional treatments often point to case histories or other descriptive studies as proof of safety and efficacy, these data rarely meet the standards of evidence required by the third-party payers and their physician reviewers. Reimbursement for unconventional cancer treatments is thus rarely, if ever, recommended.

The question of reimbursement for unconventional cancer treatments is most important when treatment charges are high and patients find it difficult to pay for them from personal funds. Critics of unconventional cancer treatments often claim that the treatments are very costly, while proponents contend that unconventional treatment charges generally are lower than those for conventional therapies. However, virtually no research has been conducted on the charges for unconventional cancer treatments, so it is not possible to determine how much cancer patients pay for them. Third-party payers are also concerned about charges for unconventional treatments, since they unknowingly may reimburse patients for these treatments.

Cancer patients who use unconventional treatments as their primary treatment are most significantly affected by the insurers' reticence to reimburse the costs of unconventional treatments. But there is a broader implication for the general practice of medicine. By refusing payment, insurers affect the use of unconventional treatments as adjuncts to conventional treatment. For instance, a physician might be less likely to prescribe a psychological treatment that the patient's insurance will not cover.[2] It is likely, therefore, that the present reinibursement

[2]Blue Cross and Blue Shield plans, for instance, generally do not cover the costs of learning visualization or imaging for relief of pai(637).

[3]For unconventional cancer treatments, this would most likely consist of eating only organically raised meats and produce, adding vitamin and mineral dietary supplements, or both.

system acts as an impediment to the incorporation of any unconventional approach into a conventional treatment regimen (8).

This chapter explores some of the issues related to charges and reimbursement for unconventional cancer treatments. Topics include a descriptive discussion of treatment charges; an estimate of total initial treatment charges for certain types of treatment or selected clinics; third-party payer criteria for reimbursement of medical services; the process of claims evaluation; court cases involving denials of reimbursement; and fraudulent insurance claims associated with unconventional cancer treatments.

CHARGES FOR UNCONVENTIONAL CANCER TREATMENTS

Cancer patients may receive unconventional treatments in many different settings. Some patients make office visits to a local practitioner, others travel within the United States to a hospital or practitioner's office for outpatient treatments, and certain individuals choose inpatient or outpatient treatment in Mexico, the Caribbean, Europe, or Asia. In this chapter, OTA has chosen one word, "clinic," to refer to any setting in which an unconventional cancer treatment is provided. With the exception of one mail-order treatment clinic, the word clinic encompasses physicians' offices; institutions that provide services, such as surgical, medical, laboratory, and diagnostic services that are typically found in U.S. accredited hospitals, and that treat both inpatients and outpatients; and institutions whose services are not as inclusive as those found in U.S. accredited hospitals, but that do offer certain services to inpatients, outpatients, or both.

Variations among charges occur both between clinics that offer different types of treatment (such as nutritional or pharmacologic) and among clinics offering similar treatments. As with any medical service, charges may vary among patients who receive similar treatments due, in part, to differences in the individual's health status. The stage of the disease, the patient's response to treatment, and the presence of other serious illnesses that must be treated concurrently could affect the intensity and duration of use of medical services. Factors most often causing variation among clinic charges for unconventional cancer treatments include: the breadth of services available (especially laboratory and diagnostic testing facilities) at the clinic; the type of treatment (e.g., nutritional, pharmacologic, herbal) that is offered; the services that are covered under the charges for an "office visit" or "cancer treatment program' the setting (inpatient or outpatient) in which treatment is delivered; and the length of initial and followup treatment.

Other factors, not unique to unconventional cancer treatment clinics, unpredictably affect treatment expenses. For example, if the treatment includes a change in dietary habits[3], the patient's food bill may increase. Those patients who are treated at outpatient clinics away from their home city must pay hotel, food, and transportation expenses for the duration of their treatment, which can range from a few days to several months or more. If family members accompany the patient during treatment (which is encouraged or required by some clinics), their travel and subsistence could be considered part of total treatment expenses for the individual as well.

OTA reviewed patient information brochures and Third Opinion, a directory of alternative cancer treatment centers (289). An OTA contractor subsequently contacted each clinic and verified and in some cases updated the information compiled on charges, duration of treatment, followup treatment, and at-home followup treatment programs. The information presented in this section was current as of May 1988, and reflects charges at 44 clinics[4] in the United States, Canada, and Mexico; this may not be representative of all available treatments. Clinics were only classified as "treatment clinics" if the patient brochures advertised treatment for cancer, or if the clinic was listed under the heading 'Treatment Centers' in Third Opinion. Since the time this information was gathered, charges may have changed, clinics may have closed, and some new clinics may have opened. This section should be only regarded as a descriptive review of charges at some unconventional cancer treatment clinics.

[3]For unconventional cancer treatments, this would most likely consist of eating only organically raised meats and produce, adding *vitamin* and mineral dietary supplements, or both.

[4]Sixty clinics were initially identified through patient brochures and *Third Opinion,* however, 16 clinics could not be included in the final study because they were closed, could not be contacted, chose not to answe OTA's inquiries, or provided incomplete information.

Presentation of Charges

Unconventional cancer treatment clinics usually present their charges in one of three ways. Some clinics charge for a "cancer treatment program," typically lasting about 3 weeks, although some may extend up to 6 or 8 weeks. The single charge generally covers physician visits, medications, room and board (if given in an inpatient setting), and certain services (such as colonic therapy) that are intrinsic to the treatment. Charges for all laboratory and diagnostic tests, or for any "medications" from the clinic that the patient continues to use at home following discharge, may also be considered part of this charge.

Other clinics charge patients by a given time period-per day, week, month, or year of treatment—and may or may not include charges for laboratory and diagnostic tests, at-home medications, etc.

The remaining clinics charge patients per treatment "component.' Separate charges are listed for physician office visits, laboratory and diagnostic testing, and for each injection or infusion. Some clinics indicate the number of components that a patient typically receives during the course of treatment. Total expenses for these treatments may be more difficult to estimate than for clinics that charge by a given time period or for a set treatment program.

Description of Charges

In the following sections, the range of charges and treatments is given by category of treatment, using the same categories as in previous chapters wherever possible. No compilation of actual patient expenses for treatment at the various clinics exists to which the charges, as reported by the clinics and presented here, can be compared. Charges for some specific patients are known, and in some cases they fall within the range given by clinic information, and in other cases they are considerably greater than expected. The general lack of validation of these figures should, therefore, be kept in mind.

Biologic

while other clinics offering biologic treatments might exist, OTA found information on only two, one located in the Bahamas and one in the United States; both offer outpatient treatment only. Treatment at one clinic lasts approximately 10 days and the charges range from $4,500 to $5,000. The other clinic charges $10,000 for 6 to 8 weeks of treatment. Treatment at both clinics includes at-home followup treatment, although neither provides information on the frequency or duration of such followup. Charges for the followup program at the first clinic are $400 to $600 per month, and $200 per month at the second clinic. The followup treatment charges at the first clinic may be reduced if the patient responds positively to treatment. The first clinic also recommends that the patient return to the clinic for a 2-day followup visit after 1 month, 3 months, 6 months, and 1 year. Charges for these visits vary. The second clinic recommends return visits of about 1 week every 3 or 6 months.

Herbal

Herbal treatments are available from a Mexican clinic and by air mail from Canada. The Mexican clinic offers outpatient treatment for 1 to 3 days and charges $3,500 for lifetime treatment. Laboratory charges, which average $450 to $850, are extra. Patients may return for followup visits (schedule unspecified). The treatment includes nutritional supplements and dietary changes which patients continue at home.

The second herbal treatment is a tonic that maybe ordered from Canada. Patients are charged $10 (Canadian dollars) for a 16-ounce bottle, and during the first 2 years, patients may use 23 to 46 bottles. After 2 years, the daily dose may decrease, although treatment may continue for 6 or 7 years. No clinic offers this treatment. Orders are relayed through the Canadian department of Health and Welfare to the private Canadian company that manufactures the tonic, and the tonic is then sent directly to patients.

Pharmacologic

One U.S. clinic offering a pharmacologic treatment charges by component. The cost of a visit ranges from $60 to $125, depending on whether it is a first visit, office visit, or hospital visit. In addition, the charge for the basic cancer program is $45 per "treatment, ' with an average of four to seven outpatient treatments per day for 2 to 4 weeks (this totals $2,520 to $8,820). A second program, for "high dose' treatment, is administered every other day and costs $685 per treatment. It is unclear if patients could receive both treatments concurrently. Charges for followup visits are $60 for an office visit, plus treatment charges, which vary by patient.

A downpayment of $3,000 to $5,000 is required before starting treatment at this clinic.

Pharmacologic and Biologic

A combination of pharmacologic and biologic treatments is offered at two clinics, one in Mexico and one in the United States. The U.S. clinic has outpatient treatment only, and the Mexican clinic treats both outpatients and inpatients. Charges range from $5,100 to $9,000 for 3 weeks of treatment at the Mexican clinic. There are two types of followup treatment provided by the Mexican clinic: 1) referral to specific physicians in the United States, and 2) treatment materials for which patients are charged $300 to $1,500 per month. The U.S. clinic charges $375 for 6 months of treatment and approximately $250 per month for supplements. The initial outpatient visit lasts 1 to 3 days. The only reference to follow-up says that it is prescribed "as needed" and that it costs approximately $100.

Pharmacologic and Nutritional

Eleven clinics, two in Mexico and nine in the United States, use a combined pharmacologic and nutritional approach. Both Mexican clinics provide inpatient treatment, and the U.S. clinics only offer outpatient treatments. Four U.S. clinics charge $1,500 to $4,500 for 3 to 4 weeks of treatment and a fifth clinic, located in Mexico, charges $7,500 for 3 weeks of treatment. The second Mexican clinic charges $1,500 per week and recommends 2 to 8 weeks of treatment; lab fees, which are extra, average $400 to $500 per week. One U.S. clinic charges by the month: the first month costs $1,500, and each month thereafter is $300, although this clinic did not provide an estimate of the total initial treatment period. Another U.S. clinic charges $4,000 to $5,000 for 1 year of treatment. The remaining three clinics in this category charge by components. Office visits range from $50 to $280; initial evaluations range from $100 to $280.

Some information on followup visits was available for eight U.S. clinics. Charges at five clinics range from $20 to $200 for a followup visit. Only the clinic with charges at the upper end of this range indicated the average length of these visits, approximately 1 to 2 days. Three of these five clinics also indicated the frequency of follow-up visits, which are recommended at periods ranging from 2 weeks to 4 months following initial treatment. A sixth clinic advises weekly, monthly, or bimonthly followup visits, and includes the charges for these visits in its initial treatment charges. Two clinics simply indicate that charges for and the frequency of followup visits vary.

Seven clinics, including both Mexican clinics, provided information on at-home treatment programs. No clinic estimated the duration of at-home followup treatment, although two clinics indicated that their treatment in part constituted a lifestyle change. Six clinics listed charges for followup supplements or medications, ranging from $50 to $300 per month.

Nutritional and Biologic

One U.S. clinic offers a nutritional and biologic treatment, given on an outpatient basis. This clinic does not estimate the length of the initial treatment period. The initial office visit costs $200, with additional charges of $80 to $350 for lab tests. The clinic recommends that patients return for a followup visit, which costs $55, after 2 to 3 months. A recommended annual "re-evaluation" costs $200. No at-home followup program is described.

Nutritional and Psychological

One U.S. clinic offers an outpatient treatment that combines nutritional and psychological components. Patients may receive 1 to 7 days of initial treatment, which costs $325. No follow-up visits or at-home followup treatment programs are deseribed for this clinic.

Miscellaneous (Hyperthermia)[5]

One U.S. clinic provides whole-body hyperthermia to outpatients. The recommended initial program consists of 25 hyperthermia treatments over 5 weeks. Patients are charged $400 per treatment, or $10,000 for the full course. The clinic suggests that patients return for followup visits after 2 weeks, then after an additional month, then every 2 months. There is no charge for the followup visits. There is no mention of at-home followup treatment.

[5]In mainstream medicine, local or regional hyperthermia is accepted as adjunctive treatment for some cancers, along with radiotherapy, but is considered investigational in other settings (694). Whole-body hyperthermia is not an accepted modality in mainstream medicine.

Combination Treatments

Approximately half the clinics (23) for which data were available offer combinations of at least three types of treatment for cancer patients. Three such clinics are in Mexico, 4 operate in Canada, and the remaining 16 are in the United States. These clinics fall into one of three categories according to how they charge for treatments: by entire initial treatment program, by periods of time, or by initial treatment components. Few of these clinics give information on the cost of followup regimens.

Ten clinics have a set charge for the full initial treatment program. Six of these clinics (one Canadian and five U. S.) operate on an outpatient basis only, with charges and treatment periods ranging from $500 to $900 for a 1+ day course, $4,000 for 2 weeks of treatment, $4,000 to $10,000 for 3 to 6 weeks, to $3,000 to $8,000 for 1 year of treatment. Three clinics (two in Mexico and one in the United States) provide inpatient treatment. The Mexican clinics charge $6,000 to $6,500 for 3 weeks of treatment; one of these also charges $1,800 for each additional week. The third clinic offers a month-long inpatient treatment for $8,000 to $10,000.

Six clinics charge by periods of time. One accepts biweekly donations of $100 to $2,000 for outpatient treatments that last from 2 to 52 weeks. Another provides 8 to 12 weeks of treatments, at a cost of $3,600 per week, on both an inpatient and outpatient basis. A third treats patients for 3 to 4 weeks at $3,100 per week. Three weeks of outpatient treatment at a fourth clinic is estimated to cost $1,500 per week. In addition, one clinic charges $1,200 to $1,400 per day for 3 to 5 days of outpatient treatment, while another charges $400 to $700 per month for 3 to 6 months of outpatient treatment.

Seven clinics (two in Canada and five in the United States) charge by treatment component. Six of these provide treatment only on an outpatient basis; the seventh treats on an inpatient basis. Charges for office visits range from $35 to $500. The clinic with the lowest charge per office visit charges an additional $50 to $400 for treatment. The wide variation in charges for the office visit results, in part, from the different services that are considered to be part of an "office visit." For example, a few clinics include costs for diagnostic tests with the office visit charge, while others list separate charges for laboratory or diagnostic tests, which range from $5 to $600. One clinic estimates total charges for the frost office visit at $300 to $1,800.

Twelve clinics provide some information on the amount and cost of followup visits. Outpatient followup visits for four clinics last from 1 to 5 days. At another, followup consists of 8 to 10 days of inpatient treatment. Charges for these clinics range widely, from $50 for a l-day visit, to between $500 and $1,000 for 2 to 3 days of treatment, $1,200 to $l,400 per day for a 5-day visit, to $1,500 for an 8-to 10- day inpatient visit. The remaining seven clinics list charges for followup visits but do not specify the duration of the visit. Five of these clinics charge from $20 to $300 for a followup visit. One clinic does not charge for the visit itself, but does charge $140 to $225 for laboratory work. Another lists $60 as the "base' price for the visit.

The charges for at-home followup programs are available for eight clinics. Supplements range from $50 to $300 per month at five of these. Two clinics appear to charge a flat fee of $100 to $150 for the followup program. Two of the seven clinics include medication in the followup charges, while a third clinic charges an additional unspecified amount for medications.

Estimating Total Initial Treatment Expenses

Based on the above information, OTA estimated the range of expenses within each treatment type for an initial treatment program.[6] To determine the range of expenses, OTA either used the single charge for "cancer treatment programs" or estimated the expenses based on the clinics' listed charges and duration of treatment. Charges for laboratory or diagnostic services are included in the total treatment expenses only if the clinic indicated a range of such charges.

6& mentioned earlier, the "initial treatment program" refers to the treatment obtained during the period of time, as determined by the clinic, that the patient receives his or her first course of treatment. This period of time was defined as the length of time indicated by the clinic in their brochures, or under the heading "Length of Treatment/Stay" in *Third Opinion,* and checked with the clinics by the OTA contractor. These charges are presented exactly as given by the clinic, and may or may not include expenses for diagnostic services, laboratory services, or room and board. Treatment continued as part of an at-home followup program is not considered part of the initial treatment program, and therefore expenses for followup programs or visits are not included in the estimated total initial treatment charges.

Table 9-1 shows the range of charges among clinics that offer only one or an indivisible package of treatments. Charges for the two herbal treatments were lower than charges for treatments at the other three clinics. The Bio-Medical Center, offering "Hoxsey" treatment, lists charges for laboratory work, examinations, and x-rays as an additional $450 to $850. It was unclear if this was the estimated additional charge for each visit, or for lifetime treatment.

The costs of initial treatment with IAT and Antineoplastons appear to be about the same, approximately $10,000. However, it is unclear if patients at Burzynski's clinic can receive the "high-dose treatment" and the standard Antineoplaston treatment in combination; if this is possible, initial treatment charges could then approach $20,000. The cost might also vary depending on the number of office or hospital visits made by a patient during the initial treatment period; a large number of visits could substantially increase the total initial treatment costs.

Table 9-2 summarizes the range of initial total treatment expenses at 25 clinics offering combinations of treatments.[7] Expenses range widely for initial treatment programs, from $100 to $52,000 for combination treatments, and from $1,500 to $16,000 in the pharmacologic and nutritional category. Clinics with lower charges often only treat outpatients; a patient's actual expenses for treatment could be higher after paying for room and board.[8]

Quality of Charge Information

It is impossible to estimate total initial treatment expenses based on the information given in some clinic brochures. Clinics that itemize charges are the most difficult; not only do the length and intensity of treatment vary, but clinics often do not report the typical range of treatment components that patients receive. Itemized charges may make a clinic's treatment appear less expensive than treatment at a clinic that charges a single fee for the initial treatment program. For example, Stanislaw Burzynski's clinic charges $45 per treatment of Antineoplastons. However, based on the dosage information in the patient brochure, total charges for a standard regimen of Antineoplaston injections alone (not including charges for office visits and laboratory tests and diagnostic tests) could be $2,520 to $8,820 for the initial treatment period. In addition, listed itemized expenses typically include only office visits and laboratory tests; it is not always clear if there is an additional charge for the treatment itself.

Total treatment expenses for an individual patient have occasionally been reported publicly, generally during litigation over reimbursement or in articles describing a particular unconventional treatment or practitioner. One patient incurred medical bills of approximately $200,000 for 21 months of treatment that began in early 1986 at the Burzynski clinic (192). This particular patient's medical bills (nearly $9,500 per month) seem substantially higher than what would be expected from the clinic's patient information materials.

Total treatment expenses may be easier to project for clinics with a single charge or charges by periods of time. For instance, the Bio-Medical Clinic in Tijuana charges patients a lifetime fee, excluding the charges for laboratory and certain diagnostic tests. These additional expenses are estimated in the patient information materials, so patients could include them when estimating total treatment expenses. One report of total expenses for a patient who received treatment at the Gerson clinic, which charges patients on a weekly basis, suggests that total treatment expenses may be accurately predicted from this type of charge information. This particular patient received 6 months of treatment in 1984, for which he was charged $10,000 (728). As of May 1988, the predicted charges for this clinic (including separate laboratory charges) were approximately $2,000 per week for a 2- to 8-week initial treatment period. Followup treatment expenses were estimated at $50 per month. For 6 months of treatment in 1988, expenses would range from $4,250 to $16,250. This patient's expenses of $10,000 fall within the expected range.

[7] In table 9-2, expenses were not estimated for the 13 clinics that listed charges by treatment component. Nutritional and biologic treatments are not shown in this chart because the only clinic included in this category charges patients by treatment component. An additional clinic, described in the pharmacologic and nutritional section, was not included because it did not provide an estimate of the duration of treatment and it was thus not possible to extrapolate total initial treatment charges.

[8] Duration of treatment at outpatient clinics ranged from 1 day to 3 months.

Table 9-l—Total Initial Treatment Charges for Proprietary Treatments

Clinic	Treatment	Duration of initial treatment	Approximate total initial treatment charges	Clinics that charge by component: Component	Charges per component	Number of components used per week	Approximate total initial treatment charges
Immunology Researching Center	Immuno-Augmentative Therapy	6-8 weeks	$10,000				
Livingston-Wheeler Clinic	Autogenous vaccines, diet, vitamin and mineral supplements	10 days	$4,500-5,000 (includes 30 days of medicine and approximately 6 months of vaccine)				
Bio-Medical Center	Hoxsey herbal tonics and salves	Lifetime	$3,500				
Essiac	Herbal tonic[a]	52-104 weeks		16 oz. bottle	$10	.9 (first 10 days) .45 (remainder)	$230-460
Burzynski		2-4 weeks		Treatment with Antineoplastons	$ 4 5	28-49	$2,520-$8,820
				High dose treatment	$685	3-4	$4,795-9,590
				Office visit	$ 6 0	Unspecified	not given
				Hospital visit	$100	Unspecified	not given
				initial consultation	$125	Only one charge for this component	$125

[a]Patients are also instructed to take vitamin and mineral supplements; charges for these supplements have not been included, nor have charges for shipping Essiac.

SOURCE: Office of Technology Assessment, 1990.

Table 9-2—Costs of Selected Unconventional Cancer Treatments

Treatment type	For clinics reporting total initial treatment charges: Number of clinics	Range of charges	Range of length of treatment	For clinics reporting charges by time period: Number of clinics	Range of charges
Pharmacologic and biologic				1	$1,700-$3,000 per week × 5 weeks of treatment = $5,100-$9,000
P maco og and triti al		$ 500-$ 500	14-21 days at 4 clinics 3+-26 weeks at 1 clinic 1 year at 1 clinic	1	,900-$2,000 per week ×2-8 weeks of treatment =$3,800-$16,000
Nutritional and psychological	1	$325	1-7 days		
Miscellaneous-hyperthermia				1	$400 per day x at least 25 days of treatment = $10,000
Combinations—three or more treatments	o	$425-$10,000	1+ days at 2 clinics 2-6 weeks at 7 clinics 1 year at 1 clinic	11	$3,600 per week x 8-12 weeks of treatment = $28,800-$43,200 $3,100 per week x 3-4 weeks of treatment = $9,300-$12,400 $400-$700 per month x 3-6 months of treatment = $12,000-$4,200 $1,200-$1,400 per day ×3-5 days of tr me = $3,600-$7,000 $100-$2,000 biweekly (donations?) x 2-52 weeks = $100-$52,000

SOURCE: Office of Technology Assessment, 1990.

The total *treatment charges estimated by OTA (see tables 9-1 and 9-2) are higher than those reported by Cassileth and her colleagues in 1984 (177). Based on interviews with 202 patients, they determined that charges for the frost year of unconventional cancer treatment were under $1,000 for most patients and less than $500 for 50 percent of patients. However, these data sets cannot be compared directly because OTA's data differ from Cassileth's in several important ways. First, OTA only looked at charges for organizations that identified themselves as treatment clinics, and these charges may be greater than those for all available unconventional cancer treatment services. Second, charges in Cassileth's study were reported by patients, and no documentation for these self-reported data was sought. Third, Cassileth includes expenses for two types of treatment, spiritual and imagery, which were not included in OTA's analysis[9]; 87 percent of patients who used imagery and 94 percent of those using spiritual treatments spent less than $500 in the first year of treatment.*

Proponents of unconventional cancer treatments often claim that charges are generally lower than those for conventional therapies. The range of initial total treatment charges as estimated by OTA (tables 9-1 and 9-2) suggest that charges may fall both above and below initial treatment charges for conventional cancer treatments. One estimate of patient expenses for conventional cancer treatments comes from a study that used data from the Medicare Continuous History Sample File (MCHSF) (66).[10] Initial treatment charges, defined as those occurring in the first 3 months after diagnosis, ranged from $6,954 for melanoma to $14,443 for stomach cancer, with the average for all sites being $10,039. Continuing monthly expenses[11] ranged from $424 (uterine corpus) to $766 (bladder), with the average for all sites being $578. For several reasons, these numbers should not be viewed as definitive estimates of the cost of conventional cancer treatments. First, that study may underestimate expenses for conventional cancer treatment, in part because Medicare coverage does not extend to all the medical services required by a cancer patient, such as prescription drugs. In addition, estimates of costs are in 1984 dollars, so an adjustment for medical cost inflation would be needed to bring the estimate up to current dollars. It was not OTA's purpose in this report to delve into the issue of conventional treatment costs; the numbers are simply provided for a rough comparison.

Summary

Charges for unconventional cancer treatments vary from a few hundred to tens of thousands of dollars and it maybe difficult for a patient to predict actual treatment expenses. It is impossible to assess the accuracy of OTA's estimates of total initial treatment charges for unconventional cancer treatments because information provided by the clinics is not always precise, and only one other researcher has attempted to estimate charges for unconventional cancer treatments. The expenses for a single patient may be more than any of these data suggest as some patients use more than one unconventional cancer treatment (177,265). While charges at many unconventional cancer treatment clinics appear to fall below the average charges for conventional cancer treatment, patients often must pay out-of-pocket for all unconventional services (see next section), and thus unconventional treatments may incur greater economic losses for an individual.

THIRD-PARTY REIMBURSEMENT FOR UNCONVENTIONAL CANCER TREATMENTS

An ongoing debate surrounds the question of whether third-party payers should reimburse for medical expenses related to unconventional cancer treatments. Many patients are frustrated when their claims are denied. Medical services that lack data showing efficacy and safety, or are not generally accepted by the medical mainstream, may not be covered by third-party payers, even if a patient believes he or she benefited from such a service.

[9]Although there are several clinics that offer psychological treatments, including imagery, these were described as "support groups" in their brochures or in *Third Opinion,* and thus were not included in our analysis of charges.

[10]Charges for inpatient hospital stays, skilled nursing facilities, home health agencies, outpatient services, physician services, and psychiatric services were all included in the dataset. Expenses were defined as the charges to Medicare, rather than the amount reimbursed by Medicare to the physician, patient, or provider.

[11]Continuing expenses were defined as all monthly charges beginning the fourth month after diagnosis and ending with the seventh month before death, if death occurred. These expenses are probably an overestimate, since, unlike the data for initial treatment, this dataset includes charges for both cancer and non-cancer-related medical services.

Patients who receive unconventional cancer treatments may believe that their expenses will be covered, because patient information materials from many clinics claim that many or most U.S. insurance companies will reimburse patients for the medical expenses of their treatment. However, most U.S. third-party payers do not knowingly reimburse claims for unconventional cancer treatments. In some cases, the insurer may pay claims unwittingly, lose a court case and be forced to pay for treatment, or settle out of court to avoid a trial.

As with coverage for any type of treatment, the language of the insurance contract is the key determinant of whether an unconventional cancer treatment will be covered. The contract language sets the criteria that a medical service must meet before the third-party payer will reimburse any patient expenses. If a particular medical service is disallowed by name in the policy, the third-party payer is not legally obligated to reimburse the expenses of that service to the consumer. However, third-party payers cannot reasonably be expected to individually specify all of the medical services that are or are not covered by the policy; therefore they rely upon phrases such as "medically necessary' and 'reasonable and necessary, to describe what is covered. Such general language lends itself to a variety of interpretations; disputes over the interpretation of these phrases form the basis of many lawsuits against third-party payers.

The criteria *used to determine coverage and reimbursement and the sources consulted for information are other points of dispute in court cases involving unconventional cancer treatments. Although each third-party payer determines its own criteria for coverage, many consult similar sources for information. The published medical literature and the opinions of medical specialty societies, individual physician consultants, or national organizations such as the American Cancer Society (ACS), the National Cancer Institute (NCI), the American Medical Association (AMA), and the U.S. Pharmacopeial Dispensing Information (USP DI) are the main sources of information used by third-party payers. These sources provide little support for unconventional cancer treatments.*

This section describes typical contract provisions and claims evaluation practices for the major U.S. third-party payers: Medicare, Blue Cross/Blue Shield (BC/BS), and commercial carriers.

Contract Provisions Relating to Unconventional Cancer Treatment Reimbursement

Medicare

Title XVIII of the Social Security Act established Medicare, a federally-funded program that covers hospital, physician, and other medical expenses for persons 65 years of age and older, certain disabled persons, and persons with certain chronic diseases (not including cancer). The Health Care Financing Administration (HCFA), the Federal agency responsible for administering the Medicare program, writes guidelines for coverage and reimbursement. Other Federal programs, including Medicaid and the Civilian Health and Medical Program of the Uniformed Services (CHAMPUS), are influenced by Medicare coverage and reimbursement decisions (791).

The law that created Medicare prohibits payment for services or items that "are not reasonable and necessary for the diagnosis or treatment of illness or injury" (Social Security Act, Section 1862(a)1, 42 USCA 1395y (l)(A)). As interpreted by HCFA, a treatment is considered medically reasonable and necessary if it has been generally accepted by the professional medical community as effective and safe for the condition being treated.[12] Colonic irrigation, cellular therapy, and laetrile are among the medical procedures or items HCFA does not consider to be reasonable and necessary; therefore, they are not currently covered by Medicare (221).

With a few exceptions, which are discussed below, drugs and biologics must have final marketing approval from the Food and Drug Administration to be considered safe and effective and, therefore, reasonable and necessary .13 Under the laws of the Medicare program, a substance is not

[12]Part A Intermediary Letter No. 77-4, January 1977, as cited in R.D. Schwartz, and R.L. Burke, ' 'Legal Constraints on the Availability of Unorthodox Cancer Treatments: Consumer Protection View" (791).

[13]"Approved indications" refers to those medical uses for which the FDA has 'et ermined the drug is safe and effective. The drug manufacturer must present clinical data for each indication sought, that demonstrates safety and efficacy; if the manufacturer presents data for more than one medical use of the drug, more than one indication may be approved to appear on the label.

considered a' 'drug' or 'biologic' unless it is listed or approved for listing in certain drug compendia. These compendia include the U.S. Pharmacopoeia, National Formulary, U.S. Homeopathic Pharmacopoeia, AMA Drug Evaluations, or Accepted Dental Therapeutics (Sec. Sec. Act Section 1861(t), USCA 42 Section 1395(t), CCH 1223,3115, 1988). Drugs and biologics used for indications other than those approved by FDA may be covered as long as FDA has not ruled that such use is unapproved specifically; and as long as other reimbursement criteria are met (221). Coverage is not available for drugs, such as laetrile, that are marketed without FDA approval (45 Fed. Reg. 110, June 5, 1980).

Charges associated with the administration of certain experimental cancer drugs, "group C" drugs, may be covered under Medicare although the drugs have not received final FDA marketing approval. Since the mid-1970s, group C drugs have been distributed by the Cancer Therapy Evaluation Program of NCI's Division of Cancer Treatment in cooperation with FDA to make promising drugs available outside of a clinical trial for some terminally ill patients. While the drugs themselves are given free of charge, there are costs, such as hospital or physician charges, associated with their administration (10,221,589). For a drug to be placed in group C, NCI must determine that the drug has shown, in at least two studies, "evidence of reproducible relative efficacy in a tumor type, which [will] alter the pattern of care of the disease' (964), or evidence indicating the drug has the potential to affect the standard of care (10). Distribution of group C drugs is limited to physicians registered as investigators with NCI, who are also required to report any adverse reactions (589).

Medicare clearly excludes coverage of treatments intended only to improve the general health of the patient, and not to treat a specific illness. For example, it is unlikely that charges for detoxification treatments, such as sweat baths or supervised fasting, given to remove toxins from a cancer patient, would be covered. However, charges for vitamin B 12 therapy for the treatment of pernicious anemia will typically be covered, since this is an accepted medical practice (877).

Medical services obtained outside the United States are not covered by Medicare, except in cases in which the foreign hospital was closer to or more accessible than the nearest adequately equipped U.S. hospital. In addition, the foreign hospital must meet HCFA's definition of 'hospital," and be accredited by the Joint Commission on Accreditation of Health Care Organizations (JCAHO) or meet local accreditation requirements equivalent to those of JCAHO (221) (42 CFR 405.153 and 42 CFR 405.313, October 1987 edition; 42 USCA 1395y(4)).

Coverage of services by physicians[14] who are not doctors of medicine (M.D.s) or osteopathy (D. O. S), or by other health care professionals,[15] is limited under Medicare. For example, coverage of chiropractic service is "specifically limited to treatment by means of manual manipulation. . . . The manual manipulation must be directed to the spine for the purpose of correcting subluxation demonstrated by x-ray to exist" (221).[16] Medical services rendered by all other types of health professional, with only a few exceptions, are covered by Medicine only if they are incident to a physician's professional services and only if there is direct personal supervision by the physician (221). Medicare does not reimburse for medical services given by several health professionals who are often associated with unconventional cancer treatments, including acupuncturists, homeopaths, naturopaths, and masseurs, even if such treatment was ordered by a physician. Nutrition services are reimbursed only to hospitalized patients (791).

Blue Cross/Blue Shield

There are 78 regional Blue Cross and Blue Shield (BC/BS) plans selling insurance within designated geographic areas and writing their own insurance contracts (56). Contract language affecting unconventional cancer treatments, therefore, may vary widely although some generalizations hold. Typically, M.D.s, D.O.s, podiatrists, chiropractors, dentists, and optometrists practicing within the scope of

[14] According to the Social Security Act, "physician" is defined as a doctor of medicine, doctor of osteopathy, doctor of dental surgery, doctor of dental medicine, doctor of podiatric medicine, doctor of optometry, or a chiropractor, who is legally authorized to practice his or her healing profession in the State in which he or she practices and who practices within the scope of that license (Compilation of the Social Security Laws 1981 section 1861(r)).

[15] Recent amendments t. Medicare now permit limited coverage for the services of selected health care professionals, including certified nurse anesthetists, certified nurse-midwives, and clinical psychologists (42 USCA supplement 1395(x) (bb)(ff)(gg)).

[16] Additionally, the chiropractor must be licensed or, in States without licensing, otherwise legally permitted to practice by the State (USCA supplement 42 1395x (r) 1988).

their licenses are accepted BC/BS providers (641). However, differences exist among plans due to ***variations in State laws and regional medical needs (641,815). Claims for medical services obtained in foreign countries are usually reviewed on an individual*** basis. Coverage may be available for such claims, as long as the plan determines the services were medically necessary (56,641).

BC/BS plans may also seek coverage recommendations from their trade association, the Blue Cross and Blue Shield Association (BCBSA). Two programs within BCBSA, the Medical Necessity Program (MNP) and the Technology Evaluation and Coverage (TEC) Program, evaluate the effectiveness, efficacy, and medical necessity of new or emerging (in the case of TEC) and well-established (in the case of MNP) procedures and devices. Except in a few cases, these programs are purely advisory, and their role is to issue coverage recommendations to member plans (56,447,851). A recent survey of plans showed that 36 percent "almost always" use TEC recommendations as issued, while another 62 percent occasionally alter TEC recommendations to better conform to local conditions. In this same survey, 58 percent of the plans indicated that "TEC Program publications [are] the single most important resource for new technologies" (343).

TEC will not recommend that a technology be covered unless it meets the following five criteria (87,88):

1. It must have obtained final approval from the appropriate government regulatory bodies (FDA approval to market for the specific indications and methods of use for which BCBSA is evaluating the technology).
2. The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes (including well designed trials, the results of which are published in scientific peer-reviewed journals).
3. The technology must improve the net health outcome.
4. The technology must be as beneficial as any established alternatives.
5. The improvement must be attainable outside the investigational settings.

Few unconventional cancer treatments meet these criteria, largely because of a lack of clinical evidence and lack of publications in scientific peer-reviewed journals. TEC has evaluated only one unconven-***tional cancer treatment so far, ozone treatment, which it labeled investigational (86). If FDA has not given a drug or biologic final marketing approval for the indication for which it was used, BCBSA usually recommends against reimbursement. Few drugs or biologics used in unconventional cancer treatments would meet this criterion. In the past, BCBSA has chosen not to evaluate or issue coverage recommendations for drugs and biologics that do not have FDA final marketing approval or are not used for the indication(s) approved by FDA. BCBSA is, however, in the process of reevaluating their role in assessing drug coverage (56,343).***

For examples of the process by which coverage policies may be determined, OTA contacted the medical directors of two large BC/BS plans. At BC/BS of New Jersey (BCBSNJ), members of the medical advisory staff determine if a medical service may be covered. They typically consult: 1) the published scientific literature, recognized experts in the field, professional organizations, reports or position papers from various technology assessment programs, including the National Center for Health Services Research and the Clinical Efficacy Assessment Program of the American College of Physicians; and 2) the recommendations of the Medical Advisory Panel of BCBSA. Additionally, in 1981 BCBSNJ createda"Multispecialty Advisory Committee," (MAC) which comprises local physicians who represent approximately 28 different disciplines. On average, this committee meets four times annually and acts in an advisory capacity. MAC may review the coverage recommendations of BCBSNJ as well as suggest new coverage policies. BCBSNJ uses criteria quite similar to those of the TEC program (described above) when determining the coverage status of a medical service (241).

BS of California uses a slightly different format, convening a' 'Medical Policy Committee" that sets coverage policies. The Medical Policy Committee, which is composed of both physician and nonphysician members of BS of California's Board of Directors, meets four to five times a year in an open session to review specific technologies. BS staff conduct literature searches and write an analysis of the state of each technology, and get written opinions from specialty societies and national organizations before meetings. In addition, BS invites oral testimony from outside experts, including health economists and members of specialty societies, to augment the written analyses. BS of Califor-

nia *follows the five TEC criteria (listed above) to determine if a technology is investigational or established (780).*

Commercial Plans

Most commercial health insurance policies cover treatments considered part of "standard medical practice," but do not offer coverage for treatments considered to be "experimental' or not 'medically necessary. ''17 Some insurers may specify the criteria necessary for a treatment to fit these terms. For example, some policies reviewed by OTA indicated that to qualify for coverage, treatments would need approval from FDA (220,659), or "the cognizant college or academy of medicine as identified by the American Medical Association" (659). Other policies do not specify criteria, although many indicate that claims will be adjudicated based on generally accepted standards of U.S. medical practice.

Many of the policies that OTA reviewed exclude the following from coverage: nonprescription drugs, nutritional supplements or vitamins (even if they are prescribed), chiropractic services (except as specified in the contract), services given by a health professional who does not meet the insurer's definition of doctor, and services given in an institution that does not meet the insurer's definition of hospital. A few policies specifically exclude colonic therapy (227); serums, preparations, and remedies (including homeopathic) that by law do not require a prescription (226,227); and chelation therapy, except in the treatment of lead, mercury, gold, or arsenic poisoning (28 1,655). Additionally, some policies contain clauses restricting coverage to those cancer treatments that are considered by most knowledgeable physicians to have a success rate of at least 50 percent survival 5 years following treatment (628).

A few policies explicitly state that medical services obtained outside the United States are not covered, except in an emergency. These policies generally do not cover even emergency medical treatments received after a designated period of time (usually 30 to 90 days) from the date of leaving the United States (225,226,227).

Some policies stipulate which licensed or certified practitioners' services are covered. In the policies reviewed by OTA, covered practitioners included M.D.s, D.O.s, podiatrists, chiropractors, dentists, optometrists, clinical psychologists, clinical social workers, psychiatric social workers, midwives, and, occasionally, registered nurse anesthetists. For selected medical treatments, a few policies extend coverage to naturopaths, homeopaths, biofeedback technicians, nutritionists/dietitians, and massage therapists (227). Other policies use more general language when defining which practitioners' services are covered; for example, "A 'doctor' is a licensed practitioner of the healing arts acting within the scope of the license" (657).

Coverage for investigational or experimental treatments may be easier to obtain under health insurance policies with case management' clauses; such policies are available to consumers at additional cost (357). Under 'case management' provisions, treatments are evaluated on an individual basis, taking into consideration the health of the patient and the possible alternatives to the selected treatment. Coverage may be possible for a treatment the insurer considers investigational, if it is the best alternative available to the particular patient. However, the insurer first would have to agree that an unconventional cancer treatment complied with its definition of "investigational" or "experimental" before reimbursement could be received. An exception may also be made for a patient who is a member of a group policy if the group agrees to pay higher premiums for the coverage of one member's unconventional cancer treatment (320). The frequency with which this mechanism is used is not known.

Claims Evaluation

At the time a claim for reimbursement is submitted, the insurer determines whether the medical services qualify for coverage under the terms of the insurance contract. Recently, third-party payers have begun interpreting contract language more narrowly as well as relying more heavily on the safety and efficacy evaluations of Federal agencies, mainly FDA (599). They are also attempting to reduce the number of fraudulent insurance claims

[17]To accurately describe the thousands of health insurance policies available in the United States would be impossible; significant variations exist not only between insurers but also among policies of a single company. This section should only be regarded as a descriptive review of several current health insurance policies.

they pay, including those for unconventional cancer treatments.

Claims for unconventional cancer treatments are usually filed either directly by patients, or on their behalf by an insurance billing consultant, who may be an agent of an insurance company, or may be affiliated with a clinic. The consultant's job is to understand the details of the contract and to obtain as much reimbursement for the patient as is legally possible (228). Patients who use unconventional cancer treatments locate billing consultants through other patients, treatment clinics, and attorneys who practice medical claims collection (951). Insurance billing consultants may be able to obtain reimbursement for an unconventional cancer treatment by providing information in the claim form that will explain why the medical services should be covered under the provisions of the insurance contract. Even if coverage is denied for the treatment itself, reimbursement for ancillary services, such as diagnostic tests, hospital room and board, or physician visits, may be provided (951).

The Process of Evaluation

Evaluating a claim for an unconventional cancer treatment may be difficult for an insurer since the treatment may be unknown, or it may involve a standard treatment used in an unconventional manner (such as low-dose chemotherapy). Claims for unconventional cancer treatments are often passed up the echelons of claims reviewers until a reviewer is found who is familiar with the treatment, or, eventually, to the office of the medical director where an individual assessment of the treatment is made. If, however, a precedent or policy exists for a particular unconventional cancer treatment, the claim may be resolved at a lower level (241,780,908). All third-party payers set their own reimbursement and evaluation policies, and more or less information may be required by any one carrier to evaluate the claim.

Medicare Evaluation Process and Criteria

HCFA relies on outside regional contractors (BC/BS plans, commercial carriers, and professional review organizations) to process Medicare claims. Although all contractors use Medicare coverage guidelines when evaluating a claim, the contractors may vary in their interpretation of the guidelines (814,870). The absence of a clear national policy concerning what is considered "reasonable and necessary" treatment, the myriad rules and regulations of the Medicare program, the high degree of independence in judgment given to contractors to adjudicate claims, and the decentralized process that controls the development of coverage guidelines all contribute to the varying interpretations of guidelines (447,814,870). The HCFA national office does make a certain number of national coverage decisions each year that are communicated to the contractors. In addition, contractors may consult a number of sources when adjudicating coverage, including HCFA's information manuals, physician consultants, and regional offices; the contractor's own medical staff; peer-reviewed scientific literature; local specialty societies; university medical centers; a national insurance association; or colleagues from another third-party payer (447,870).

While HCFA clearly prohibits coverage for some unconventional cancer treatments, such as colonic irrigation, cellular therapy, and laetrile (221), policies for other unconventional cancer treatments are not stated explicitly.

BC/BS Plans

The Medical directors of BC/BS plans[18] assess questionable cases in light of current trends and accepted practices of the U.S. medical community. The director may consult Federal agencies, peer-reviewed scientific literature, specialty groups, individual and local physician consultants, or members of an advisory panel made up of local physicians, for advice (56,241,780). In some cases, a medical director may ask the treating physician to explain the rationale for using a particular treatment (641).

Commercial Carriers

Medical directors of commercial carriers assess questionable claims in light of current trends and accepted practices of the U.S. medical community, and consult many of the same information sources used by HCFA and BC/BS. A 1987 survey of a subset of commercial insurers described the sources of information these companies most frequently use

[18] As mentioned earlier, the individual BC/BS plans set their own coverage and reimbursement policies.

when evaluating claims for cancer chemotherapy drugs.[19] All the companies surveyed used FDA, a local physician consultant, NCI, and AMA in their process of adjudicating claims. Nearly all the respondents consulted the ACS Unproven Methods Committee, 39 percent referred to a national physician consultant, 28 percent requested information from a university cancer center, and 28 percent consulted the Association of Community Cancer Centers. Several also indicated that they independently reviewed the medical literature (577).

Commercial carriers are becoming more attentive to claims evaluation, and are requesting evidence of safety and efficacy before reimbursement is approved. For some, a drug is not considered safe and effective unless it has been approved by FDA. In the 1987 survey of insurers mentioned above, half the respondents mentioned that FDA approval of a drug, device, or biologic was necessary for reimbursement; however, a significant percentage of companies also used more subjective criteria such as medical necessity (44 percent), safety and efficacy (28 percent), and acceptance by the medical community (28 percent) (577).

Appealing Reimbursement Decisions

Patients who are denied reimbursement but feel they deserve coverage under the terms of their contract may pursue several avenues of recourse. First, an appeal maybe made directly to the insurer. All insurance contracts indicate how an appeal may be fried, as well as the time period in which the insurer must respond to the claim. If the patient is unsatisfied with the outcome of the appeal, often another appeal may be submitted, or the patient may appeal directly to the medical director. A patient who remains unhappy with the reimbursement decision may write a letter of complaint to the State Insurance Commissioner. Because each State sets its own insurance laws, the State Insurance Commissioner is responsible for making certain that companies practicing in the State operate according to law (357).

Complaints submitted to an insurance commissioner are reviewed to ensure that the company has acted in accordance with the State insurance laws. As part of this process, the State Insurance Department may request a detailed report of the insurance company's finding and compare this information to the patient's insurance contract. An insurance commission may only determine if an insurer has violated any of the State insurance laws; insurance commissions typically do not have the authority to interpret the insurance contract, including phrases such as "medically necessary." If the insurance department determines the company violated the terms of the insurance contractor State law, it will request that the company pay the benefit. Depending upon State law, this request may or may not have the force of law. If the insurance commission believes the insurer has acted improperly, but did not in fact violate any State laws, the commission may recommend that the patient litigate (567,601,788). Since many disputed claims for unconventional cancer treatments center on the interpretation of the contract, especially phrases such as "medically necessary," a State insurance commission finding may have minimal effect on claims for unconventional cancer treatments.

Legal Challenges

As a last resort, patients who have been denied reimbursement for an unconventional cancer treatment have sued their insurers. Though the outcomes of these cases have varied, to a great extent patients have been successful in their suits. Two factors have contributed significantly to the success of patients in cases gaining reimbursement for unconventional cancer treatments. First, it is a basic tenet of contract and insurance law that a contract be viewed in the way most favorable to the insured.[20] The other contributing factor that has, in some cases, helped the insureds is the tendency of insurance companies to use language such as "usual and customary" or "reasonable and necessary," to describe covered services, making the contracts vulnerable to broad interpretation.

[19]Surveys were sent to the top 25 for-profit health insurance companies; 18 (72 percent) responded. Since no survey has been conducted on this topic with respect to unconventional cancer treatments, it is not possible to say whether the same information sources are used and whether they are used as frequently.

[20]Insurance contracts are usually considered adhesion contracts, the distinctive feature of which is that the weaker party (the insured) has no realistic choice as to the terms; they are given a take-it-or-leave-it option they cannot negotiate. In considering a dispute involving an adhesion contract, the law requires that the weaker party be given the benefit of the doubt, meaning any ambiguity in the contract is construed in the weaker party's favor (458). As noted by the judge in one such case, the court "must consider all the evidence in the light and with all reasonable inferences most favorable to the plaintiff" (687).

Disputes over the interpretation of unclear or ambiguous contract language have formed the basis of several lawsuits between third-party payers and patients who have used unconventional cancer treatments. The criterion used by courts for deciding whether a treatment should be covered is based on the *City of Carter Lake v. Aetna* decision in 1979: the court asks, What would a lay person believe is covered after reading the insurance policy? The answer to that question is then the criterion used by the court in its decision (194). However, the advantage that patients have in these cases is not insurmountable, as the outcomes of *R.A. v. Prudential* and *Free v. Travelers* show. In these cases, the policyholders claimed they expected reimbursement for laetrile and nutritional therapies because these treatments were 'reasonable and necessary' for the treatment of their cancer. However, the judges in these cases did not find this argument convincing, because it was demonstrated that the patients knew prior to treatment that neither laetrile nor nutritional treatments were considered to be effective by the American oncologic, medical, or regulatory communities. In both of these cases, the patients had signed informed consent documents or affidavits (to obtain laetrile) stating that the treatments were not FDA-approved or were not considered effective by the majority of physicians (37,304,734).

Other grounds for suit concern the medical standards by which therapies are judged to be reasonable and necessary. Plaintiffs often cite their interpretation of this clause when asserting that they reasonably expected reimbursement. In *Henne v. Mutual of Omaha, the* insured's policy in part excluded "services and supplies not prescribed by a doctor in accordance with generally accepted professional medical standards. The plaintiffs argued that nutritional and vitamin treatments conformed to "generally accepted professiona.l medical standards," because a significant minority of U.S. physicians used such therapy, and because the Commonwealth of Virginia had not disciplined the physician for improperly practicing medicine. The court ruled against the plaintiffs, however, finding that the treatment did not fit "generally accepted professional medical standards,' in part because it was not accepted by "a majority of practicing physicians' (394).

In *McLaughlin v. Connecticut General the* judge held that the insurance company should not have used FDA approval as the medical standard by which coverage was approved or denied, since this requirement was not specified in the contract (600). In this case a cancer patient's claims for reimbursement for Immuno-Augmentative Therapy (IAT) had been denied by Connecticut General for the sole reason that the treatment was not FDA-approved.

Similarly, in *Shumake v. Travelers the court ruled* that the insurer had to reimburse for laetrile and vitamins, because they were determined to be medically necessary in accordance with the terms of the insurance policy. The plaintiff's policy permitted reimbursement for a treatment if the "duly qualified attending physician" determined such treatment was medically necessary. The company argued that the court should consider "general standards of medical or scientific acceptance' in its ruling. The court rejected this argument, finding that if the insurer intended to use "general standards of medical or scientific acceptance' in deciding whether to reimburse, it should have clearly defined such standards (801).

Plaintiffs have also argued that improvement in their physical condition should be the medical standard used to determine coverage. In *Zuckerberg v. Blue Cross and Blue Shield,* one of the three issues the court looked at in order to determine whether the plaintiff should receive reimbursement was the subjective benefit of the Gerson therapy. The court posed this question to the insurer: "[effectiveness is measured by its results. How could defendant exclude this treatment as ineffective without ever looking at the results?' The fact that the third-party payer did not consider the subjective benefit to the patient contributed to the court's ruling in favor of the plaintiff (992). However, upon appeal both the State appellate and supreme courts overturned the ruling on other grounds (related to the other two original issues) (993). Similarly, in *Dallis v. Aetna the court,* after refusing the insurer's motion for an immediate judgment, allowed testimony from IAT patients who testified that the treatment in question had benefited them (247).

The argument of subjective benefit, however, does not ensure coverage. In *Dallis v. Aetna,* the appeals court judge allowed the testimony because it "was relevant to the determination of a fact in issue, namely, whether the IRC treatment was a 'necessary' treatment for cancer,' and because the witness' opinions "were rationally based on their own perceptions.' But, he noted that "[t]o the

extent that the witnesses' opinions lacked a scientific basis, appellant had the opportunity to expose this fact" (247), which presumably would have undermined the effect of their testimony to some extent. In another case, Free v. Travelers, testimony of subjective benefit was rejected by the judge because, "[a]s one court noted, it is simply not enough to show that some people, even experts, have a belief in [the] safety and effectiveness [of a particular drug]. A reasonable number of Americans will sincerely attest to the worth of almost any product or even idea" (629).

There are also several cases in which courts have confirmed the insurer's right to limit medical benefit coverage. In Wehmeyer v. Prudential, the judge upheld a patient's right to free choice of treatments, but also affirmed the insurer's "right, in the course of reasonable judgment, to confine its coverage to those treatments proven to be effective and medically productive" (944). The court in Risner v. Blue CrosslBlue Shield of Michigan ruled that insureds could not expect to "obtain any treatment whatsoever he chooses at any facility he chooses and afterwards collect from his health insurance carrier' (759).

Other judges have ruled in favor of insurers by upholding their responsibility to promote public good. In R.A. v. Prudential, the judge did not permit a liberal interpretation of the term "necessary," because that could result in payment for many ineffective or less effective therapies. Increases in benefits paid to insureds would create higher premiums for all; "[t]hose who accepted the logical limit of effective treatments would, as a condition for coverage of same, be forced to pay for worthless treatments as well . . . there is no public good in this" (734).

The success of patients in getting the courts to find in their favor seems to have prompted responses from both insurance companies, who are more precise in their contract language, and their lawyers, who have developed at least one new strategy for defending suits that do arise. More and more, insurance companies have had cases removed from State courts to Federal courts, arguing that the jurisdiction of a Federal law, the Employee Retirement Income Security Act (ERISA), which covers group medical plans, preempts the State laws that would otherwise apply. The standards of evidence required by ERISA are different from those required in contract law. ERISA gives the administrator of a group health plan discretionary authority to decide claims. Further, ERISA requires that denial of coverage "must be upheld unless it was arbitrary, capricious, made in bad faith, not supported by substantial evidence or erroneous as a matter of law" (462). These are standards of evidence that are more favorable to the insurer than those required under contract law. Because this strategy is just evolving, particularly in the context of unconventional cancer treatments, it is not clear how successful it will be. However, in one of the earliest pertinent ERISA cases, McLaughlin v. Connecticut General, the more stringent standards did not help the defendant. In this case, the two major claims by the plaintiffs were breach of insurance contract and breach of implied covenant of good faith and fair dealing. The insurance company argued, among other things, that ERISA preempts the State insurance and contract laws. The judge found, however, that although ERISA covered the insurance plan involved, it "did not preempt State law claims for breach of contract and implied duties of good faith and fair dealings' (600). The court found in favor of the plaintiff. In other ERISA cases (e.g., Filary v. General American Life Ins. Co., 711 F.Supp. 258 (D.Ariz., 1989)) involving unconventional treatments, but not for cancer, decisions have favored the insurance companies.

The above examples represent a few of the legal issues raised during court trials. According to one advocate of unconventional treatments, by threatening to sue, many patients can obtain payment for the treatment through an out-of-court settlement (951). However, if an insurer will not settle out of court, patients must be prepared to pay attorneys' fees, wait until the trial can be heard by a jury or judge, and endure a possibly long trial. In one case recently decided in favor of the patient, the trial lasted only 3 days, but attorneys' fees for the patient were $97,361, and the patient's out-of-pocket expenses were approximately $24,000.[21]

[21] In this case, the judge ruled that cancer treatment given by Stanislaw Burzynski to a woman with a malignant brain tumor was "usual and customary" under the terms of the insurance contract. Among other provisions, the patient was awarded payment of all past medical bills, which totaled approximately $200,000 (192).

Fraudulent Insurance Claims

Fraudulent insurance claims of various types are submitted for all kinds of medical services (412,769), including unconventional cancer treatments.[22] U.S. third-party payers allege that several unconventional cancer clinics and at least one billing service company have committed what falls into the category of insurance fraud, but the prevalence of fraudulent claims is unknown. Many fraudulent claims submitted for unconventional cancer treatments request reimbursement for "chemotherapy.' A minority of unconventional health care providers treat patients with chemotherapeutic regimens that are recognized by the medical community (321). Unconventional cancer treatment claims have also been submitted for chemotherapy or "non-toxic chemotherapy' followed by a set of initials; for example, "chemotherapy AMGL" has been used to represent laetrile treatments. Third-party payers disagree about whether such claims deliberately misrepresent the services rendered, thus constituting fraud, or simply reflect the clinic's definition of their treatment. In this and all other possible identifications of fraud, the pattern of claims submissions ultimately determines if an individual is deliberately and knowingly committing fraud (250,320,856,908).

More sophisticated insurance fraud often involves billing service consultants familiar with numerical coding systems used by providers and insurers in the United States. Two of the coding systems used are the International Classification of Diseases (ICD-9th revision) and the Current Procedural Terminology (CPT-4th edition). The ICD codes represent various diagnoses and CPT codes denote the treatment administered to the patient. If the CPT code is an appropriate match for the ICD code, the insurer will generally approve coverage without further investigation. Billing companies that allegedly commit fraud give the unconventional treatments CPT codes that not only match the ICD code for the patient, but also represent accepted medical treatments. For example, treatments that are not covered under the terms of the policy, such as coffee enemas or laetrile, might be coded as a type of chemotherapy, which would be covered under the contract (228,321). Claims submitted in this manner appear on paper to be valid, and some insurers believe many fraudulent claims of this type go undetected by their claims departments (228,320,321).

Third-party payers have increased their efforts to reduce the number of fraudulent claims that are reimbursed. More commercial carriers have established fraud divisions, both at company headquarters and at regional and local offices (228,250,269,856). In addition, several private insurers, BC/BS plans, and State and Federal agencies have joined the National Health Care Anti-Fraud Association (NHCAA), a group whose stated mission is to improve prevention, detection, and prosecution of health care fraud (269). The recent application of an old law, the Racketeer Influenced and Corrupt Organizations Act (RICO), to insurance fraud may represent a new mechanism for insurers to prosecute fraudulent providers. An insurer only needs to show it was hurt by the practitioner's " 'pattern of racketeering activity' (allegations of several counts of mail or wire fraud will suffice) in furtherance of an enterprise (such as a professional corporation) that affects interstate commerce (the insurance business)' (412). The drawback of RICO cases is that they require a large allocation of resources to prove the charges because the plaintiff must show the elements of fraud (927). One case involving a RICO action is currently pending against an unconventional practitioner. The suit is a counterclaim in the legal battle between Stanislaw Burzynski and Aetna.

It is important to note that many patients and practitioners do not believe they are committing an illegal act if they misrepresent on an insurance claim form the treatment they received. These individuals believe their claim would otherwise be rejected outright, without being reviewed by medical professionals who the patient and practitioner believe are most capable of evaluating the effectiveness of the treatment.

SUMMARY

Medicare, BC/BS plans, and most commercial third-party payers typically do not cover unconventional cancer treatments, though at least some unconventional cancer clinics imply that they do. Coverage is limited by clauses requiring covered medical services to be recognized as medically necessary by the U.S. medical community; limiting

[22] Note that in this chapter, "insurance fraud" is defined as an intentional misrepresentation of the facts in order to obtain reimbursement. This is distinguished from "health fraud," in that it does not necessarily involve false or unsupported claims of a treatment's effectiveness.

coverage of drugs and biologics to those approved by FDA or included in drug formularies; and (especially for Medicare) restricting coverage of medical services to specified health care professionals.

Third-party payers may permit coverage of patient care expenses associated with clinical trials or the Group C drugs. Although these drugs or biologics remain investigational until given FDA final marketing approval, most third-party payers do not consider these drugs comparable to unconventional cancer treatments. For most third-party payers, a crucial distinguishing feature of investigative drugs is that clinical data exist that suggest some degree of efficacy. Furthermore, the drug is identified and described, as is the scientific method used to produce the clinical results. At the same time, coverage for investigational drugs or for drugs that are used for other than FDA-approved indications is becoming more difficult to obtain.

Some claims for unconventional cancer treatments may be reimbursed unwittingly, but third-party payers are focusing their efforts on halting such reimbursements. Patients who choose to pursue their claims may be able to obtain some reimbursement, especially through an out-of-court settlement, though the outcomes of court cases have been mixed. Unless insurers undergo a major shift in their reimbursement policies, it is unlikely that it will become easier to obtain coverage for these treatments, as the general trend among insurers is to be tougher about reimbursement criteria for all types of medical services.

Chapter 10

Laws and Regulations Affecting Unconventional Cancer Treatments

CONTENTS

Box

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INTRODUCTION

Laws and regulations governing medical treatments are predicated on the idea that State and Federal Governments have a legitimate interest in protecting the health and safety of their citizens. At the same time, both State and Federal Governments have an interest in protecting individuals' rights of privacy in matters of their own health and welfare. Issues concerning the availability and use of unconventional cancer treatments illustrate some ways in which these two interests may conflict. In recent years, laws and regulations designed to protect patients from drugs, biologics, or other substances of unknown safety and efficacy have been challenged for limiting patients' access to unconventional cancer treatments, impinging on their ''fi-eedom of choice' in medical care. From the opposing point of view, that of "consumer protection," State laws permitting access to specific unconventional cancer treatments that otherwise would be illegal have been criticized for posing a public health hazard and for violating Federal requirements for uniform national drug standards. The effects of these opposing arguments on the use of unconventional cancer treatments is discussed in the first section of this chapter.

Though few are written with the specific intent of influencing the use of unconventional cancer treatments in the United States, many Federal and State laws and regulations ultimately do have a significant effect on the use of these treatments by restricting their availability, marketing, and advertising. The second part of this chapter examines the major Federal and State laws and regulations that affect the use of unconventional cancer treatments and the ways in which Federal and State agencies enforce them. Though these regulations may affect practitioners' activities (particularly practitioners who manufacture and distribute their own treatments), they are not directed solely at them. Laws that restrict availability are designed to ensure that drugs are both safe and effective, while laws that regulate marketing and advertising of products and services (not limited to medical treatments) are intended to prevent such crimes as mail fraud and false advertis***ing.*** This ***chapter examines those aspects of law*** that ***relate*** to the ***availability and marketing of*** unconventional cancer treatments. Statutes that explicitly regulate the practice of medicine are discussed in chapter 11.

Instances where laws have been challenged in court and the activities that have led to prosecution of some practitioners have been highlighted. These cases rarely involve a single, self-contained issue and are very difficult to characterize into general categories. Both the effort to challenge, or even bypass, the intentions of the laws that prevent use of unconventional methods, and the efforts to effectively enforce the laws have evolved over the years as lawyers have devised different arguments to support claims. In addition, the decisions of the courts have sparked further innovation. Throughout this chapter and the next, court cases illustrate the evolution in this area of law.

CONSUMER PROTECTION V. "FREEDOM OF CHOICE" IN UNCONVENTIONAL CANCER TREATMENTS

The ***forces acting*** to ***legally*** restrain or ***expand the availability of*** unconventional cancer treatments in the United States can be divided generally into two opposing camps: advocates of "consumer ***protec***tion" ***and*** advocates ***of "freedom of choice" in*** cancer treatment. Individuals in the former group basically favor the legal status quo. That is, they ***support laws such*** as the ***Federal Food, Drug, and Cosmetic Act (FDCA), which requires substantial evidence of safety and efficacy of drugs before they may become widely available, evidence*** that ***does*** not currently exist ***for*** unconventional cancer treatments. The latter group, objecting to the status quo, argue for patients' greater access to unconventional cancer treatments without restrictions.

The proponents of the consumer protection view reason that, based on the U.S. Constitution, State and Federal Governments have a responsibility to protect the health and safety of their citizens. This responsibility includes protecting people from un-

safe and ineffective drugs-the rationale and purpose of the FDCA. It is argued that the safety and efficacy requirements of FDCA are a rational extension of the government's overall responsibilities to promote public health. In an early case that reached the U.S. Supreme Court involving the 1938 Food, Drug, and Cosmetic Act, Justice Frankfurter articulated the need for government regulation:

> The purposes of this legislation . . . touch phases of the lives and health of people which, in normal circumstances of modem industrialism, are largely beyond self-protection. (913)

For unconventional cancer treatments, the rationale for consumer protection extends beyond simply protecting the public health and safety through the regulation of practitioners and treatments. It also includes protecting the public from inaccurate or fraudulent claims about treatments. For instance, the purpose of FDCA provisions that regulate packaging and advertising of prescription drugs is to protect consumers from false and inaccurate claims made for products.

The argument for 'freedom of choice' in medical care is based on the concept of an individual's fundamental right of privacy. It is argued that this right prohibits governmental and private restraints on individual rights to make choices regarding treatments and therefore that individuals should be allowed to decide whether to use any treatment of their choosing: as stated by one ''freedom of choice' proponent, "the patient should be permitted to opt for treatment consistent with his views of higher quality of life. . ." (416). A parallel argument is made for a physician's right and responsibility to provide medical care. It reasons that well-informed physicians, following their best judgment and having assessed the risks and benefits of a treatment, should be allowed to provide the care they deem best for their patients without outside interference (950).[1]

Proponents of "freedom of choice" in medical care support implementation of a variety of mechanisms, ranging from State laws exempting certain unconventional cancer treatments from safety and efficacy requirements, to elimination of FDCA requirements for proof of both safety and efficacy of drugs distributed in interstate commerce, to an amendment to the U.S. Constitution that would guarantee "freedom of choice" in health care.

The main route by which the argument for open access to unconventional treatments has been pursued is through the courts, and it is in response to such court cases that the argument for consumer protection has been further developed. In State and Federal courts such questions as the right of privacy,[2] the right of parents to choose unconventional treatments for their children, and the ability of patients to take responsibility for their treatment decisions through informed consent (in a malpractice case), have been addressed. So far, no legal right has been established that would allow patients general access to unapproved drugs.[3] The outcomes of the cases described below show that the straightforward argument for an absolute right to choose any treatment has not been upheld by the courts. In all the cases where the right of privacy in choosing medical treatments has been invoked, the issue of free choice has immediately been blurred by controversies over whether treatments have any demonstrated benefit. However, by addressing the issue of informed consent, the court leaves the door open for a patient to take on some responsibility for choosing an unconventional cancer treatment, broadening the legal interpretation of free choice.

Litigation Involving "Freedom of Choice" in Unconventional Cancer Treatments

In California, the right of privacy was ***addressed by the State Supreme Court in 1979, in*** a case

[1] The legal restraints on physicians who offer unconventional cancer treatments are discussed in ch. 11, which deals directly with the Practice of medicine.

[2] The right of privacy generally encompasses various rights recognized as inherent in a free society, including a general right to be left alone and to be protected from governmental interference. It also includes the freedom of the individual to make fundamental choices involving the individual, his or her family, and relationships with others, except where such choices prove to be harmful to others and possibly oneself. Limitations on such fundamental rights are justified only by a compelling State interest. Although the Constitution does not explicitly mention the right of privacy, "zones of privacy' have been created by specific constitutional guarantees based on the Bill of Rights and on Amendments to the Constitution. TheU.S. Supreme Court has created zones of privacy in areas such as marriage, procreation contraception abortion, family relationships, childrearing, and education. The right of privacy has been invoked in some cases involving medical decisionmaking, including the right to refuse treatment (as in the widely publicized *Quinlan* (441) and *Bouvia* (94a) cases.

[3] Such access is currently limited to unapproved drugs that are under an investigational new drug (IND) exemption, drugs brought from foreign countries for personal use, or to particular States where laws have been enacted to exempt certain unapproved drugs from safety and efficacy requirements.

involving a ***physician charged*** with ***violating the State's Health and Safety Code.[4] In this*** case, the ***physician, James*** Privitera, had been convicted by a jury of a felony, conspiracy to sell or prescribe an unapproved drug (laetrile) to cancer patients. The verdict was appealed on the grounds that the statute was unconstitutional; Privitera's lawyers contended that the right to obtain laetrile is a fundamental right of privacy. The California Court of Appeals overturned the conviction because it found, among other things, that the State Health and Safety Code violates patients' rights to privacy under the California and U.S. Constitutions (716). When the State appealed the decision, the case went to the California Supreme Court, which found that the right to obtain drugs of unproven efficacy is not encompassed by the right of privacy embodied in either the State or Federal Constitutions.[56]

In his argument for the right of privacy, Privitera relied heavily on cases, such as ***Roe v.*** *Wade,* ***where the right*** to ***privacy in*** medical ***decisions was expanded by the courts' decisions. However, in*** its ***decision*** on the *Privitera case, the* court ***pointed*** out that *Roe v. Wade* ***established*** that the right of privacy in ***decisions pertaining*** to ***medical care*** is not ***absolute, noting*** that, "the ***lesson of*** *Roe v. Wade* for our case is that a requirement that a drug be certified effective for its intended use is a reasonable means to 'insure maximum safety for the patient' " (717). Having decided that the State's Health and Safety Code did not violate a fundamental right of privacy, the court concluded that, "section 1707.1 [of the statute] amply satisfies the applicable standard by bearing a reasonable relationship to the achievement of the legitimate state interest in the health and safety of its citizens" (717). Privitera was unsuccessful in an attempt to have the U.S. Supreme Court review the case (718).

To date, the only Federal case testing the right of privacy in access to unapproved drugs for cancer treatment is *United States v. Rutherford.* Because every decision was appealed successfully by the ***opposing parties,*** this case made its way to the U.S. ***Supreme Court. However, as*** it ***progressed through the Federal*** court system, new issues were brought into consideration, making it impossible to characterize it solely as a case about patients' rights of privacy in choosing their medical treatments.

Originally, Glen Rutherford, on behalf of a class of cancer patients, brought suit in Federal district court to stop FDA from prohibiting interstate shipment of laetrile. The court found the drug to be nontoxic and effective if given in the correct dosage, and permitted its limited purchase. The government appealed the decision. The U.S. Court of Appeals for the I0th Circuit upheld the lower court's injunction but directed the district court to remand the case to the Food and Drug Administration (FDA) for determination of whether laetrile was a' 'new drug' (within the meaning of the FDCA) and, if so, whether it was exempted from the safety and effectiveness requirements by falling under either of two "grandfather" clauses. FDA's determination that laetrile was a new drug that did not fall under either grandfather clause brought the case back to the district court. The presiding judge concluded that FDA's determination was incorrect (he determined that the drug was grandfathered), and that by denying cancer patients access to laetrile, FDA was infringing on the constitutionally protected right of privacy. Again the decision was appealed. However, in its decision, the court of appeals did not address the lower court's ruling, but introduced anew issue: the court found that FDCA's standards for safety and efficacy had ''no reasonable application" to terminally ill cancer patients and allowed terminally ill individuals to receive laetrile. FDA appealed the decision to the U.S. Supreme Court, which focused only on the issue of whether the safety and efficacy requirements applied to drugs for terminally ill patients. In a unanimous decision, the Supreme Court reversed the lower court's ruling by upholding the FDCA provision, and remanded the case to the lower court (918).[7] The circuit court upheld the

[4]This code requires Federal or State approval of drugs used to treat cancer patients.

[5]The court's decision was split 5 to 2. The Chief Justice dissented, arguing that the constitutional right to privacy for both the patient and physician was violated. In a separate dissent another Justice expressed the opinion that the majority opinion condoned action that appeared to him to be cruel and inhuman treatment (717).

[6]Each court's decision to view this as a right to privacy issue or not determined the legal standard by which the court judged the statute. The Appeals court saw the right to choose any medical treatment as constitutionally protected and applied the compelling interest standard, which requires that the 'State have a compelling interest that overrides the right to privacy. The State Supreme Court, however, did not see it as a protected right and therefore applied the rational basis test, which requires that a statute bear "a reasonable relationship to the achievement of a legitimate state interest" (717).

[7]The Supreme Court did not address the right of privacy issue because that was not the basis of the appeals court decision, the subject Of the appeal.

FDCA provision and dismissed the argument that the right of privacy extends to the use of unapproved drugs (920). A petition for a writ of certiorari, which would put the case before the court of appeals again, was denied by the Supreme Court (919).

Two court cases concerning the use of laetrile have addressed the issue of parents' rights to choose an unapproved treatment for their child, both of whom had cancers that, in all probability, were curable with appropriate mainstream treatment. In both cases, the State requested that courts declare the children wards of the State, arguing that the parents' actions constituted parental neglect. However, the circumstances surrounding the parents' decisions led the courts to different opinions (525,692). In Massachusetts, Chad Green, a 2-year-old boy with acute lymphocytic leukemia, was declared a ward of the State when his parents stopped his chemotherapy while he was in remission and put him on what they called a metabolic therapy (laetrile and a nutritional regimen). Though his parents had already left the State with Chad, the State Supreme Court upheld a court order requiring he receive State-supervised chemotherapy and cease taking the unapproved treatment. The court acknowledged that parents have natural rights that encompass a private family life, but viewed the child's well-being as an overriding interest. The court based its decision of what was in the child's best interest on strong medical evidence that the unconventional treatment was not improving the child's condition, while, until the parents stopped treatments, conventional treatment had controlled the leukemia. It found the nutritional therapy "useless and dangerous' (692). Chad Green died in Mexico shortly after his parents took him there for unconventional treatment (627).

A similar case in New York, *In re Hofbauer, involved* a *7-year-old boy, Joey Hofbauer,* with *Hodgkins* disease. *Again the State tried* to *prevent the parents* from *continuing* to treat the child with *metabolic therapy (including laetrile) by pursuing* a *child neglect* case. *However, in this* case the New *York Court of Appeals found* that the *parents, who had found* a *licensed physician* to prescribe laetrile, *had not "failed* to exercise a minimum degree of care" (653) since they were following a recommended treatment that had 'not been totally rejected by responsible medical authority" (439). In addition, the court found some evidence that the unconventional treatment might be effective, while there was also evidence that conventional treatment was failing (440). Joey Hofbauer died a few years later, in 1980. In both cases, how the courts weighed the evidence of effectiveness of the available treatments seems to have played more of a role in their decisions than the concern for a right to family privacy (692).

In a malpractice case that is still in the court system, another aspect of ''freedom of choice' in unconventional cancer treatments was addressed: whether patients can assume the risk for the treatments they choose, thereby relieving practitioners of legal responsibility. In *Schneider v. Revici, Edith Schneider and her husband sued Emanuel Revici and the* Institute of Applied Biology, Inc., for fraud and medical malpractice in connection with his use of unconventional treatments in treating Schneider's breast cancer. Before the trial began, the defendants tried to modify their answer to the charges "to include express assumption of risk as an affirmative defense" (786). The trial judge denied the motion. If the judge had allowed the motion, during the trial the defense would have argued that Edith Schneider had assumed the risk of her treatment by signing a release form. The jury found in favor of Mrs. Schneider only on the malpractice claim and awarded her and her husband $1.05 million.[8] Revici appealed the verdict, arguing, among other things, that the trial judge erred in not allowing express assumption of risk as a defense. The appeals court agreed, finding that express assumption of risk provided a complete defense. The case was remanded to the lower court for a jury to consider the issue of assumption of risk.

The appeals court's decision adds a new dimension to the argument for "freedom of choice" in medical care by expanding the potential of the patient to take on responsibility for treatment choice. In its opinion, the court specifically noted:

> [W]e see no reason why a patient should not be allowed to make an informed decision to go outside currently approved medical methods in search of an unconventional treatment. While a patient should be encouraged to exercise care for his own safety, we believe that an informed decision to avoid surgery and conventional chemotherapy is within the patient's right "to determine what shall be done with his own body." (786)

[8]However, they also found that she was 50 percent negligent and reduced the award accordingly to $525,000.

In the upcoming trial, the jury will have to decide whether the consent form signed by Mrs. Schneider constitutes an assumption of risk.

Summary

The cases described above demonstrate that the courts generally have not agreed with the arguments put forth for "freedom of choice" in unconventional cancer treatments. Though they are sympathetic to the plight of cancer patients, they see the laws, such as the FDCA, as both fulfilling Congress' intent and playing a necessary role in protecting the public from unproven treatments that might not be safe or effective. *Schneider v. Revici* has brought a new issue to the forefront of this area of law that could have an impact on both patients' and physicians' attitudes toward these treatments by extending the potential for patients to take on more responsibility for their treatment choices, relieving the practitioner of some liability.

FEDERAL AND STATE REGULATION OF UNCONVENTIONAL TREATMENTS

Both Federal and State Governments, through their appropriate agencies, are responsible for regulating the manufacturing, marketing, and advertising of drugs and the advertising of health products in general.[9] At the Federal level, the Food and Drug Administration (FDA) is responsible for approving new drugs for interstate commerce; stopping interstate marketing of adulterated, misbranded, or unapproved drugs[10]; and regulating advertising of prescription drugs, among other responsibilities. The Federal Trade Commission (FTC), along with FDA, is responsible for stopping false advertising of most products and services, including over-the-counter drugs, devices, and treatment regimens. The U.S. Postal Service (USPS) is responsible for protecting consumers from false and deceptive mail-order advertising. Regulation of intrastate commerce involving drugs unapproved by FDA falls under the jurisdiction of each State. In addition, States have their own laws about false advertising and health fraud. This section discusses how the Federal and State Governments carry out their responsibilities in this area, describes their effect on unconventional cancer treatments, and, where possible, provides examples of relevant litigation arising from violations of the laws.

Federal Regulation of Manufacturing and Marketing of Drugs

FDA has regulatory authority over the manufacturing and marketing of food, drugs, devices, and cosmetics in order to ensure their safety and (in the case of drugs and devices) efficacy. The Federal Food, Drug, and Cosmetic Act (FDsCA) (21 U.S.C. § 321-393) authorizes FDA to prohibit the interstate marketing of unsafe or ineffective drugs (21 U.S.C. § 331), and provides for sanctions against manufacturers, distributors, or promoters who violate the terms of the FDCA (21 U.S.C. § 333). It does not include sanctions against patients who use these drugs. The FDCA requires that the safety and effectiveness of a drug be established before FDA grants formal approval for the drug to be shipped in interstate commerce. (See box 10-A for a description of how the safety and efficacy of drugs are established.) FDA determines whether a sponsor has shown ''substantial evidence" of the safety and efficacy of a new drug it wishes to market, but is not responsible for carrying out investigations necessary to prove drug safety and efficacy (791).

FDA also has the authority to collect additional information on substances that are, or are suspected of being, marketed or promoted in violation of the FDCA. FDA can collect samples and conduct examinations and inspections of the substance in question; examine records to determine whether the substance has been marketed in interstate commerce; enter and inspect manufacturing sites and warehouses; refuse imported products that appear to violate the FDCA; and not@ manufacturers or promoters that they may be violating FDA regulations in time for them to make corrections voluntarily before FDA initiates legal or administrative proceedings (21 U.S.C. §372,373,374, and 381).

FDA regulations apply only to specific substances used in treatments, not to treatment regimens or practices. Among unconventional cancer treatments,

[9]The discussion of FDA authority applies generally to specific substances—drugs, biologics, and foods—for which medical claims can be made. It does not extend to psychological, behavioral, or spiritual techniques, or to general dietary regimens (except in some cases to specific *dietary* products).

[10]Unapproved drugs are drugs that have not been approved by FDA for marketing in the United States.

Box 1O-A—HOW the Safety and Efficacy of New Drugs Is Established

Under the FDCA, the requirements for evidence of safety and efficacy ("effectiveness") apply to those substances that FDA classifies as "new drugs. " A "new drug" is defined in part as:

> any drug . . . the composition of which is such that such drug is not generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, as safe and effective for use under the conditions prescribed, recomrnended, or suggested in the labeling thereof. (21 U.S.C. § 321(p)(l))

A key provision of the statute specifies that a new drug cannot be approved, and therefore cannot be shipped in interstate commerce, until there is "substantial evidence' that it is safe and effective for its intended use. The term "substantial evidence" refers to evidence derived by:

> adequate and well-controlled investigations, including clinical investigations, by experts quali.tied by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof. (21 U.S.C. § 355 (d))

Before initiating "well-controlled investigations" (as specified in the section of the statute quoted above), FDA requires that drugs be studied experimentally in animal systems; if the results of those tests fulfill FDA criteria, FDA allows the drug to proceed to a final stage of testing in specific clinical (human) trials. Any person or company wanting to conduct clinical research on an unapproved drug must submit an investigational new drug (IND) application to FDA. If the application contains sufficient detail to meet FDA's requirements, the IND is allowed to proceed, exempting the sponsor from the FDCA prohibition against shipping unapproved drugs in interstate commerce for the study or studies specified in the IND, and ensures that FDA can monitor the clinical research process (474). Usually, a progression of clinical trials is required, culminating in large, randomized clinical trials.

The rationale for adequate and well-controlled trials set by the statute is one of consumer protection; it is meant to assure that a certain standard of evidence has been met for all new drugs. In a regulation promulgated by FDA (21 C.F.R. § 314.126(b)), an "adequate and well-controlled investigation" is defined as having the following characteristics:

- . it includes a clear statement of the objectives of the investigation and a summary of the proposed or actual methods of analysis in the protocol for the study and in the report of its results;
- . it uses a design that permits a valid comparison with a control to provide a quantitative assessment of drug effect;
- . its method of selection of subjects provides adequate assurance that they have the disease or condition being studied;
- . its method of assigning patients to treatment and control groups minimizes bias;
- . measures are taken to minimize bias on the part of the subjects, observers, and analysts of the data;
- . its methods of assessment of subjects' response are well-defined and reliable; and
- . there is an analysis of the results of the study adequate to assess the effects of the drug.

the FDA regulations apply to ***pharmacologic agents (e.g., laetrile*** or Burzynski's ***Antineoplastons), biologic agents (e.g.,*** vaccines or the ***biologic products used in Immuno-Augmentative Therapy (IAT)), herbal preparations (e.g., the Essiac*** or Hoxsey tonics), and homeopathic preparations. Under the terms of the FDCA, drugs are defined as ''articles," including chemical or biological substances, '(other than food) intended to affect the structure or any function of the body of man' and 'intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man" (21 U.S.C. § 321(g)(l)) .11

Most other types of unconventional cancer treatment ***(e.g., psychological and metaphysical approaches,*** nutritional regimens) would not be considered drugs and therefore would not be subject to regulation under the FDCA as long as drug-type claims were not made for them.

Drugs manufactured, sold, or used in interstate commerce are ***subject*** to ***FDA regulation. This includes drugs*** that are ***sold*** to ***patients who*** then transport them across state lines or drugs whose components or packaging are produced in another State before sale to a patient (168). FDA's authority

[11] FDA examines product labels, promotional materials, advertisementa, and oral representations to determine whether a substance is intended to be used therapeutically.

Anecdotal evidence from patients or physicians who have used the drug is not sufficient to exempt it from the new drug classification. As one judge explained:

> . . .it is simply not enough to show that some people, even experts, have a belief in safety and effectiveness. A reasonable number of Americans will sincerely attest to the worth of almost any product or even idea. To remove the aberrations in uniformity which can result from a well-staged ' 'swearing match," the law requires more. Indeed, it has been heretofore held that the purpose of the normal inquiry is not to determine safety and effectiveness at all, but to ascertain the drug's general reputation in the scientifc community for such characteristics. It is certain that a conflicting reputation is insufficient to establish general recognition.
>
> Therefore, what is required is more than belief, even by an expert; it is a general recognition based upon substantial scientific evidence as delineated in the regulatory guidelines. (910)

The standards of safety and effectiveness specified in the FDCA apply regardless of the type or severity of disease for which a drug is intended. However, depending on the benefits a drug provides and the severity of the condition being treated, different risks are acceptable; for all drugs, the risks must be balanced against the benefits derived from them. It is known and accepted that a number of drugs used to treat cancer have adverse effects so serious that they would not be acceptable in treating, e.g., self-limiting conditions or other non-life-threatening diseases.

Until 1988, use of drugs under INDs was limited to the patients involved in the clinical trial. In a rewrite of the IND regulation, a new provision, often referred to as "treatment IND," was added. Under a treatment IND, patients with life-threatening or serious diseases may obtain certain drugs that have not yet been approved by FDA for marketing (474). The purpose of this rule is:

> . . .to facilitate the availability of promising new drugs to desperately ill patients as early in the drug development process as possible, before general marketing begins, and to obtain additional data on the drug's safety and effectiveness. (21 CFR § 312.34)

This new rule permits drugs that are in phase III trials (the final stage of clinical investigation before a new drug application is submitted), or sometimes phase II trials, to be available to patients with serious diseases or immediately life-threatening diseases who are not enrolled in a clinical trial. In these cases, FDA requires that there be a proper treatment protocol in place to obtain the treatment IND, which requires the collection of certain experimental data. FDA may deny the treatment IND if it decides that there is insufficient evidence for concluding that the drug may be effective or if the drug would expose the patient to an unreasonable risk.

Drugs are approved by FDA for the specific indications studied in the clinical trials. These indications appear on the package insert and are the only ones for which the product maybe labeled. Once a drug is approved by FDA, however, physicians are legally free to prescribe it for any medical conditions they wish.

also covers drugs ***imported*** into the ***United States*** to ***be sold here. Drugs*** that are ***produced, packaged, sold, and used entirely*** within a ***given State*** (from ***components grown, synthesized,*** or ***manufactured*** within that ***State)*** or ***completely outside the country fall outside FDA's*** jurisdiction (168,791).[12]

FDA can also take action to stop the interstate distribution of unapproved substances used in unconventional cancer treatments if the substances are shown to be 'adulterated' or 'misbranded. Under the FDCA, a drug is considered adulterated if it has not been made according to current good manufacturing practices or if its strength, purity, or quality falls below that which it is represented to have. A drug is ''misbranded' if its labeling contains unfounded claims or inadequate directions for use, ***inadequate warnings of potential dangers,*** or inaccurate information about 'the contents 'of the product (279).

Enforcement of the FDCA

Violations of the FDCA requirements can lead to a variety of penalties, such as seizure and destruction of the drugs in question, injunctions to restrain further violations, and criminal penalties (e.g., frees and imprisonment) (21 U.S.C. $332,333, and 334). Violators of the FDCA may also be subject to penalties under the Criminal Fines Enforcement Act and the Comprehensive Crime Control Act (which amended Title 18 of the U.S. Code) authorizing frees of up to $500,000 for corporate or organizational defendants and $250,000 for individual defendants

[12]However, the FDA can coordinate with Customs and Immigration officials to control the importation of unapproved drugs into the United States.

(181). Cases of possible violation of the FDCA are reviewed by FDA attorneys, the U.S. Department of Justice, and by local U.S. Attorneys, who decide whether to proceed with civil or criminal action (168,791).

Litigation Involving the FDCA

Several cases involving unconventional cancer treatments have challenged specific provisions of the FDCA and the way in which FDA has carried them out. In other cases, practitioners who use unconventional methods have been charged with violating provisions of the FDCA. Examples of both types of case are given below.

The most intensive legal challenge to any provision of the FDCA was the Rutherford case (discussed above). When Rutherford originally brought the case to court requesting the injunction to prevent the FDA from prohibiting distribution of laetrile, he challenged the legality of FDA's actions. Later, after FDA determined that the drug fell under the FDCA requirements for new drugs and was not eligible to be exempted under a grandfather clause which would have exempted it from efficacy requirements, the district court found that FDA's interpretation infringed on a constitutionally protected right of privacy. When the case reached the U.S. Court of Appeals, that court did not address the statutory and constitutional issues on which the lower court ruled (that the drug was entitled to an exemption and that the law violated a constitutional right of privacy). The court of appeals did find, however, that the Act's standards of safety and effectiveness have no reasonable application to the terminally ill. This issue was also taken up by the U.S. Supreme Court. In a unanimous decision, the Supreme Court held that the FDCA contained no express exemption, nor did Congress intend there to be an implicit exemption, with respect to drugs used by the terminally ill. The "effectiveness" requirements of the Act applied equally to drugs used by terminally ill cancer patients, who are entitled to the same protections under the FDCA as other patients; this included the assurance that the drugs they use are safe and effective and that these drugs will not increase their pain and suffering (918).[13] The Supreme Court remanded the case to the circuit court to resolve the statutory and constitutional issue brought up earlier. This time, the district court found that the drug was not exempt from FDCA requirements because of a grandfather clause and that the law did not infringe on a constitutional right of privacy. The fact that the Supreme Court denied a request for a writ of certiorari that would reopen the issue before the appeals court indicates that the court agreed with the district court's decision (919). In the end, the courts upheld both the provisions of the FDCA and FDA's interpretation of them.

In a more recent case in Texas, Stanislaw Burzynski, M.D., the developer of Antineoplastons, and his patients, challenged parts of the FDCA in a countersuit against the government. Originally, in a civil action in 1983, FDA accused Burzynski of violating two provisions of the FDCA. Specifically, Burzynski was charged with selling his unconventional cancer treatment, Antineoplastons, in interstate commerce. In addition, the government sought to stop the manufacture and distribution of the treatment on the grounds that drugs were adulterated within the meaning of the Act, because the facility did not comply with FDA regulations concerning good manufacturing practices (912). The judge issued an injunction that granted most of FDA's requests. In particular, it ordered Burzynski to bring his facility up to FDA standards for good manufacturing procedures, but also ordered FDA to cooperate in an IND by acting promptly on a submission for approval. Burzynski was explicitly allowed to continue manufacturing and prescribing the drug in Texas. Two years later, in 1985, as part of a criminal investigation based on a referral from FDA, the Department of Justice searched the administrative offices of the Burzynski Research Institute. During the investigation, the government legally seized the patient-treatment records. Burzynski and some of his patients filed a counterclaim seeking return of the records, financial compensation for damages, and other relief. The district court dismissed these counterclaims. Burzynski and his patients appealed the decision to the Fifth Circuit Court of Appeals, but again the court found in favor of the government in regard to seizure of the records and most of the other counterclaims (911). The appellate court did agree that Burzynski and his patients were denied the opportunity for discovery, unfairly preventing them from supporting any counterclaim that might

[13]It has also been argued that seriously ill patients are entitled to even greater protection than less seriously ill patients since the serious retie of their illnesses may interfere with their ability to make informed decisions about using risky or unapproved drugs (902); and 21 CFR § 56.ill(b).

have entitled them to injunctive relief in order to stop the government from disseminating false information to outside parties (911). On this issue, the case was remanded for further proceedings and is still pending. In addition, in December 1987, the patients petitioned the Supreme Court for a writ of certiorari, which would have brought the lower court's decision up for reexamination. Their petition was denied (967).

In an earlier case, Andrew Ivy, a Chicago physician and promoter of Krebiozen, an unconventional cancer treatment popular in the 1950s, was indicted along with another physician and two manufacturers of Krebiozen, on forty-nine separate criminal charges, ranging from violations of the FDCA to conspiracy and mail fraud (937).[14] Ivy countered by bringing suit against the Attorney General of the United States and the U.S. Attorney for the Northern District of Illinois seeking to enjoin them from proceeding against him. He requested instead that an impartial medical commission be appointed to conduct a clinical test of the drug (supervised by the court) to determine its efficacy in treating cancer. Ivy claimed that he could not receive a fair trial, with all the rights guaranteed by the Fifth and Sixth Amendments of the Constitution, if the trial proceeded. The judge ruled in favor of the State and Ivy appealed. The appeals court judge affirmed the lower court's decision, asserting that the criminal trial against Ivy, prior to an impartial test of the drug's effectiveness, would not violate Ivy's rights to a fair trial and due process. The judge noted that though 'resolution of the efficacy issue was beyond the intelligence and comprehension of the jury. . .mere complexity of the factual issues involved in a criminal case is not constitutional basis for precluding the trial' (452). The appeals court agreed with the district judge, who pointed out that juries are regularly required to decide issues not within their scope of knowledge or understanding. In such cases the expert witness is used to bridge the gap in knowledge.

Federal Regulation of Advertising

Three Federal agencies, FDA, FTC, and USPS, are involved in regulating advertising claims made for health products. As discussed in the previous section, manufacturers and promoters of foods, drugs, devices, and cosmetics who make false claims for their products are in violation of the FDCA's misbranding provision. While FDA is primarily responsible for the accurate *labeling* of foods and drugs and for advertising of prescription drugs to professionals, FTC is primarily responsible for the consumer *advertising* of foods and over-the-counter drugs.[15] Both FDA and FTC have jurisdiction over advertising of medical devices (791). The ways in which FTC and the Postal Service (which is responsible for monitoring mail order advertising) can regulate advertising claims for unconventional cancer treatments are discussed below.

Federal Trade Commission

FTC learns of potentialm problems with advertising, including ads for health-related products, through consumer complaints or through its own monitoring efforts. The Federal Trade Commission Act (FTCA) (15 U.S.C. § 41 *et seq.),* which authorizes FTC to regulate advertising claims, contains both a general prohibition of unfair or deceptive acts or practices in or affecting commerce (15 U.S.C. § 45 (a)) and a provision that specifically prohibits the false or deceptive advertising of foods, drugs, devices, or cosmetics (15 U.S.C. § 52). FTC is authorized to stop advertisements if they contain a representation or omission that would likely mislead reasonable consumers and that representation or omission is material (203). It is not necessary for FTC to show that deception has actually occurred or that an advertiser intended to deceive consumers (36,191).

FTC has several alternatives in enforcing the FTCA. In most false or deceptive advertising cases, FTC issues an administrative complaint against the advertiser. Following a hearing held before an administrative law judge, the Commission may issue a cease-and-desist order prohibiting future deceptive advertising (15 U.S.C. § 45(b)). FTC also has authority to seek preliminary and permanent injunctions from Federal district courts for violations of the FTCA (15 U.S.C. § 53). In cases where FTC has entered a cease-and-desist order against an advertiser, it may seek refunds or other restitutions for injured consumers from a State or Federal court, if it can be shown that the violations were fraudulent or dishonest (15 U.S.C. § 57(b)). FTC can also promulgate industry-wide guidelines and trade regu-

[14] After a very well-publicized trial that took over a year to complete, Ivy and his co-defendants were acquitted of all charges against them (915).

[15] FDA, however, does have jurisdiction over direct-to-consumer prescription drug advertising (181).

lation rules in response to widespread violations of the statute (15 U.S.C. § 57(a)).

If FTC seeks to initiate proceedings to obtain monetary civil penalties, it generally must go through the Department of Justice (15 U.S.C. § 5(a)). The FTC can seek civil penalties for violations of its trade regulation rules or of previous orders (15 U.S.C. § 45(l)-(m)).

Litigation Involving the FTCA—FTC has used its authority to stop false advertising of unconventional cancer treatments. In 1975, FTC sued Travel King, Inc., for false claims about its "psychic surgery' treatment for cancer and other disorders. The company advertised and sold trips to the Philippines where the treatment was performed. Following a trial, FTC ordered the company to stop selling its treatments. The company was also required to send a warning letter to consumers who requested information (857). In a more recent case, FTC obtained a preliminary injunction, stopping Pharmtech, the manufacturer of an unconventional nutritional treatment ("Daily Greens," capsules containing vitamins, selenium, beta-carotene, and dehydrated vegetables) from advertising that its product could reduce the risk of developing certain types of cancer (283). In the ads, the promoters based their claims on findings in a report, *Diet, Nutrition, and Cancer,* published by the National Academy of Sciences. FTC argued successfully that the report did not substantiate the promoter's claims and that the report stated that the findings did not apply to dietary supplements, such as Daily Greens. The court, agreeing with FTC's contention that the promoter's claims for this product were false, misleading, and deceptive, issued the preliminary injunction prohibiting advertisements containing these claims. In addition, Pharmtech signed a consent agreement prohibiting it from claiming, without substantiation, any health benefits for its products (724).

A similar case, brought against General Nutrition, ' Inc., was also concluded with a consent agreement (282). In 1984, General Nutrition was accused of making false and unsubstantiated claims about its products, in particular, one called "Healthy Greens." The company implied that findings of the National Cancer Institute, and American Cancer Society, and the National Academy of Sciences in the Academy's report, *Diet, Nutrition and Cancer, associated the product* with a reduction in cancer incidence. In February 1989, the company signed a consent agreement obliging them, among other things, to refrain from implying that the findings of those organizations support a finding that the company's products could reduce the risk of cancer; to stop advertising, packaging, promoting, or labeling its products as being able to cure, treat, prevent, or reduce the risk of disease in humans; and to pay $200,000 each to the American Diabetes Association, American Cancer Society, and American Heart Association for the support of research. The order also prohibits the company from making false claims about any other products, putting specific restrictions on the claims that could be made in advertising, labeling, and packaging of certain products. In addition, General Nutrition must make available, upon request from FTC, all materials used for advertising and disseminating information about its products, and studies used as the basis for claims it makes about its products (442).

U.S. Postal Service

Unlike FTC, *which has very broad* authority, *USPS jurisdiction* over *false advertising is limited* to mail *order products (where money* or *property is sought through the* mail) *under the civil False Representation Statute (39 U.S.C. § 3005). The* Postal Inspection Service investigates potential violations of section 3005. It reviews direct mail advertising, television commercials and a number of health and general publications for mail order health products for possible false claims. Another source of information is complaints from consumers and health professionals concerning such advertising.

Enforcement—Promoters who are investigated for false advertising through the mails have the right to an evidentiary hearing before an administrative law judge and may appeal any adverse decision to the USPS Judicial Officer, who then renders the final decision. Upon finding a violation under section 3005, the Judicial Officer may issue two orders: an order directing that all mail containing product orders addressed to the promoters be returned to the consumer and an order that the promoter cease and desist from similar advertising practices. Violations of cease-and-desist orders bring a $10,000 a day penalty for each day of violation (463).

Administrative proceedings, however, are necessarily time-consuming and USPS cannot issue any remedial orders until the process concludes. Therefore, Congress gave USPS authority to seek from a

U.S. district court judge an injunction detaining the promoter's incoming mail while proceedings are pending (39 U.S.C. § 3007).

In those cases where the product poses a serious health hazard or the claim is blatantly false, the Inspector may decide to present the case to the U.S. Attorney for criminal prosecution in Federal court under the Mail Fraud Statute (18 U.S.C. § 1341). Under this statute, a person who uses the mail in a scheme to intentionally defraud consumers may be subject to up to $1,000 in fines, up to 5 years in jail, or both, for each violation.

*Litigation Brought by USPS—During the 6-*month period from October 1, 1986 to March 31, 1987, the USPS concluded 34 civil actions dealing with claims for medical products and services (907). Some criminal cases have also been brought. In one recent civil case, promoters of what they call 35% "food grade" hydrogen peroxide (H_2O_2) were charged with misrepresenting their product as a cure for AIDS, cancer, alcoholism, Alzheimer's disease, and arthritis, among other diseases. In settling the case, the promoters agreed that the Judicial Officer could issue an order to stop their representing hydrogen peroxide as having a therapeutic effect on human disease and injury, unless claims could be supported by reliable and competent evidence (443).

Other Relevant Federal Statutes

There are several additional Federal criminal statutes that may affect the marketing and advertising of unconventional cancer treatments. Allegations of crimes are investigated and, if pursued, prosecuted by a U.S. Attorney where the crime allegedly occurred. They are usually based on either consumer complaints or recommendations of government agencies, such as FDA and FTC, who believe the crimes have been or are being committed.

The Federal wire fraud statute (18 U.S.C. § 1343) prohibits the use of telephone, radio, or television to make false representations for products and services in interstate or foreign commerce. Violation of this statute can lead to criminal penalties of fries up to $1,000, imprisonment for up to five years, or both. In one case, a woman in Salt Lake City, Utah, operated an organization called "Western Health Research" and the "Western Research Center." Patients who contacted her through a toll-free number were referred to a clinic in Mexico run by James Keller, and were given travel arrangements and appointments at the clinic. The clinic was eventually closed down by Mexican authorities, and the woman in Utah was indicted for interstate wire fraud (568).

The Federal smuggling statute (18 U.S.C. § 545) prohibits unlawful introduction of products into the United States. Possession of such products alone is sufficient for conviction under this statute; in addition, any such products are confiscated by the Government. Penalties for violating this statute include fines, imprisonment for up to five years, or both. In one case, *United States v. Richardson,* John Richardson, M.D., and three co-defendants (Ralph Bowman, his office manager, and Robert Bradford and Frank Salaman, two members of the Committee for Freedom of Choice in Cancer Therapy) were convicted of several crimes including conspiracy to smuggle laetrile from a clinic in Mexico into the United States (962). The defendants argued that FDA's classification of the drug, which prohibited its being brought into the country, was an act of governmental misconduct; they claimed their actions were justified because laetrile was unavailable but necessary in the United States. Their conviction was upheld on appeal (917). Bradford was freed $40,000, Richardson $20,000, and Salaman and Bowman $10,000 each (962).

The Federal conspiracy statute (18 U.S.C. § 371) prohibits "two or more persons [from] conspiring] to commit any offense against the United States, or to defraud the United States.' The statute authorizes frees up to $10,000, imprisonment for up to 5 years, or both. There are several examples of litigation where practitioners have been charged with conspiracy in connection with their involvement with an unconventional cancer treatment. For example, the defendants in *United States v. Richardson* were charged and convicted of conspiring to possess and distribute laetrile, and the defendants in *United States v. Durovic (the Ivy* case, see previous discussion) were charged with, but not convicted of, conspiracy (915,917).

Several Federal criminal fraud statutes have been used in cases involving unconventional cancer treatments. These statutes make it a criminal offense to deliberately falsify and conceal facts from the Federal Government (18 U.S.C. § 1001) or to deliberately present false claims to any agency or department of the Federal Government (18 U.S.C. § 287). These two statutes have been invoked in

prosecutions concerning false statements on claims submitted to Medicare and Medicaid by practitioners (see ch. 9).

The Federal Racketeer Influenced and Corrupt Organizations (RICO) Act (18 U.S.C. § 1961-1968) classifies a variety of criminal offenses, including bribery and welfare fraud, as racketeering activity. To date, no unconventional practitioners have been convicted of offenses under RICO (79 l). One suit in the complicated legal battle of Burzynski and his patients versus Aetna involves a RICO suit. In December 1987, in response to an insurance claim from a cancer patient for reimbursement of the costs for Burzynski's treatment, Aetna Life Insurance Co. filed a counterclaim against Burzynski and the Burzynski Research Institute, alleging that Burzynski planned to defraud insurers and patients, and engaged in a pattern of racketeering activity by forwarding misleading and deceptive claims for insurance reimbursement (630). This case is still pending (631) (see ch. 9).

State Regulation of Manufacturing and Marketing of Drugs

While Federal laws regulate the marketing and advertising of some unconventional cancer treatments in interstate commerce, State laws extend regulation to commerce within States (intrastate commerce). In addition, some State laws explicitly regulate intrastate use and possession of particular unconventional treatments.

In addition to prescribing any approved drug or device, licensed physicians may legally "manufacture, prepare, propagate, compound, or process drugs solely for use in the course of their professional practice" (21 USCA § 360 (a)). This means it is legal for physicians to prescribe treatments they manufacture that are unapproved by FDA, but only in the State in which they manufacture the treatments. It is illegal to transport unapproved drugs across State lines and laws pertaining to good manufacturing practices apply to physicians as well as to commercial medical manufacturers. However, treatments made from the patient's own tissues that are customized for each patient are not regulated under Federal or State laws; theoretically, this would include the Livingston-Wheeler autogenous vaccine (which is manufactured individually for each patient) (791). This section summarizes the scope of State regulation of marketing and advertising of medical products and services and discusses State laws that apply specifically to unconventional cancer treatments.

Stale Food and Drug Laws

Following the passage of the Federal FDCA in 1938 covering interstate activities, it was proposed in 1940 that all States adopt a uniform food, drug, and cosmetic law in order to provide the same coverage for intrastate activities (56a). To date, 23 States have adopted the uniform law, in whole or in part, in State laws regulating the intrastate manufacture, promotion, labeling, and distribution of drugs and devices. The uniform law uses nearly identical definitions for adulteration and misbranding of drugs as the FDCA, so any State law based on the uniform law is likely to have similar provisions for dealing with these issues.

One difference between the uniform law and the FDCA, however, is that the uniform act includes a provision against false advertising, which at the Federal level is split between the FTC and FDA. Another difference is that nearly all of the States that have adopted some form of the uniform act have a provision in their food and drug law that prohibits public advertising of any treatment as effective against certain conditions, including cancer. It is argued that justification for this prohibition was based on the assumption that certain diseases should be treated only by professionals and that public advertising of treatments available directly to consumers could encourage patients to treat themselves without professional care (526).

State Regulation of Advertising

In addition to the advertising provisions of food and drug laws that some of the States have adopted, all States have laws prohibiting false advertising of products and services. These State laws, whose provisions are similar to those of the FTCA, are enforced by each State's Attorney General.

One recent case involved United Sciences of America, a company whose advertising claimed its nutritional treatment could help prevent cancer. The Attorneys General of Texas, California, and New York filed suit jointly, charging the company with false advertising under their States' false advertising laws by making improper claims. Initially, the company advised its distributors of the actions against it, including an injunction barring it from

marketing and shipping its products without appropriate correction and disclosure statements and barring it from making false claims. Several months later, the case was settled when the defendants, without admitting fault, agreed to pay $35,000 to each State and refrain from making unproven and misleading statements about United Sciences products (68).

In another case, the State of California sued a company, Ancient Gold, also know as the Colostrum Research Foundation, for falsely representing that their product, colostrum, could inhibit the symptoms of cancer and other diseases. The company was sued in both criminal and civil State courts for violation of the State Food, Drug, and Cosmetic Act; the civil suit also sought an injunction to prevent the firm from making further false representations (85).

State Laws Pertaining to Cancer Treatment

In addition to State laws regulating intrastate commerce of drugs, at least 30 States have passed laws pertaining specifically to cancer, a few of which have provisions for regulating unconventional cancer treatments. overall, these cancer laws provide for a variety of activities, including organizing and providing resources to combat the disease, establishing registries and advisory boards, and assisting patients in paying for cancer treatment (279). Some of these laws specify that cancer can be treated only by certain categories of licensed health professional. Others authorize the State health agency to approve cancer treatments before they can be used in the State (791).

The oldest and most comprehensive State cancer statute is California's (149). This statute established criteria for cancer treatments similar to those of the FDCA and provided a mechanism for informing the public about treatments that are considered to be unsafe or ineffective. This law also incorporated regulations making it illegal to use certain unconventional cancer treatments, including laetrile and the Hoxsey tonic, within the State. Under this statute, James Privitera, a medical doctor, and four co-defendants were convicted by a jury of conspiracy to sell and prescribe an unapproved drug, laetrile, for the alleviation or cure of cancer, a felony (described above).[16] The law authorizes the State health agency to issue cease-and-desist orders to those who violate the State cancer law (see, e.g., ch. 5, discussion of the case of Virginia C. Livingston, M.D.). Failure to comply with these orders can lead to injunctions against the promotion of the treatments and to criminal penalties against the promoters.

Legalization of Specific Unconventional Cancer Treatments Under State Laws

In contrast to State laws that prohibit the use of unconventional cancer treatments, several States have enacted laws that specifically *exempt certain* unconventional treatments from State drug regulation and from some aspects of medical practice acts. These laws only affect the intrastate use of the substances, so they do not conflict with the interstate provisions of the FDCA. They may conflict, however, with the safety and efficacy provisions of State food and drug laws and with the objectives of the uniform national drug standards. These exemptions have not been challenged in court (791).

One State offered the following rationale for its provision legalizing the use of laetrile in cancer treatment:

> In a free society, people should be able to choose their own forms of treatment for disease as long as doing so does not expose them to harmful products. In other words, the safety of drugs needs to be assured by government but not necessarily the effectiveness of drugs. (665)

At present, at least 19 States have laws legalizing the prescription and intrastate sale of laetrile to cancer patients (2 other States had this provision but repealed it). Several States enacted (and later repealed) provisions legalizing the use of IAT Many of these laws require certain types of informed consent or limit the use of the substance to physicians. Some of the statutes prohibit State licensing boards from disciplining physicians who prescribe laetrile. Other laws protect manufacturers from penalties associated with the manufacture or distribution of the substance.

[16] The defendants appealed the conviction on the grounds that the right of the patient to obtain, or the physician to prescribe, a treatment was ensured by the 14th Amendment to the U.S. Constitution. After being overturned by the appeals court, the conviction was affiied by the California Supreme Court (see earlier discussion of case) (717).

SUMMARY

The laws and regulations discussed in this chapter fall into two categories. There are those that, at both State and Federal levels, have a major impact on the availability of unconventional cancer treatments because they determine whether a drug or treatment can be made available legally. Laws included in this category are the Federal FDCA, State Food and Drug laws, and Health and Safety Codes. These laws are the focus of controversy for the opposing sides of consumer protection and "freedom of choice" in medical care. The other regulations discussed in this chapter play a secondary role by monitoring available treatments, their promoters, and to some extent practitioners who offer them. Though they too have an impact, their effect on the users and practitioners of unconventional cancer treatments is never likely to be at the center of this controversy.

Chapter 11

Laws and Regulations Governing Practitioners Who Offer Unconventional Cancer Treatments

CONTENTS

Box

Chapter 11

Laws and Regulations Governing Practitioners Who Offer Unconventional Cancer Treatments

INTRODUCTION

The activities of practitioners who offer unconventional cancer treatments are regulated and monitored through several mechanisms. The most basic are licensing of physicians and other health professionals by each State and criminal prosecution of individuals who practice medicine without a license. This chapter discusses the laws and regulations governing licensed and unlicensed practitioners who offer unconventional treatments. It also describes the disciplinary actions taken against violators.

The authority to license and discipline health care practitioners is based on each State's legal responsibility to protect the public health, safety, and welfare (654,878,930). All State legal codes include acts that define the practice of medicine; stipulate the requirements for licensing health care practitioners; describe the conditions that can lead to disciplinary action against a licensed health professional; and specify the organization, membership, and function of licensing and disciplinary boards (448,872,878,930). In most States, the same body that grants medical licenses has the authority to order investigations of medical practices and to discipline doctors, but some States mandate separate licensure and disciplinary boards, the latter generally referred to as "medical boards" (295,448).

In addition to the States' involvement, professional peer groups also exert significant influence over the practice of medicine. Peer groups may publicly criticize practitioners, exclude them from referral networks, or discourage patients from consulting with practitioners whose standards differ from the norm, including practitioners of unconventional medicine (82,354). Professional associations may develop official positions on medical practice that influence their members. For instance, until recently, the professional code of the American Medical Association prohibited physicians from maintaining contact with "non-scientific" health care practitioners (e.g., chiropractors) (879). Though they are without legal standing, these professional peer activities may have the effect, similar to the *State's laws and regulations, of restricting* a *practi*tioner's professional activities.

Two other influences on the practice of medicine are the rules that govern hospital admitting privileges and the criteria for reimbursement from third-party payers. Hospital admitting privileges are generally given by the governing body of an institution, based on the recommendation of its medical staff (712), and can be revoked. For example, Max Gerson, M. D., who prescribed unconventional cancer treatments in the 1940s and 1950s, reportedly lost his hospital admitting privileges because of the treatments he offered. (See ch. 3 for more details.) In addition, reimbursement from third-party payers for unconventional cancer treatments may be limited or unavailable. Some practitioners cite these reimbursement policies as impediments to practice, since patients may have to discontinue nonreimbursed medical treatments (216). (See ch. 9 for a discussion of insurance and unconventional cancer treatments.)

Besides directly affecting physicians who offer unconventional cancer treatments, these limits on practice may also have an inhibiting effect on physicians who see some value in certain unconventional treatments, particularly in conjunction with conventional treatments, but fear being the target of sanctions. The prospect of being censured (formally or informally), prosecuted, or just identified negatively because of unconventional practices, might make it difficult for some practitioners to comfortably offer patients care they believe is beneficial to them if they believe their ability to practice medicine might be jeopardized (82).

THE PRACTICE OF MEDICINE

Though there is some variation among States, in general they agree on a broad definition of what constitutes the practice of medicine. (See box 1 l-A.)

Almost all States allow the "practice of medicine" by non-physicians in special circumstances, such as emergencies or in administering domestic (or prescribed) remedies to family members (50). Unlicensed practitioners may also be permitted to

Box n-A-States' Definition of the Practice of Medicine

The Federation of State Medical Boards of the United States defines the practice of medicine to include the following:

1. advertising, holding out to the public, or representing in any manner that one is authorized to practice medicine in the jurisdiction;
2. offering or undertaking to prescribe, give, or administer any drug or medicine for the use of any other person;
3. offering or undertaking to prevent or to diagnose, correct, and/or treat in any manner or by any means, methods, devices, or instrumentalities any disease, illness, pain, wound, fracture, infirmity, deformity, defect, or abnormal physical or mental condition of any person, including the management of pregnancy and parturition;
4. offering or undertaking to perform any surgical operation upon any person; and
5. using the designation Doctor, Doctor of Medicine, Doctor of Osteopathy, Physician and Surgeon, Dr., M.D., D. O., or any combination thereof in the conduct of any occupation or profession pertaining to the prevention, diagnosis, or treatment of human disease or condition (unless such a designation is in addition to the designation of another healing art (e.g., dentistry), for which one holds a valid license in the jurisdiction). (284)

practice medicine in the context of defined religious ministries. In some States, faith healers, Christian Science healers, and other clergy are specifically exempted from regulations that apply to health care providers. California, for example, exempts faith healers from licensure, as practitioners who "treat exclusively by prayer in accordance with the teachings of a bona fide religious sect or organization. ' If, however, faith healers combine prayer with other methods, such as diet, drugs, or massage, they would not be protected by the exemption and could be prosecuted for practicing medicine without a license (791). In one case, a minister in Arizona, Kenneth Lee Anderson, was prosecuted for practicing medicine without a license after he and a doctor of osteopathy treated patients with a substance called "Tumorex," the composition of which was undisclosed (51).

Licensure

Physicians must be licensed before they may legally practice medicine in the United States. State licensing laws identify the basic qualifications an individual must have in order to practice as a health professional, define the permitted scope of practice, and provide general standards of expected professional competence and conduct. Although requirements vary among States, in general, a person must be a graduate of an accredited medical school,[1] have completed 1 year of residency training in a program approved by the Accreditation Council for Graduate Medical Education,[2] and have passed the Federation Licensing Examination sponsored by the Federation of State Medical Boards. Osteopaths and allopaths are included in the definition of physicians; currently, about 500,000 allopathic physicians (M.D.s) and 25,000 osteopathic physicians (D. O. S), are licensed in the United States (711).

All States require periodic licensure reregistration. When reregistering, physicians may be required to inform the board of any administrative sanctions, adverse liability awards, or felony charges that occurred since their last contact with the licensing board. Physicians may also be required to report substance abuse, physical illness, or mental illness that may affect the competent and professional practice of medicine. The completeness of such reporting and its effects on reregistration are not documented. Approximately 25 States mandate continuing medical education as a prerequisite to reregistration (284a), and a few may soon require a periodic competency reexamination (703).

For physicians who offer unconventional cancer treatments, continuing licensure may present more difficulties than initial licensure. If these physicians receive administrative sanctions or an adverse ruling in a liability case, State law may mandate reporting

[1]The Liaison Committee on Medical Education is the accrediting body for educational programs leading to the medical doctor degree.

[2]In most States, physicians can become licensed after 1 year of clinical training following medical school, but six States require more postgraduate training and four require none (699).

of that information, possibly making license renewal more difficult.

The statutory scope of practice for licensed, non-physician health care providers (e.g., nurses, chiropractors, acupuncturists, naturopaths) is also defined within State laws, but there is variation among States in how these health care providers are regulated and whether licensing is required. Depending on the State, these health care professionals may legally provide psychological, spiritual, or other non-drug unconventional treatments (791). Homeopaths and naturopaths are licensed separately in the States where they are allowed to practice (791). However, the majority of licensed homeopaths are M.D.s or D.O.s who use homeopathic medicine as part of the medical care they provide (909).

The Practice of Medicine Without a License

Several practitioners of unconventional cancer treatments have been prosecuted for the criminal charge of practicing medicine without a license. In California, Milan Brych claimed to have received a medical degree outside of the United States, but was treating patients without having a State license. Brych was convicted on a number of charges, including practicing medicine without a license, grand theft, and grand theft by false pretenses (714). In another case, two health food store owners in Indiana, Harry Graham, a "nutritional therapist" and Ellen Graham, a registered nurse, treated a breast cancer patient with laetrile and colonic irrigations. The patient eventually died and the Grahams were tried and convicted of practicing medicine without a license, criminal recklessness, and involuntary manslaughter (438). In another California case, an unlicensed healer was prosecuted for treating a leukemia patient with lemonade, salt water, herb tea, special light therapy, and deep abdominal massage. The patient died as a result of massive internal bleeding, possibly as a result of the abdominal massage. The practitioner was convicted of practicing medicine without a license and the illegal sale of certain drugs. The initial conviction also included the charge of second degree murder but was later reversed because causation could not be established (715).

Some States are developing legislation that ***would*** restrict ***anyone except registered*** dietitians or physicians from counseling *patients* ***about*** nutrition, making it illegal for many nutritional advocates and non-physician practitioners to give nutritional advice (855). Some nutritional advocates have already been found guilty of practicing medicine without a license. Geraldine Matson, an unlicensed nutritional consultant, was sentenced to 40 hours of community service at the American Cancer Society after pleading guilty to practicing medicine without a license in Washington State. The Washington State Department of Licensing began an investigation of Matson after a physician reported that the employees of a local wig salon had given a cancer patient information on nutritional treatments. Two undercover agents posing as a cancer patient and her husband went to the salon, and were then referred to Matson. Matson was charged with practicing medicine without a license after advising the 'cancer patient" that she had scurvy and that she should ''discontinue chemotherapy because it would prevent nutritional therapy from working" (707,730).

PHYSICIAN DISCIPLINE

Because their practices fall outside of what is generally considered standard medical practice, physicians who offer unconventional cancer treatments may be particularly vulnerable to investigations for alleged violations of State or Federal laws, medical incompetence, or unprofessional behavior. A finding of guilt in these cases may result in frees, a jail sentence, or an injunction prohibiting whatever action is under investigation. Physicians may also be subject to administrative sanctions that directly affect their ability to practice medicine. Sanctions, ranging from license revocation to a private reprimand, are typically imposed by the State medical board.

This section describes the types of disciplinary action that can be taken against physicians. A discussion of all potential restrictions is beyond the scope of this section. Licensed physicians are emphasized, because, among the 50 States, requirements for licensure and grounds for disciplinary action are more uniform for physicians than for other health care professionals. Examples of sanctions against physicians who have offered various unconventional cancer treatments are highlighted.

[3]In this chapter, the term "physician" refers to both M.D.s and D.O.s.

Administrative Sanctions

States delegate to one or more boards, generally referred to as "medical boards," the authority to discipline physicians through administrative sanctions. Depending on State laws and the offense committed, possible disciplinary actions include revocation, suspension, limitation, or restriction of a physician's license; fries; private or public reprimand; letters of censure or concern; collection of the proceedings costs; mandatory competency testing; and additional training or education (284a). At times, informal disciplinary actions are used because of insufficient resources for full investigations, a backlog of current cases, or simply as an educational measure. Unlike formal sanctions, informal actions are often confidential matters between the medical board and the disciplined physician (872,878).

Other factors, such as the amount and type of evidence available in a case and the propensity of the medical board to pursue disciplinary actions, play a role in determining the kinds of sanctions administered (872,878). In addition, the magnitude of sanctions varies. For example, the maximum length of a suspension may be 75 days, 2 years, 5 years, or indefinite, depending on the State (284a).

Typically, physicians are disciplined for "unprofessional conduct' or 'professional incompetence. These terms cover violations of a physician's ethical and legal responsibilities, such as cheating on a licensure exam, conviction for a felony, fraudulent licensure application, sexual exploitation of patients, abuse of drugs or alcohol, or "making untruthful or exaggerated claims relating to professional excellence or abilities" (872). Other actions, such as fee-splitting,[4] overcharging, or reimbursement fraud can also lead to disciplinary actions (872).

Often, physicians who believe they have been unfairly disciplined may appeal to another State committee or to a court of law. All States provide physicians with some recourse to have administrative sanctions that have been imposed on them reviewed by another body (70 Corpus Juris Sec. 51). Some unconventional cancer practitioners who have received administrative sanctions have had their sanctions lessened after administrative review (see discussion of Revici case below).

Though the total number of physicians disciplined has increased since 1982 (the number rose from 953 in 1982 to 1,381 in 1984), it is still not high (878). Factors contributing to the relative rarity of disciplinary actions include inadequate economic, a administrative, and investigative resources; insufficient personnel; and the high standard of evidence required. In addition, the opportunity for disciplined physicians to sue peer review organizations, medical boards, and their members for antitrust violations and defamation of character or discrimination discourages physicians from reporting instances of possible misconduct by other physicians (242,878). States and the Federal Government have enacted laws which, under certain conditions, protect physicians from these lawsuits (448). Whether these laws have contributed to the recent increase in the number of disciplinary actions is not known.

Administrative Sanctions Against Physicians Using Unconventional Cancer Treatments

It is possible that disciplinary boards find it easier to initiate or act on charges of alleged incompetence against a physician who offers unconventional cancer treatments than against a mainstream practitioner, because many unconventional treatments are considered to fall clearly outside of standard medical practice. In addition, the circumstances under which an unconventional cancer treatment is administered are often important in determining the grounds for disciplinary action. For instance, several physicians have been cited for administering experimental treatment without a protocol or for failing to obtain proper informed consent from patients (103,195,437).

Members of the unconventional cancer treatment community have claimed that medical boards are more persistent in the discipline of unconventional than conventional physicians (216). According to Cassileth, 3 percent of the 83 physicians (M.D.s) she surveyed who offered unconventional treatments had had their licenses suspended for "reasons related to their unorthodox practices' (177). However, the Federation of State Medical Boards does not make available to the public detailed information such as the number, type, and causes of disciplinary action taken against physicians who offer unconventional cancer treatments. Thus, it is not possible to estimate accurately the number of physicians using

[4]Fee-splitting involves one physician receiving a percentage of another practitioner's fee in payment for having referred the patient to the second practitioner.

unconventional cancer treatments who have been involved in some type of disciplinary proceeding.

Charges against physicians who prescribe unconventional cancer treatments have included gross negligence, gross incompetence, negligence and incompetence on more than one occasion, unprofessional conduct (e.g., willful violations of laws, or inadequate recordkeeping), and practicing fraudulent medicine (this can include misrepresenting their ability to cure a patient of an illness). Grounds for these charges include: use of unapproved drugs (e.g., laetrile) (103,195,437); use of unapproved substances for the treatment of cancer (e.g., Hoxsey herbs, wheatgrass juice, and pangymic acid) (832); and maintaining inadequate patient records (214,923).

Examples of efforts to discipline physicians for such violations follow. These cases reveal the complexity of disciplinary hearings.

Stanislaw Burzynski, M.D.—Besides being involved in court battles described in earlier chapters, Stanislaw Burzynski is the subject of an investigation by the Texas Board of Medical Examiners for possible violations of the Texas Food, Drug, and Cosmetic Act, which prohibits the prescribing of drugs not approved by FDA or, alternately, by the State Department of Health. The board argues that this, in turn, is a violation of the Texas Medical Practice Act. A date for a hearing, the next formal step, has not been set (as of May 1990); motions to dismiss submitted by Burzynski's attorney have been rejected. If the board finds Burzynski in violation of these laws there is a broad array of sanctions it may impose on him (458,790).

Michael Gerber, M.D.—This case was initiated by an independent oncologist who treated a former Gerber patient in her terminal phase, when her uterine cancer had metastasized widely. The central issue in this case was Gerber's unconventional treatment of the patient when she was first diagnosed. The oncologist believed that Gerber, while practicing as a self-described "orthomolecular practitioner," inappropriately treated a potentially curable patient for 27 months with Hoxsey herbs, megavitamins, chelation therapy, Wobe Mugos enzymes, Chaparral tea, pangymic acid, benzaldehyde, wheatgrass juice, coffee or enzyme enemas, apricot pits, red clover, and slippery elm (832).

Gerber contended that he was not attempting to treat the patient's cancer, but rather to nutritionally and metabolically support a patient who had refused conventional treatment. The Board dismissed that assertion because the witnesses for Gerber testified that the above substances typically were used because they were believed to be "cancer inhibitors. The Board did not find convincing the testimony about the nutritional and metabolic value of any of these treatments for a patient with endometrial cancer (832).

The Board agreed with the State's expert witnesses that with immediate conventional treatment, the patient would have had a 90 percent chance of long-term survival. The Board found that Gerber:

> . . . should have known and recognized that surgery and/or radiation treatment were the recognized, effective, and sole medically acceptable means of treatment of adenocarcinoma of the endometrium, according to the standard of medical practice in California. (832)

Further note was made that the patient apparently canceled a scheduled surgery several days after first consulting Gerber, and although he documented in her chart that she was being treated by several other unconventional practitioners, he did not record that he suggested she seek conventional care. The Board wrote:

> The accepted standard of medical practice for a patient [presenting] with a well-differentiated adenocarcinoma of the endometrium, and who adamantly refuses conventional accepted treatment therefore, is: 1) continuously and emphatically to encourage the patient to seek conventional treatment; 2) strongly discourage any patient attempts to seek out unproven modalities . . ., and 3) not to undertake courses of unproven treatment and/or substance use, because these have the effect of lulling patient fears or misleading her to conclude that effective cancer therapy is in progress. It was established and it is found that such activity falsely reassures cancer patients concerning their prognosis and discourages them from seeking effective and timely treatment. (832)

With no previous offenses noted, Gerber's license to practice in California was revoked in June 1984. The Board of Medical Quality Assurance found him guilty of gross negligence and incompetence, repeated similar negligent acts, and other similar charges. The finding of guilt was due, in part, to his use of substances unapproved by either State or

Federal authorities for the treatment of cancer, and excessively prescribing and administering diagnostic tests and ineffective drugs and treatments (832).

Emanuel Revici, M.D.—Emanuel Revici has been the subject of prolonged controversy because of his unconventional treatment for cancer. Professional societies and health authorities in New York State, where Revici practices, began questioning his treatments more than 20 years ago; however, an official investigation was completed only recently. Revici's medical license was officially suspended in 1984 (for a short time) in response to New York State Department of Health charges of medical misconduct including practicing medicine fraudulently, practicing with gross incompetence, practicing with gross negligence, and substandard practices of these types on more than one occasion.

A committee of the New York State Board for Professional Medical Conduct, referred to as the hearing committee, initially held hearings on Revici's medical practice for a total of 19 days between January 1984 and May 1985 (923). While investigation into the charges proceeded, Revici continued his unconventional cancer treatment practice under specified conditions. During the investigation, Revici agreed to:

1. ***only treat patients for cancer if they had an established "outside" diagnosis (including a pathology report);***
2. ***provide fully informed consent (including the recommendation that patients consult a trained oncologist); and***
3. ***manufacture or administer any "experimental drugs or substances" in accordance-with State and Federal laws. (666)***

In September 1985, the hearing committee completed its initial investigation and found Revici guilty of gross incompetence, gross negligence, negligence and incompetence on more than one occasion, violating a particular Rule of the Board of Regents, and unprofessional conduct. In particular, the committee cited Revici's attempts to dissuade at least two patients from seeking conventional cancer treatment, treatment of at least three patients with agents unapproved for the treatment of cancer, maintaining inadequate patient records, "willful violation of laws regarding unapproved agents," and "fail[ure] to realize that his method was not effective' in the treatment of cancer. The committee found that Revici produced 'no persuasive evidence that [his] ***method for treating cancer is effective or that it benefited [patients]. " However, they specifically reported that Revici did*** *not* promise patients ***that*** his ***treatments would cure cancer (grounds for "misrepresentation,' another basis for license revocation) (923). In November 1985, the New York State Commissioner of Health joined the committee in recommending to the New York State Board of Regents that Revici's medical license be revoked (923).***

In March 1986, however, a separate Regents Review Committee recommended that the case be remanded to the hearing committee because Revici's original attorney was suffering from the strains of terminal disease during his defense, and Revici's right to council (guaranteed by the Sixth Amendment) may have been compromised. The hearing committee met again in August 1987 but Revici and his new lawyer chose not to attend because they felt the hearings were a sham and that 'no valid purpose would be served by continuing or participating in hearings before OPMC [Office of Professional Medical Conduct]" (923). By refusing to attend, Revici lost his opportunity to introduce new evidence and witnesses, and present further defenses to the OPMC's charges. The hearing committee noted this, and then reaffirmed their original recommendation of September 1985 (923).

In March 1988, Revici and his lawyer submitted additional information and testimony directly to the Regents Review Committee. Although the review committee ruled that Revici "may not obtain a de novo hearing before us and thereby bypass the statutory hearing process, " they did review the record from the hearing committee's proceedings. On June 27, 1988, the Regents Review Committee issued a report in which they accepted many, but not all, of the original findings of the hearing committee. Some modifications were made to the original findings, but overall, the committee felt that Revici's practices endangered his patients and found them "far below the legal standards required of a licensed physician.' The Regents Review Committee emphasized that the charges against Revici were "based on specific acts and violations' and were not brought against him for "engaging in research or writing about new, non-traditional methods for treating cancer" (923). This committee found Revici guilty of the charges and unanimously recommended in June 1988 that his license be revoked for at least 1 year beginning October 1, 1988 (923).

On July 29,1988, the New York Board of Regents accepted the Review Committee's modified findings of guilt, but decided in a 4 to 3 vote (with 2 abstaining) to mitigate the committee's recommended measure of discipline. Revici's medical license revocation was stayed and he was placed on probation for 5 years (921). During his probation, Revici is allowed to continue practicing medicine under specific terms, similar to those agreed to while his license was under investigation (922).

Medicare Sanctions Against Providers of Unconventional Cancer Treatments

Another avenue for regulating physician's activities is through the Medicare program. Under the Social Security Act, the Department of Health and Human Services (DHHS) is authorized to impose administrative sanctions on providers who defraud or abuse the Medicare program (414). DHHS delegates this authority to the office of the Inspector General. Some providers of unconventional cancer treatments have been among those excluded from the system because their services have not met the program's requirements. Medicare sanctions may include temporary or permanent exclusion from Medicare payment, or the imposition of monetary penalties if it is demonstrated that the provider:

1. *overcharged Medicare for services;*
2. *deliberately misrepresented on Medicare claims the services that were rendered; or*
3. *deliberately provided services that were either* in excess *of* patients' needs *or of* poor quality (substandard), as judged by local professional standards.

When monetary penalties are imposed, practitioners wishing to remain eligible for future Medicare payments must reimburse the Medicare program for the previous overcharging or inappropriate payments (414,876).

heal insurance carriers and Utilization and Quality Control Peer Review Organizations (PROs),[5] under contract to DHHS, monitor medical care provided to Medicare beneficiaries, identify possible violations, and recommend disciplinary action to the Inspector General's Office (878). Unless a practitioner's actions immediately threaten patient well-being, PROS initially impose remedial actions, such as a requirement of further education or warnings, before recommending that the Office of the Inspector General exclude or suspend the practitioner (221,872). PROS may consider a variety of factors when determining the severity or duration of the disciplinary sanction they propose, such as other related offenses, any adverse impact a sanction may have upon Medicare beneficiaries or the community, potential savings to the program, and the amount of financial damage incurred by the Medicare program (221). Professional sanctions are reported to the public through local newspapers and are also reported to State licensing boards.

Of the almost 500 practitioners excluded participating in Medicare between 1982 and 1988 (547), at least 6 were excluded for practices related to their prescribing of unconventional cancer treatments.[6] Two examples of such actions are summarized below.

The late Virginia Livingston, M.D., a physician who developed and prescribed an immunologic unconventional cancer treatment (discussed in ch. 5), was originally excluded from Medicare beginning on March 29, 1986, for providing care that was considered by the Office of the Inspector General to be both substandard and substantially in excess of patient needs. Livingston argued that her treatment was experimental and therefore not substandard; however, the judge found insufficient compliance with a study protocol and informed consent procedures to allow that interpretation. On appeal, however, the judge found that while the evidence showed Livingston's treatment was not recognized as standard practice by the medical community, it was of a unique nature and should be regarded as "nonstandard" rather than "substandard." He determined that too little was known about the treatment to find that the services she provided were either substandard or substantially in excess of her patients' needs, and he overturned the exclusion. He found also that the Inspector General's Office was remiss in both apprising Livingston of the seriousness of the charges and nature of the perceived offenses and in making educational visits before imposing sanctions. Livingston became eligible to

[5]PROs are used by DHHS to monitor the care hospitals and their physicians provide to Medicare patients in order to ensure that services are medically necessary, provided in the appropriate setting, and meet professionally recognized standards of care (872).

[6]Virginia C. Livingston, M.D., William Goldwag, M.D., John Potts, M.D., James Privitera, M.D., Donald Cole, M.D., Victor Bagnall, M.D. (791).

reapply for reimbursement status under Medicare in 1987 (444).

Another practitioner of unconventional cancer treatment, Donald Cole, M.D. was excluded from Medicare reimbursement for 5 years beginning in 1983. Medicare's carrier in New York State originally identified Cole's cancer treatments as "nonstandard" and referred the case to the Inspector General's Regional Office. A local PRO convened a review panel of three practicing oncologists. After reviewing Cole's patient records, the panel reported that his medical care did not meet the professionally recognized standards of cancer treatment in that community. They specifically noted that Cole was administering standard chemotherapeutic agents in an inappropriate regimen (low-dose, high-frequency), along with laetrile, dimethyl sulfoxide (DMSO), vitamin B12, and mixed respiratory vaccines. The panel of oncologists found that the services furnished in every case reviewed were substandard and clear threats to the health of the patients (791).

Of the four other practitioners, three were excluded from Medicare for periods of time ranging from 3 to 10 years for providing services in excess of the needs of patients and providing care that does not meet professionally recognized standards. The fourth was excluded from Medicare because he was convicted of illegally manufacturing, distributing, prescribing, or dispensing a controlled substance (706).

COMMON AND STATUTORY LAWS AFFECTING PRACTITIONERS

The activities of physicians and others who provide unconventional cancer treatments may also be regulated through the application of common law or general State laws. Common law is law made by courts and judges, as opposed to statutory law which is passed by a legislative body. Usually, when one private citizen sues another, the basis for the lawsuit arises from common law. Only a State or the Federal Government may criminally prosecute an individual for violating statutory laws, and only a criminal prosecution can result in a jail sentence (791).

Criminal Charges

A typical criminal charge against practitioners of unconventional cancer treatments is the practice of medicine without a license. As described earlier, at least one unlicensed physician and several nonphysicians have been convicted on this charge in the context of unconventional cancer treatments. Other criminal charges may include murder, fraud, grand theft, involuntary manslaughter, or criminal recklessness, also in the context of unconventional cancer treatments.

Bruce Halstead, a practitioner of unconventional cancer treatments, has been convicted of multiple criminal charges. In 1986, after 3 years of investigation by the California Board of Medical Quality Assurance and the resolution of several complex international and interstate legal issues, Halstead's medical license was permanently revoked and he was convicted of several criminal charges. Halstead used an unconventional treatment called Agua del Sol (ADS) to treat patients with cancer and other chronic diseases. ADS has been described as a homeopathic herbal treatment[7] consisting of mulberry, hydrangea, and poppy, that is reportedly incubated in outdoor tanks containing water and bacteria. The ADS administered to Halstead's cancer patients had been manufactured in Costa Rica, shipped through Japan, and then purchased through a distributor in the United States (371).

The charges brought against Halstead under California's Penal Code and Health and Safety Code originally included:

- *conspiracy to cheat and defraud by false pretenses;*
- *false advertising of a drug;*
- *falsely advertising a drug to have an effect upon cancer;*
- *selling and offering for sale an adulterated drug;*
- *selling and offering for sale a misbranded drug;*
- *grand theft by false pretenses;*
- *unlawfully selling drugs or compounds for the alleviation of cancer; and*
- *fraudulently providing treatment as being effective in treating cancer. (371)*

Unassisted by an attorney for much of the litigation, Halstead relied on the testimony of his patients, family, friends, ministers, and colleagues.

[7]However, ADS and two of its components are not listed in the *Homeopathic Pharmacopeia*, making this description inaccurate (909).

A special "Hearing Report," submitted on his behalf by the National Center for Institutions and Alternatives, urged that only a probationary sanction be issued. Halstead, who denied wrongdoing, asked to be allowed to continue practicing medicine under terms of probation, or community service, or both. He maintained that in prescribing ADS, he "followed [his] own deep scientific, conscientious convictions [and]. . . did everything in [his] power to attempt to save the lives of [his] patients" (371).

However, at the sentencing hearing, the probation officer assigned to the case testified that the current charges against Halstead were not isolated incidents. Halstead had been called before the Board of Medical Quality Assurance in the past, his license had been suspended at least once, and he had previously been placed on probation. This history, combined with the probation officer's finding that Halstead "shows little or no remorse for his . . . crimes,' led to the conclusion that unless his license was revoked, Halstead would continue to prescribe unconventional treatments. In addition, the probation officer noted that Halstead 'used his position of trust, as a physician" to sell unconventional treatments to terminally and chronically ill patients. He recommended that Halstead "be removed from the community for as long a period of time as is legally possible" (371). The court found Halstead guilty of 20 felonies and several misdemeanors. In addition to the permanent revocation of his medical license, he was sentenced to 4 years in prison and fined $10,000 (372).

Civil Charges

Because their practices fall outside of standard medical practice, physicians who offer unconventional cancer treatments are vulnerable to the civil charge of malpractice. Suits can be brought by former patients and their relatives. The basis for malpractice is the physician's negligence in fulfiling professional duties, such as selecting the best treatment for the patient; informing patients about the treatment effects; determining the correct dosage for the treatment; storing, preparing, or using the treatment; warning the patient about possible adverse reactions; monitoring the patient's needs and changing dosages or treatments as the condition warrants; and providing appropriate informed consent (791). Emanuel Revici recently lost a medical malpractice case brought against him in Federal District Court involving a patient with a rectal tumor, who was under his care for 2 years before dying. This case, Boyle v. Revici, *was brought by the nephew of the deceased patient. The jury found in favor of Boyle and awarded him $1.5 million. Revici is appealing the verdict on evidentiary grounds.*[8]

Surviving family members also may sue a practitioner for loss of support caused by death under a "wrongful death' theory. Oftentimes, the allegation of wrongful death is combined with a "survival action, where the surviving family member sues on the deceased's behalf for pain and suffering sustained before death. In civil suits, plaintiffs may request financial compensation for economic losses or for emotional damages. In some cases, punitive damages also may be awarded (791). Organizations, such as third-party payers, may also bring civil charges. When Medicare and other third-party payers act as plaintiffs in civil litigation, they often sue practitioners for fraudulent insurance claims (631). (See ch. 9 for a discussion of insurance coverage for unconventional treatments.)

Some physicians have defended their use of unconventional treatments by arguing that patients, when fully informed about the treatment, its alternatives, and attendant risks, may legally assume some of the risk inherent in receiving the treatment. In at least one case, Schneider v. Revici, *a Federal Appeals Court found this argument valid and suggested that it may alleviate or diminish the physician's liability for negligence. The Federal court has remanded the case to the original trial court for consideration of whether the consent agreement signed by the patient constitutes an assumption of risk. It was set to be retried starting in November 1989 (631), but was postponed (70). (See ch. 10 for discussion of the case.)*

[8]Under what is called the "dead man's statute" in New York State, a recounting of conversations between the decedent and the defendant is inadmissible as evidence. Revici is appealing the judge's application of that statute to this case (150).

Chapter 12

Evaluating Unconventional Cancer Treatments

CONTENTS

Chapter 12

Evaluating Unconventional Cancer Treatments

INTRODUCTION

Chapters 2 through 6 of this report provide information about a variety of unconventional cancer treatments. To the extent possible, the composition of treatments and the ways in which they are used were described, the rationales and theories provided by their supporters discussed, and the evidence available concerning their effects on cancer patients presented and critiqued. In these treatment "portraits," there are pieces of information, ideas, various fragments that some might find provocative, or suggestive of a worthwhile approach, and other pieces suggesting that a treatment is groundless.

This report undoubtedly will be used selectively by individuals wishing to portray various points of view, in support of or in opposition to particular treatments. The reason this is possible is that, by and large, the treatments have not been evaluated using methods appropriate for actually determiningg whether they are effective. No amount of digging through descriptive information, theoretical discussions, laboratory tests, or individual case histories of exceptional patients can adequately answer the question of whether the treatment works—whether it prolongs or otherwise improves life, or affects a cure. The background information is useful, vital in some cases, to move the process to the point of evaluation. However, regardless of the nature of the treatment or of its intended effects, in the final analysis, except for those treatments whose effects are dramatic, gathering empirical data from clinical trials in cancer patients using valid, rigorous methods is the only means for determiningg whether a treatment is likely to be of value to cancer patients in general or to a class of patient. This fact is as true for unconventional as it is for mainstream treatments. For none of the treatments reviewed in this report did the evidence support a finding of obvious, dramatic benefit that would obviate the need for formal evaluation to determine effectiveness, despite claims to that effect for a number of treatments.

Pursuit of evaluation by practitioners and supporters varies considerably among the wide range of treatments covered in this report. As portrayed by members of the project Advisory Panel, it may be proponents of the "middle ground" (mainly psychological, behavioral, and dietary approaches used along with mainstream treatment) who would be most interested in testing and refining their treatments, but who apparently find the current system for doing so unsupportive (8). An additional difficulty is posed by the different orientations of evaluation in the social sciences (a source of middle ground approaches) as opposed to medicine. The former rests on a stronger belief in inference based on nonexperimental situations, though the methods have not generally been used to study medical endpoints such as life extension. A concomitant rejection of some experimental methods, particularly randomized trials, for psychological or multifaceted approaches for cancer patients by some psychological practitioners and researchers (7) is one of the factors that has led to relatively little mutually acceptable evaluation.

New evaluation methods, including any adapted from social sciences, should they be developed and validated, would apply equally to unconventional and mainstream treatments. That remains for the future, however.

This chapter ***discusses*** approaches ***to*** acquiring valid ***information about the efficacy and safety of unconventional cancer treatments, including some approaches for dealing with the practical problems of carrying out evaluations.***

THE NEED FOR EVALUATION

There is a demand on the part of cancer patients for information about the safety and effectiveness of unconventional treatments to validate the claims made for them. If they are contemplating spending time and money, and forgoing other options at a critical time in their lives, they want to know whether a treatment is likely to work for them. Many practitioners and their supporters believe that the information that exists already, the fragmentary evidence presented in this report, is sufficient, and do not pursue evaluating their treatments in a way that would produce valid evidence. Lack of development and evaluation through mainstream science, however, is axiomatic of unconventional treatments (with the possible exception of "middle ground"

approaches). Presumably, valid evidence from evaluations would either cause treatments to become accepted by mainstream medicine (if the treatment is effective) or to be abandoned once and for all (if the treatment is ineffective).

Individuals knowledgeable about unconventional treatments have their own explicit or implicit criteria, based at least partly on intuition, for choosing among unconventional cancer treatments (e.g., Ironer differentiates by such factors as the training of the practitioner, whether the treatment is completely "open' or has "secret' components, whether the charge for treatment is "reasonable, ' what claims are made regarding outcomes (530)). Other people have other approaches (e.g., McGrady's CANHELP computerized data bank (594)), and since every treatment has its adherents, there clearly must be conflicts among the lists of "good" and "bad." Without formal clinical research, however, it is not possible to get beyond this unsatisfactory status quo.

On a more pragmatic level, evaluation may also be important for legal and financial reasons. For unconventional cancer treatments that involve substances that would be classified as new drugs or biologics, evidence of safety and efficacy (and formal approval by the Food and Drug Administration (FDA)) are required before they may be offered legally in this country. In general, acquiring this evidence entails carrying out a series of prospective clinical trials, including randomized trials. For unconventional cancer treatments that do not involve substances that require FDA approval, e.g., psychological, behavioral, or dietary approaches, no regulatory requirement applies. However, health insurers may require evidence of efficacy and safety as a condition for covering those treatments. Evaluation may also be of benefit to health care professionals who are incorporating "middle ground" treatments into their practices, but who fear professional sanctions for doing so (218).

MAINSTREAM EVALUATION OF CANCER TREATMENTS

Legal approval and widespread ***use of medical drugs and biologics, and, ideally, the adoption of new medical practices, are based on evidence of efficacy and on knowledge and acceptance of adverse effects. A decision about whether to use a product requires weighing the risks against the benefits. In the ideal system, medical treatments do not become part of standard practice until adequate evidence exists. The system has not worked perfectly. There are probably many ineffective treatments, for cancer and for other conditions, that are believed effective on the basis of inadequate evidence. Some of these are being reexamined in new clinical trials, and the process of updating and weeding out treatments is likely to continue.***

Extension of life and improved quality of life are the hallmarks of a successful cancer treatment. Tumor shrinkage (antitumor effect) is an intermediate endpoint that is easier to study than is life extension, and is regarded as good evidence on which to proceed to studies that can measure life extension and quality. All conventional cancer treatments known to extend life thus far do, in fact, have antitumor effects, but some treatments with strong antitumor effects do not appear to be beneficial in the long term. It is important, therefore, that promising treatments eventually be studied directly for life extension and quality of life in randomized trials (discussed later in this chapter).

Before new cancer treatments are given to patients for clinical testing, in the current mainstream approach to evaluation, extensive "preclinical" laboratory and animal studies are carried out to establish a reasonable presumption that an agent might ultimately be of value to cancer patients. Both natural and synthetic agents are normally screened and tested in various animal tumor models (323,351). Preclinical studies are used to determine whether the compound is active against cancer cells, to attempt to learn about mechanisms through which the agent has its effects, to learn as much as possible about adverse effects, and to estimate the doses that might be tried in patients.

Screening and Preclinical Testing of Potential Anticancer Drugs

Until recently, the ***most common type of primary screening test*** for botanical products (and other substances) involved the ***use of*** tumor-bearing rodents—mice ***or rats with tumors that arose and were maintained in inbred strains. (Examples of such systems include P388 leukemia, L1210 leukemia, B16 melanoma, Lewis Lung carcinoma, Ehrlich ascites, Walker 256 carcinosarcoma, and Sarcoma 180 tumor models.) Generally, these animals would be treated with a range of doses of an***

experimental agent. An antitumor effect would be indicated by an increase in survival of the experimental animals compared with the untreated control animals. Cytotoxic (cell killing) or cytostatic (blocking further cell division) effects are measured in some of these tumor models, while others measure immunologic responses of the host animal to the experimental agent.

The National Cancer Institute (NCI) once used the L1210 mouse leukemia tumor model (from 1956 to 1971) and the P388 lymphocytic leukemia (from 1971 to 1985) as primary screening tests for new antitumor agents (841). Agents that tested positive in these tests were generally tested further in animal systems[1] before being considered for human trials. Those that tested negative might have been retested in the same or similar systems a number of times. For botanical products, such retesting might have involved the use of different parts of the original plant, different dose ranges, or different ways of administering or preparing the experimental solution.

Animal tumor tests can generate information about a new agent's biological properties, e.g., its immunologic and pharmacologic effects, in a whole animal system. The usefulness of such data depends on the degree to which they predict corresponding effects in human beings. The information gained from animal tumor tests can be used to select agents for clinical testing in human beings.

The limitations of animal tumor tests are well known. Their results do not necessarily correlate with results in human patients with cancer, although the degree of correlation varies with the type of test and the type of human cancer. There are many examples in which the response in an animal tumor system failed to predict a similar response in humans, in addition to examples in which animal results correlated closely with clinical responses. One way around this problem has been to use a variety of different tests to study each new agent. In general, the greater the number of animal tumor systems that show antitumor responses to a drug, the greater the chances that the drug will be active in humans. Activity in only one or two animal systems tends to correlate with little chance of activity in humans (99).

In 1985, NCI discontinued the use of animal tumor systems for routine, primary screening testing, in part because of these problems. In their place, a test system of human tumor cell lines grown in culture is currently being setup for initial screening of possible antitumor agents. The new system focuses on identifying substances that maybe active in specific tumor types. Substances that test positive in this new system would then be tested in human tumor-bearing athymic (nude) mice, and then in other whole animal systems for toxicology testing as a final step before use in human subjects (2,841).

Clinical Trials of New Anticancer Agents

"Phase I" clinical trials are often the first *time new anticancer treatments are given to human beings (except in cases in which new treatments for cancer have been used for other purposes). Patients with very advanced cancers, with virtually no hope of recovery, are asked to participate in these trials, as investigators attempt to determine appropriate dosages and learn about unwanted toxic effects, as well as to look for evidence of anticancer effects. These trials involve relatively few patients, usually in the range of 15 to 30, who are observed intensively.*

Phase II studies serve the purpose of generating information about antitumor effects and additional information on unintended adverse effects. These studies span a rather wide range, initially often including a number of different tumorsina"screening" study to see if any tumor types are particularly sensitive to the treatment, progressing to phase II studies focused on one or a small number of tumor types (phase III studies, if eventually undertaken with a particular agent, almost always include only a specific tumor type).

Patients eligible for phase II studies generally have advanced cancers and no available proven treatment options. Often, these patients already have had surgery, radiation, several different chemotherapy regimens, or a combination of these treatments. Anywhere from 15 to 30 or so patients are generally enrolled in single arm phase II studies, but they may include more patients. Accurate information about patients' clinical status and the status of their tumor (quantitative measurements) are obtained at the start of the trial, and patients are reassessed at specified intervals to determine changes in their status. While

[1]Animal tumor models commonly used for secondary testing include spontaneous or carcinogen-induced tumors (autochthonous tumor systems) or human tumors transplanted into athymic (nude) mice. These tests are considered impractical as primary drug screening tests.

survival data and 'quality of life' information may be recorded, without a control group the analysis of the information can only suggest that either the treatment has a positive effect, no effect, or a negative effect.

The vast majority of phase II studies are "single arm" studies, that is, they have no control groups, but they can be of other designs. It is the endpoints, not the design, that cast a study as phase I, II, or III. Several randomized phase II designs are available (see e.g., Carter, 1984 (172)). Once an agent has shown promise in phase II studies, a phase III study may be planned.

Phase III studies are designed *to measure the efficacy of treatments in prolonging life, in prolonging the time before disease recurrence ("disease-free survival"), or both, the effect on quality of life, and adverse effects. It is necessary to go beyond a phase II finding of antitumor properties because those properties do not always lead to life extension or improved quality. In the longer term, responses to these agents may be transient, conferring no survival benefit, and they may have serious toxic side-effects that could actually lead to premature death. Phase III clinical trials are typically randomized, and should be large, including at least hundreds of patients, preferably thousands. For agents that are moderately beneficial-e.g., producing a 10 percent increase in long-term survival--one randomized trial of typical size is generally considered insufficient proof, and the trial is replicated at least once before the results are considered sufficiently proven.*

ISSUES IN EVALUATING UNCONVENTIONAL CANCER TREATMENTS

The same principles of evidence apply to unconventional as to conventional treatments. The need ultimately for unbiased clinical trials, in all likelihood randomized clinical trials, is not obviated by any factor specific to unconventional treatments. In general, appropriate methods exist for evaluating all types of treatment, but the organization of clinical trials involving unconventional treatments may differ significantly from those in the mainstream, and the importance of various endpoints may differ as well. These issues are discussed below.

Endpoints

The aims of unconventional treatments and the claims made for them by practitioners or their supporters may include regression of tumors and improvements in survival, which correspond closely to the aims of mainstream cancer treatments. Another strong vein, however, relates to attempts to improve the quality of cancer patients' lives, e.g., general medical status, pain levels, activities of daily living, mood or emotional state, sleep patterns, medication use, rehabilitation status, stress management skills, self-esteem, abstract criteria (e.g., sense of purpose, meaning, belonging, inner strength), and nutritional status (7). While mainstream cancer researchers have begun incorporating quality of life assessments into clinical trials of conventional cancer treatments, few treatments in the mainstream are developed and tested specifically for their ability to enhance the quality of cancer patients' lives in the absence of direct antitumor effects. In most cases, a concern is that mainstream treatment, even if effective, may cause short-term or permanent changes leading to an impaired quality of life.

A variety of scales has been developed for assessing aspects of quality of life, both for cancer patients specifically and for general use (941). These have been applied in various types of psychological research, though not generally in clinical trials of interventions designed to enhance the quality of cancer patients lives. This is an area in which collaboration between researchers familiar with quality of life measurement and clinical trials experts is needed.

Organizational Issues

Regardless of the type of treatment or the context in which it is given, the aim of evaluation is to provide unbiased information about its effect on cancer patients. In this sense, the inferential basis for determining effectiveness will always be the same: is the patient better off with the treatment than without, all other things, on average, being equal. The way this comparison is achieved may need to be somewhat different for some unconventional treatments than is customary for mainstream treatments.

For treatments following the "medical model," those that consist of drugs or other regimens that can be specified according to a protocol, and for which the treatment setting is not thought to play an important part, clinical trials can be organized as for

other cancer treatments. Most of the pharmacologic and biologic treatments, whether used as primary treatments or adjunctive to mainstream treatment, would fall into this category. The clinical trials of laetrile, Vitamin C, and hydrazine sulfate (see ch. 5 and below), for example, were appropriately carried out in a conventional medical setting (the criticisms of the vitamin C trials did not have to do with setting).

Psychological, behavioral, and dietary treatments used adjunctively with mainstream treatments can also be studied using existing clinical trial designs, as long as they can be specified and isolated. Spiegel's randomized trial of a psychological intervention (824) serves as a good model. In that study, patients with breast cancer were randomly assigned to be offered a psychological intervention or not. Decisions about other types of medical treatment were left to the women and their physicians, and were not considered part of the clinical trial. The two groups were compared in the end by their survival. Dietary regimens and other behavioral and psychological approaches could be studied similarly.

It would also be possible for adjunctive treatments to be studied in the context of randomized clinical trials of primary treatments. In the simplest version of what is called a "factorial" design, patients would be assigned independently to two treatments, so four groups would result: 1) primary treatment plus adjunctive treatment, 2) primary treatment only, 3) adjunctive treatment only, 4) neither treatment. Comparing groups 1 and 2 combined with 3 and 4 combined would give an assessment of the primary treatment; and groups 1 and 3 combined versus 2 and 4 combined would give an assessment of the adjunctive treatment. These adjunctive treatments might also be tried in mainstream phase I and phase II clinical trials along with other experimental treatments to gather preliminary data for planning larger, more definitive trials. Studies of this type could be arranged in a medical setting, even if the adjunctive treatment were administered outside.

Treatments that would be difficult to isolate from their usual setting or to duplicate elsewhere, or treatments tied closely to an individual practitioner pose some greater challenges. (These would also generally pose the greatest difficulties in making them available widely to cancer patients.) These might *include, e.g., the Gerson treatment (though it is possible to isolate components of that treatment), IAT, treatment by Revici, and the macrobiotic regimen (although a particular diet could be isolated). If they desired to do so, practitioners (aided by experts in research design) could initiate studies of patients coming to them for treatment using conventional phase I and phase II designs. If preliminary evidence suggested an effective treatment, randomized clinical trials could, theoretically, be organized outside the treatment center, with patients randomized either to the center or to other treatment, but such studies entail greater practical and ethical problems. The discussion below, concerning 'best case reviews,' suggests a mechanism that might facilitate randomized clinical trials in such situations.*

Clinical Trials and INDs

Another issue to be dealt with is the desirability of conducting formal evaluations, such as clinical trials, under an IND. In most cases, this will be a legal requirement (for evaluations of new and unapproved drugs and devices).

The requirement that clinical trials be carried out under FDA-approved INDs may be seen as a formidable barrier by unconventional practitioners. Securing such approval is, indeed, a significant effort. But, as the case of Stanislaw Burzynski has demonstrated, it is possible, and it can be facilitated by help from FDA.

A big issue facing an unconventional practitioner contemplating applying for an IND is divulging proprietary aspects of how the treatment is made and administered. The FDA has been entrusted over the years with the trade secrets of large and competitive corporations, and has maintained their trust through vigilant protection of this information. Even the fact that an application has been filed is completely confidential, unless disclosed by the applicant. (During the course of this assessment, FDA would not inform OTA about the existence of IND applications.) The content of the IND application always remains confidential. While these safeguards will not convince some unconventional practitioners that the FDA can be trusted, the fact is that the practitioners cannot cite instances of unwarranted disclosure of this confidential information.

USING INFORMATION RETROSPECTIVELY FROM TREATED PATIENTS: EFFICACY

Before patients use new cancer treatments developed through conventional research and development, extensive testing in laboratory tests and in animals is conducted, and the specific progression of clinical studies described above is followed. Unconventional cancer treatments, by their very nature, do not follow this progression. There is no question that existing unconventional treatments could be treated like new treatments in the conventional pipeline, tested in the laboratory, in animals, and then in humans. But that is highly unlikely to happen, since most unconventional practitioners have not recognized the need for such testing, and the government would not undertake such an effort without a reason to believe the treatment might be effective. The operative question becomes, then, can the experience of patients taking these treatments be used in any way to determine whether they might be effective, and worth evaluating further, and also whether they pose particular dangers for patients?

A "best case review" approach is discussed in terms of gathering preliminary efficacy information, and a reporting system for adverse effects, to address the issue of safety. Some of the more commonly used approaches to assessing efficacy which are not valid are included as well, with explanations of why they don't work.

Efficacy: Some Techniques That Are Prone to Producing Invalid Information

Comparison With the Literature

It is tempting *to use the* records of patients already *taking unconventional treatments to try to derive some type of "response rate' or "survival rate' that could be compared with a' 'standard' rate, thus providing a quantitative estimate of the comparative "efficacy' of a particular treatment. While this approach has some intuitive appeal, it fails because there are no "standard" rates with which to make the comparison. The reason for this is that there is tremendous heterogeneity among cancer patients, even among those who have nominally the same type of cancer. While for most cancers it is possible to identify several important variables, "prognostic factors" (e.g., age, sex, stage of cancer), that are predictive of the likelihood of survival for a group of patients, the heterogeneity reaches beyond easily identifiable factors.*

Even more so than the particular patients who are treated at a given hospital, patients who opt for unconventional treatment are strongly self-selected, and as a group, may have very different characteristics from those of the total cancer patient population, some of which may be related to prognosis. In chapter 6, OTA's review of peritoneal mesothelioma patients treated with IAT is discussed. Clement and colleagues (202) compared survival of this group of patients with the average survival of peritoneal mesothelioma patients reported in series published in the literature. They concluded that IAT produced a two to three times longer survival time than conventional treatment. The authors did not note, however, that the ranges of survival times in IAT patients are similar *to the ranges* noted in reported series *of mesothelioma patients. A range of 7 to 80 months is reported for IAT-treated patients, while the literature reports they cite give survival statistics ranging from 1 to 60 months. One of the comparisons made in the paper by Clement, Burton, and Lampe is with a series of 45 patients whose mean survival was 6 months. For the 11 IAT-treated patients, the mean survival time was 9 months before they began treatment with IAT. This demonstrates some of the problems with comparing groups of patients outside of appropriately designed clinical trials.*

A recent study by Cassileth and colleagues (178) illustrates some of the differences in the distribution of known prognostic factors between a group of IAT patients and cancer patients in general. They reported:

> *The total of 79 subjects, all of whom were white, tended to be younger and of higher socioeconomic status than are cancer patients in general. The majority (82 percent) had received conventional cancer therapy prior to IAT, and 86 percent had completed their prescribed course of conventional treatment. Patients began IAT an average of 17 months following diagnosis. Prior to their first receipt of MT, 76 percent of patients were ambulatory.*

All of the characteristics noted by these investigators would have tended toward better outcomes in these patients than in cancer patients in general. Younger age, white race, higher socioeconomic status, and being ambulatory are all associated with

better prognosis. The fact that these patients began IAT on average about a year and a half after diagnosis means that they survived their period of highest risk (the portion of the survival curve with the steepest slope) of dying from their cancer. These patients already were 'survivors." None of this can be taken as evidence that IAT did or did not help them, but it does point out differences in the distribution of known prognostic factors. The authors recognized this, concluding:

> These characteristics make it impossible to draw valid inferences from this dataset concerning treatment efficacy and safety. . . The deficiencies of this dataset underscore the need for an unbiased, methodologically sound comparison of IAT and conventional cancer treatment modalities.

Cassileth and colleagues' study, however, was interpreted by the IAT Patients' Association (IATPA) as proving that IAT was effective. A "Dear Senator" form letter produced by the Patients' Association (for members to fill in their names and mail to the appropriate Senator) contains the following, which states that 'dramatic new evidence' emerged from Cassileth's study:

> The IAT patients studied were alive nearly twice as long as the average patient who is treated conventionally. Statistically, the odds against this being a chance occurrence are 100 million to one! (431)

This study and its interpretation by the IATPA illustrate the difficulty in presenting accurately and unequivocally the severe limitations of such data.

At the present time, it is not possible to compute rates of survival (or other response) that can be related meaningfully to particular treatments, using only the records of patients who have had those treatments, and attempting to compare them with some 'standard' survived (or other response) information. This statement can be qualified to except the unlikely case of an extraordinarily successful treatment, in which case no comparison might be necessary at all.

"Matching"—Another approach that is often tried is to "match" patients taking a particular treatment with patients who have similar personal and disease characteristics, and then track their survival. This approach fails on the same grounds as comparisons with overall statistics or with reports in the literature: the impossibility of identifying and matching on all the important prognostic factors, since important ones may be elusive.

A study of "ECaP" (Exceptional Cancer Patients) participants, by Morgenstern and colleagues (639), discussed in chapter 2, is a good example of a matched study. In that study, women with breast cancer who had participated in ECaP support groups were matched on age at diagnosis, stage of disease, whether they had had surgery, and "sequence of malignancy. On initial analysis, a significant benefit emerged for the ECaP group. But the matching factors did not take into account the very large effect of the "lag period" between diagnosis and entering the ECaP program. Some of the controls had actually died during the time corresponding to the lag period before the ECaP patient joined up. In addition, the matching factors did not cause the groups to be equivalent in their use of chemotherapy. This suggests that other personal and disease characteristics also differed, and some of these may have been related to prognosis. The final analysis showed no difference in survival once the known prognostic factors were accounted for. Studies such as this are bound to be inconclusive because of the virtual impossibility of successfully "matching' patients.

Efficacy: "Best Case Reviews"

One objective measure of the efficacy of a cancer treatment is its effect on the tumor itself. Not all treatments that shrink or slow the growth of tumors ultimately turn out to be of survival value to patients, but while antitumor effects are not "sufficient" to predict efficacy, they are, for treatments as we know them, "necessary." A first step toward determining the ultimate value of a treatment is to determine whether it has antitumor effects. (This is the main purpose of phase II studies of anticancer treatments.) Nearly all the unconventional treatments learned of in the course of this assessment do make claims for tumor shrinkage or disappearance, so it is not unreasonable to look for these effects in patients. The mechanism of claimed effects are relatively unimportant here, but the time scale for effects should be taken into account: some proponents claim that their treatments have direct cell-killing effects, which may happen rather quickly (e.g., laetrile, Hoxsey tonics), while for other treatments that claim to work by building and stimulating the patients' immune systems, the effects are described as more gradual (e.g., macrobiotics, IAT).

One way to determine whether a treatment has antitumor effects is to test it in a phase II trial. Given a treatment that has been used by hundreds or thousands of patients, however, is there another way of efficiently generating some, at least preliminary, information before a prospective trial is contemplated? NCI's laetrile case review (274), described in chapter 5, was an attempt at this. The results were disappointing because a relatively small number of evaluable cases were submitted, but still, valuable lessons were learned from it about laetrile and about the method itself. This "best case" approach, with modifications, could be used more prominently in determining which might deserve further investigation. One element that may be crucial to the success of a best case review is the active participation, or at least support, of the unconventional practitioner.

The objective of the best case review is to produce evidence of tumor shrinkage (or, in particular cancers, other accepted objective measures of lessening disease) in a group of selected patients (either current or former), with evidence documenting that the patients had the particular unconventional treatment under study and, as far as possible, that they did not have any other treatments during that time period.

The basic elements of each case in a best case review would be: 1) documented diagnosis by an appropriate licensed professional, including pathology reports and microscope slides of the tumor; 2) history of prior treatments; 3) length of time between the most recent treatment and the treatment under evaluation; 4) x-ray studies from before and after the treatment under evaluation was administered; and 5) a statement from the physician and the patient saying that no other treatments were administered at the same time as the particular treatment under evaluation.

These elements require a significant amount of documentation. Clearly, many patients who benefit from cancer treatment-mainstream or unconventional--could not be included in a best case review, because their records would not be sufficient to meet these demands. However, an adequate and convincing review could be based on as few as 10 or 20 successful cases. If a treatment is even moderately successful and has been used for many years, that number meeting the criteria should be available. Such a review will require time, patience, perseverance, resources, and the cooperation of professionals in the mainstream community, such as pathologists, oncologists, and specialists in nuclear medicine, which may seem a steep climb for an unconventional clinic to undertake. The Gerson Institute, one of the major unconventional clinics treating U.S. patients in Tijuana, has embarked on such a best case review, however. Results have not been reported, but it could prove to be the first successfully completed study of its type mounted by an unconventional treatment proponent.

It is important to note that a best case review is not the end of the evaluation line; some cautions must be kept in mind. This type of study cannot, except possibly in exceptional cases, provide definite proof of efficacy in terms of life extension, nor any estimate of rate of response to the treatment. In addition, the concerns expressed in the report of NCI's laetrile review are relevant: the possibility of falsified information being used, omission of information, either intentional or unintentional; other mainstream or unconventional treatment that may have been used by the patient without the unconventional practitioner's knowledge; the possibility of mistaking the natural variability of cancer for true regression; and the possibility of "spontaneous regression.' This last point is worth pursuing a little further.

So little data exist about the nature and rates of spontaneous regression that is almost impossible to discuss informatively. Spontaneous remissions are often invoked to explain otherwise unexplainable recoveries from cancer, yet such remissions are usually considered to be exceedingly rare phenomena. It is worth noting that two instances of "otherwise unexplainable regressions" have been described in chapter 5 of this report. One of the NCI-file patients in the laetrile review, who had had no treatment, was deemed to have had a partial remission (274); and the only long-term survivor in the first Mayo Clinic vitamin C study was a pancreatic cancer patient who had both subjective and objective evidence of lessening disease (though tumor status itself was not reported), and who was taking the placebo.

Overall, the best case review may be a powerful tool for supporters of unconventional cancer treatments who want to begin the evaluation process. It can be carried out relatively easily independent of major cancer research centers, although specialized expertise is needed for reviewing pathologic diagno-

ses and for interpreting scans and other medical testing information. It also is not free: patient followup and medical expertise can be expensive, and a large investment of time is required on the part of the unconventional practitioner or his or her representative. Nevertheless, it is doable, it poses no particular legal problems, and it does not involve securing an IND or the approval of an Institutional Review Board (IRB). OTA has recommended to Lawrence Burton and supporters of IAT a best case review of his selected, successfully treated patients as a prerequisite for carrying out a prospective clinical trial under Federal Government auspices. Importantly, NCI and independent researchers would look seriously at evidence from well-documented best case reviews of unconventionally treated cancer patients. The end result should be, if the evidence warrants, a somewhat eased entry into further evaluation through prospective clinical trials.

CAPITALIZING ON THE EXPERIENCE OF TREATED PATIENTS: SAFETY

Just as described above for assessing efficacy, there are some informative and some not very informative ways of using patient experience to assess the safety of treatments. Examples of both will be described in this section.

In cases where unconventional practitioners or clinics keep detailed patient records, it would theoretically be possible to examine them for adverse side-effects that might be related to the treatment. The practitioners themselves might also be good sources of this information, if they noted particular patterns of unintended effects. Such a means of detection is not unlike the way newly discovered adverse drug effects are reported to the FDA, at least for rarer effects that would not necessarily be detected in formal premarketing clinical trials. OTA found no reports of systematic records-based studies of adverse effects by unconventional practitioners, however, and it is probably not realistic to expect many, if any, to undertake these studies.

Another possible approach to gathering information on adverse effects in past (and possibly current) patients is by examining medical reports from physicians and hospitals who have seen patients after they leave unconventional treatment or who are seeing them concurrent with the unconventional treatment. Results of laboratory tests not generally carried out at unconventional clinics (e.g., liver function, kidney function, cardiac tests), descriptions of clinical symptoms, and autopsy reports for patients who have died are available in some cases. This type of investigation is most likely to be undertaken by mainstream groups concerned with unknown adverse consequences of unconventional treatments. Given that it is not the type of study in which the unconventional community is likely to participate, locating patients and confirming information about their unconventional treatment may be a difficult exercise. Several approaches are possible.

There may be cases in which the clinic or practitioner will cooperate by providing lists of current or former patients. Associations of patients (see ch. 7) have formed around particular clinics and treatments, and the associations may be willing to provide the names of members, or the names of members who have died. These associations are often autonomous and have somewhat different perspectives from the practitioners. Another approach, which has been tried, is to survey physicians and ask about their experiences. One such example, described in chapter 5, was the NCI/American Society for Clinical Oncology (ASCO) survey of ASCO members concerning patients they had seen who had been treated with IAT. After a significant effort, the authors found that the survey could not be viewed as a "definitive analysis of IAT efficacy or toxicity. No rates could be calculated, as the appropriate denominator for the sample could not be ascertained, and because the nature of the survey would have had the effect of eliciting responses from physicians who had particularly bad experiences. More to the point on the toxicity side, however, for the type of information collected to be valid, it would have to be "evaluated with a thorough chart review to determine whether other factors may have accounted for the findings. " Unfortunately, this survey approach has quite limited usefulness.

Another attempt to find information about adverse effects of IAT was made in 1981 by a physician who advertised in the Florida Association of Clinical Oncology Journal *(987). The advertisement asked physicians to send narrative reports of patients known to them who had been treated at the IAT clinic in the Bahamas, with the idea of starting a "registry" of such cases. Seven physicians responded reporting on a total of 21 patients (989).*

This, again, is probably not a particularly useful approach.

Aside from doing surveys, it is possible that useful information about adverse effects of unconventional treatments could be collected if physicians had an easy, open channel to report findings as they are noted, similar to their reporting of adverse effects of legal pharmaceuticals to FDA. There is currently no Federal agency with such a charnel. A' 'registry' could be opened to accept and keep on record documented cases of adverse effects resulting, with a high degree of probability, from unconventional cancer treatments. Currently, adverse treatment effects collected and reported by individuals or groups perceived as "quackbusters" often are not well-documented, though they may be accurate, and reach the public only through specialized newsletters, occasionally the popular press in a sensational way, and rarely, the medical literature. If reporting were perceived as a responsibility of any treating physician, and if available patient records were reevaluated by an office in a Federal agency, the registry of reported effects has the potential to be a useful reference for physicians and the public, for research, and possibly for legal actions.

TESTING TREATMENT MATERIALS FOR POTENTIAL ANTICANCER ACTIVITY AND STERILITY

Testing Treatment Materials for Potential Anticancer Activity

Currently, the Federal Government does not systematically seek out and screen substances in commonly used unconventional cancer treatments in the United States. NCI does test substances of plant and animal origin (including undersea organisms) collected from around the world by botanists, anthropologists, and oceanographers. Many herbal compounds popular in the United States, in some cases mixtures of more than one component, or individual components, are readily available in health food stores or by mail. The investment involved in acquiring and testing these materials in the current battery of preclinical screens, while not negligible, may be worthwhile.

If some of these materials were to demonstrate promising activity in preclinical tests, they could be considered for development in the rigorous system that has been devised for all conventional potential anticancer drugs. This would involve identification and isolation of active molecules, possible synthesis of the compound in the laboratory, and further biochemical and safety testing in animals. The other path open would be to try to study these products in clinical trials (after some preclinical safety testing) in the way that they are used by cancer patients in unconventional treatments.

Testing Treatment Materials for Composition and Sterility

Substances used in unconventional cancer treatments are often "proprietary," their composition deliberately kept secret, and they are often manufactured only at the treatment site, or by unregulated manufacturers. In these cases, there is often interest in the mainstream community in finding out whether the composition of these materials resembles descriptions by the proponents, and whether they may be contaminated by various types of organism. Treatment materials have been turned over to U.S. authorities by patients or the families of patients, and subsequently analyzed. The best known recent example of this was testing of IAT materials by NCI, which was reported in the Journal of the American Medical Association (246) in 1986. *In that case, significant contamination was reported, and the composition of the materials was reported to be mainly albumin. That testing, it is widely believed, led to the closure of the IAT clinic by the Bahamian Government.*

The claims of contamination are denied by Burton, who asserts that his preparation procedures precluded the possibility of contamination (114). There seems to be no way to ascertain the facts of this case, which has become celebrated in both the mainstream and unconventional communities.

Although the IAT example might suggest otherwise, it is possible that some practitioners might be willing to submit their materials for testing specifically for contamination, if procedures could be worked out to assure propriety on both sides.

CONCLUSIONS

Opportunities may exist to gather valid information about the efficacy and safety of unconventional cancer treatments; these are largely unexplored. The same types of study that are used to determine the safety and effectiveness of mainstream treatments—including ultimately randomized clinical trials—would be required to determine the value of unconventional treatments.

A potentially useful tool for beginning to evaluate unconventional treatments is the "best case review, which could be a first step toward prospective clinical trials. There may also be ways to gather some information about possible hazards of unconventional treatment, by opening a "registry" into which cases with appropriate documentation could be entered. Conventional physicians would probably be the main contributors to this.

OTA's experience with IAT was discouraging, but it may not be a good example of the way in which an unconventional treatment might enter the evaluation system. Burton did not seek the evaluation, and he never became fully engaged in seeing it move forward. Other practitioners or their supporters, such as Burzynski, and the Gerson Clinic personnel, have attempted to initiate some form of evaluation, with assistance from experts, and these efforts suggest that other practitioners might be interested in doing so as well.

Appendixes

Appendix A
Method of the Study

The Assessment Process

John Dingell, Chairman of the U.S. House of Representatives Committee on Energy and Commerce, wrote to OTA in August 1986 asking that a study be done of treatments for cancer that are "out of the mainstream." The request stated:

> Many of these treatments maybe without benefit, some may actually be harm.ful, and some, probably a small number, may have value. However, there is a general lack of objective information about them, thus making rational decisions about such alternative therapies extremely difficult.

The letter asked OTA to describe the *treatments and look into policy issues surrounding their availability and evaluation. Congressman Dingell's letter also recognized the letters OTA had received from then-Congressman Molinari and 42 other Members of the House and Senate requesting that OTA review the existing data on the efficacy of a particular treatment, Immuno-Augmentative Therapy (IAT), and design a formal evaluation plan for that treatment. Congressman Dingell suggested that OTA consider the IAT work as a case study within the larger study.* [1]

In response to Congressman Dingell and the requests about IAT, OTA proposed a study titled "Nontraditional Methods of Cancer Management: Science and Policy Issues,' which was approved by the Technology Assessment Board (TAB; OTA's governing body) in September 1986. (The title was changed twice, based on advice of the Advisory Panel and others, ending with the published title of Unconventional Cancer Treatments.) The study was to begin in January 1987, *with a final report to be* delivered to TAB in June 1988 *(with* publication *some months later), and preceding that, the case study on IAT to be delivered in December 1987. Because of the difficulty of gathering information for the study and the extensive interactions with the public and Congress concerning it, the TAB delivery date was extended four times, and the report was finally delivered to TAB in July 1990.*

Project Advisory Panel and IAT Working Group

One of the first tasks was the appointment of an Advisory Panel, a feature of every major OTA project. Advisory Panels include individuals from outside the Federal Government with expertise in the various areas covered in the assessment, and representing the important points of view on the issue at hand. Advisory Panels do not write, nor do they take responsibility for, the content of OTA reports, but their participation is considered essential to producing fair and authoritative reports.

Choosing an Advisory Panel for this study required OTA to go beyond the mainstream medical sphere in which it usually operates. Many contacts with unconventional representatives were made through an initial contact with Michael Lerner, President of Commonweal, who was asked to be a special consultant to the study. In addition, a long list of individuals recommended to be on the Advisory Panel was received unsolicited from a group called the "Coalition for the Evaluation of Alternative Therapy," a coalition of preexisting groups that appeared to have formed in response to the OTA study. (The Coalition no longer exists.) The Advisory Panel was chosen with consultation from Dr. Lerner. The chairperson, chosen by OTA, is Rosemary Stevens, a medical historian who had not worked specifically in the area of unconventional medicine. The Advisory Panel contains individuals generally supportive of unconventional treatments (8 members), individuals who were openly opposed (2), and individuals with technical expertise clearly allied to mainstream medicine and research, but who had not taken a position against unconventional treatments (8). Dr. Lerner also functioned very much like an Advisory Panel member in his capacity as special consultant.

In addition to the Advisory Panel, the project staff appointed a second group, the "IAT Working Group," to assist with designing a clinical trial protocol for IAT. This group consisted of individuals with technical expertise in clinical trial design, plus an appointed representative each from the National Cancer Institute (NCI) and the Food and Drug Administration (FDA). Lawrence Burton, developer of IAT, was asked to participate as well; he appointed a patient, the founder of the IAT Patients Association, to represent him and also asked that a statistician (the husband of one of Burton's patients) who was interested in IAT, be included. This was done. Dr. Lerner was associated with this group as well.

[1] By statute, OTA may undertake assessments at the request of the Chairman of any full committee of the Congress. The Chairman may request the work personally, on behalf of a ranking minority member, or on behalf of a majority of the committee members. OTA's Board may request work, as may the Director of OTA, but individual Members of Congress, such as then-Congressman Molinari, do not have authority to request assessments.

Meetings of the Advisory Panel

First Meeting

The Advisory Panel first met in July 1987. A preliminary outline of the report was presented by the project staff. Areas for ***contract work had been identified,*** as ***had*** some ***potential contractors.*** At that time, ***however, only*** one contract had been let, **to** Michael Lerner, to produce a "conceptual framework" for analyzing the various treatments to be covered, and to provide background information on a wide range of treatments. Advisory Panel guidance was solicited for prospective contractors for the other areas.

The meeting was notable for bringing the unconventional treatment supporters together with the mainstream in a neutral forum. Discussion was generally non-confrontational and informative. However, undoubtedly because of the difficulty of the topic and lack of precedence for a study of this type, no clear direction for the report as a whole emerged.

Second Meeting

The second Advisory Panel meeting was held in late July 1988. A partial draft of the report was sent to the Advisory Panel for discussion at this meeting. OTA had asked the panel not to circulate this draft to others because of its preliminary nature, but, as it turned out, it was widely copied and circulated, and a large number of observers at the panel meeting had copies. One, Robert Houston, had prepared a critique, "Objections to a Cover-Up: The OTA Report on Alternative Therapies," which he distributed at the meeting. Other groups, e.g., Project Cure and the IAT Patients' Association, also passed out literature. Observer comments were allowed by the chairperson as appropriate. The tense atmosphere and combative nature of many of the observers and panel members strained the discussion. There was a great deal of criticism of the draft, largely from the panel members on the unconventional side. Their main concerns were that there had not been enough time for them to review the draft, that the draft was incomplete, and particularly, that policy issues were presented orally at the meeting, but had not yet been written. There was also criticism that too much emphasis had been placed on adverse effects, that the "scientific development" of the treatments was not discussed sufficiently, and that traditional practitioners and New Age approaches were given too prominent a place.

Third Meeting

The latter half of 1988 and all of 1989 was spent rewriting the report almost in its entirety, relying less on contract papers and more on OTA staff research, which proved necessary for a thorough treatment of the subject. A complete draft, with policy options, was sent to the Advisory Panel about one month before a meeting in early March 1990. Copies of the draft were also sent to more than 200 other individuals and groups for review before the meeting. OTA invited requests from outside reviewers to address the meeting if they had serious criticisms of the report. Sixteen responded and their statements took up the morning of the meeting. These were:

- Seymour M. Brenner, M.D., Community Radiology Associates, P.G.;
- Peter Chowka;
- Michael L. Culbert, The Committee for Freedom of Choice in Medicine, Inc.;
- Michael Evers, Project Cure;
- Robert G. Houston;
- Richard A. Jaffe, attorney for Stanislaw Burzynski;
- Wolfram Kuhnau, American Biologics;
- Virginia Livingston, Livingston-Wheeler Clinic;
- Clinton Ray Miller, National Health Federation;
- Ralph Moss, The Cancer Chronicles;
- Vivien Newbold, M.D.;
- Maryann Roper, M.D., National Cancer Institute;
- Janet I. Smith, MSAM, Consumer Health Strategies;
- Patricia Spain Ward, University of Illinois; and
- Frank D. Wiewel, IAT' Patients' Association, Inc.

The presentations ranged from reasoned critique to presentation of additional information to shouted personal attacks on the integrity of the project staff.

In the afternoon, the panel discussed the draft. There seemed to be two major themes: first, that throughout the draft, OTA had failed to highlight the "middle ground," except in the chapter on psychological and behavioral approaches. Second, that what was needed for fair treatment of unconventional cancer treatments was a "level playing field. " There was also considerable discussion about the tone of the report, which was perceived as unduly critical of unconventional treatments. To the extent possible, given the hostile atmosphere, policy options were discussed, as well as other parts of the report. As at the second meeting, many spectators, in addition to those scheduled, were allowed opportunities to speak.

The OTA Director, along with the Assistant Director for Health and Life Sciences, the Health Program Manager, the project staff, and other OTA officials, were present for the entire meeting. A number of TAB staff and other Congressional staff members also attended.

IAT Case Study

The conduct of the IAT case study is discussed in the latter part of chapter ***6. The IAT*** Working Group met twice during the course of the study, in March 1987 and May 1988. OTA staff (accompanied by an FDA official on the second trip) met with Burton and his representa-

tives in the Bahamas twice. These meetings are all discussed in some detail in chapter 6.

Workshop on Evaluation Methods

Early in the project, in October 1987, OTA held a 2-day workshop at Commonweal, in Bolinas, California, hosted by Michael Lerner, to explore issues related to evaluating unconventional cancer treatments. The idea was to bring together experts in evaluation methodology with individuals knowledgeable about the details of unconventional cancer treatments. Some members of the Advisory Panel, members of the IAT Working Group, one evaluation expert from the National Cancer Institute, and several others attended. Some of the ideas that arose from the workshop are discussed in chapter 12.

The Review Process

About 250 copies of the February 1990 draft were sent out for review. Comments were requested by the end of March, but the deadline was extended for anyone asking for more time. Comments were received through the end of May from a total of approximately 75 individuals and organizations. Many comments consisted mainly of attacks on the integrity of the project staff and other OTA officials. Others were of a more substantive nature. Eight members of the Advisory Panel generally supportive of unconventional treatments wrote a set of joint comments, including discussion of the "middle ground" and "level playing field" issues of the third panel meeting. Robert Houston again wrote along critique, which was published in March 1990 by "People Against Cancer," entitled "Misinformation from OTA on Unconventional Cancer Treatments. "

Revisions to the report included attempting to obtain and incorporate, to the extent possible, new material suggested by reviewers, and some restructuring in response to comments (e.g., elimination of the chapter on spiritual approaches). The final report is significantly more complete as a result of the review. In addition, the IAT case study, whose planning with Burton had recently come to an unsuccessful end, was folded into a separate chapter about IAT.

In addition to the usual editing done at OTA, the Advisory Panel chairperson offered to edit the summary and options chapter (chapter 1), as the last step before the final draft was sent to TAB, to assist with what were referred to as "tone problems" by Advisory Panel members. In their joint letter to OTA, a group of panel members referred to the "distinguished Advisory Board chairman, Rosemary Stevens, Ph.D.," stating that they would be "very happy with a tone that reflected her judicious historian's balance." All of Dr. Stevens editing suggestions were incorporated into the final version.

Mail-in Campaigns Relating to the Project

OTA, and Members of Congress, particularly the membership of TAB, have been the object of mail-in campaigns by several unconventional treatment advocacy groups during the course of the project. Thousands of pre-printed postcards and letters (e.g., from the Coalition for Nutrition and Health, Project Cure, the Foundation for the Advancement of Innovative Medicine), and tearsheets from an alternative magazine *(Health Freedom News, the* magazine of the National Health Federation) have been received. The content of these has varied, but they have generally been highly critical of OTA practices, the project staff and other OTA officials, and the draft report. OTA did not, in general, respond individually to these form letters.

TAAC Meeting

The February 28, 1989 meeting of OTA's Technology Assessment Advisory Committee (TAAC)[2] was devoted to this project. Rosemary Stevens, the Chairperson of the Advisory Panel, Michael Lerner, special consultant to the project, and Richard Riegelman, a member of the Advisory Panel, also participated in the meeting. In a memorandum to TAAC members, the Director of OTA gave this purpose to the discussion:

> The **sharpness of the controversy about the substance and** approach **to this study has greatly exceeded the normal** clash of opinions accompanying OTA's studies. For this reason, we are asking the TAAC and three **guests to** consider the fairness and thoroughness of the study approach and **results.**

Briefing materials were sent to TAAC members before the meeting, acquainting them both with the assessment itself and the controversies that had arisen around it. At the meeting, the history of the project was reviewed, in both content and process. Plans for finishing the project and for ensuring objectivity to the end of the process were discussed in detail. After finishing at OTA, TAAC met with TAB and discussed its review of this study.

Communication With Congressional Staff

Over the course of this project, about half of all the Congressional offices contacted OTA by letter or telephone for information. These requests were usually in followup to contacts by constituents, who either wrote individual letters or participated in one of several mail-in campaigns organized by advocacy groups. Project staff discussed the project by telephone and provided current

[2]TAAC is a Congressionally mandated group of 10 eminent individuals appointed by the Technology Assessment Board to advise OTA. In addition, the Comptroller General of the United States and the Director of the Congressional Research Service serve as statutory members.

''one-pagers' on the main project and on IAT in response to these requests.

Communication With the Public

OTA received hundreds of telephone calls and letters (both individual and mass-produced) about this study. Most phone callers were looking for information about particular treatments, usually on behalf of a friend or relative with cancer. Most had found out about the study through articles in alternative magazines or papers or by word of mouth. To the extent possible, project staff provided general information or directed them to other sources of information. The one-page study descriptions were also sent to the public. Particularly during the period of the draft review, many people called and wrote to register disapproval of the report. In general, these were not people who had seen copies, but were repeating views publicized by advocacy organizations.

Other Inputs To Report

Contractor Papers

Michael S. Evers, J.D.: "Legal Constraints on the Availability of Unorthodox Cancer Treatments: Freedom of Choice Viewpoint"

The purpose of this contract was to describe the laws, regulations, and other legal constraints on unconventional cancer treatments, specifically giving the legal basis for the "freedom of choice" point of view. Evers heads one of the major unconventional treatment advocacy groups. It was used in writing chapters 10 and 11. A similar contract was awarded to Ronald D. Schwartz and Rebecca L. Burke, to represent the "consumer protection" point of view.

Vicki S. Freimuth, Ph.D.: "The Public Search for Information on Unorthodox Cancer Treatments: The CIS Experience"

The purpose of this contract was to describe the way in which the National Cancer Institute's Cancer Information Service handles requests for information about unconventional cancer treatments. The contract included an analysis of all calls recorded by the CIS over a 4-year period in which unconventional treatments were discussed. Information from this contract appears in chapters 7 and 8.

Janice Guthrie: Sources of Information on Unorthodox Cancer Therapies" and "Personal Narrative"

Under this contract, Ms. Guthrie provided OTA with a comprehensive list of sources of information on unconventional cancer treatments and she obtained for OTA brochures, audio tapes, and other sources of information from specific clinics and practitioners. Her narrative, referred to in chapter 7, describes her personal experience with unconventional cancer treatments. The material provided under this contract was used in many places in the report.

Sharon Hammond: "An Examination of the Public Education Efforts of Three Mainstream Cancer Organizations'

The purpose of this contract was to describe the educational activities related to unconventional cancer treatment of the American Cancer Society, the National Cancer Institute, and the American Society for Clinical Oncology. Some of this information appears in chapter 8.

David J. Hufford, Ph.D.: "Cultural and Social Perspectives on Unorthodox Cancer Treatment"

This report provided general background and context for unconventional cancer treatments. It is referred to in several places in the report.

David J. Hufford, Ph.D.: "Selected Unorthodox Cancer Practitioners'

This report describes "New Age" and traditional healers, faith healers, Christian Science healers, and others. Hufford's report was instrumental in helping to understand these healing systems and in deciding not to cover them in detail in the report.

David J. Hufford, Ph.D.: "Health Food Store Survey on Alternative Cancer Treatment Information"

Under this contract, Hufford coordinated a survey by graduate students of information about unconventional cancer treatments available in health food stores in three cities. The results are reported in chapter 7.

Michael Lerner, Ph.D.: "Toward a Framework for the Analysis of Unconventional Cancer Therapies'

This contract report served to help categorize treatments generally by content, and described positive aspects of a number of specific treatments in each category. It also provided general background material. Material from this report is referred to in a number of places in the report.

Daniel J. Morris, M.D.: "Feasibility of Identifying and Gaining Access to Medical Records of IAT Patients Who Have Also Been Seen in Florida Medical Facilities Since January 1986"

The purpose of this contract was to determine whether any useful information about IAT could be gathered from other medical institutions where IAT patients had been treated. Dr. Morris discussed this approach at an IAT Working Group meeting. It is discussed briefly in chapter 6.

Anne Paxton: "Practitioners of Unorthodox Cancer Treatments"

The purpose of this contract was to describe various types of unconventional practitioner (e.g., holistic physicians, naturopaths, homeopaths). Little of the information from this contract was used in the final report.

Terence M. Phillips, Ph.D., D.Sc.: "Critical Review of Published Pre-Clinical Studies by Lawrence Burton, Ph.D."

The purpose of this contract was to review Burton's published work of the 1950s and 1960s, on fruitflies and mice, mainly, which Burton says is the basis of Immuno-Augmentative Therapy (MT). Phillips is a clinical immunologist and protein chemist. Material from his report appears in chapter 6.

Terence M. Phillips, Ph.D., D.Sc.: "Review and Analysis of Lawrence Burton's Patented Processes and Products"

OTA was urged by Burton's supporters to review his patents. Phillips was asked to analyze the patents, critique the procedures, and determine, if possible, what materials would be produced by them. He was also asked to determine any relationship to Burton's published preclinical work. Material from this patent review appears in chapter 6.

Ronald D. Schwartz, J.D., and Rebecca L. Burke, J.D.: "Legal Constraints on the Availability of Unorthodox Cancer Treatments: Consumer Protection Point of View"

The purpose of this contract was to describe the laws, regulations, and other legal constraints on unconventional cancer treatments, specifically giving the legal basis for the "consumer protection" point of view. It was used in writing chapters 10 and 11. (See above, report by Michael S. Evers.)

Patricia Spain Ward, Ph.D.: "History of Hoxsey Treatment,"" History of Gerson Therapy," and "History of BCG"

The purpose of this contract was to describe the historical antecedents and development of three popular unconventional cancer treatments. (A fourth, macrobiotics, was included in the statement of work but was dropped by mutual consent of the contractor and OTA.) Material from these reports appears mainly in chapters 3 and 4.

Robert Watson: "Quality of Life Assessment Instruments: A Review of 32 Current Measures and One Classic"

The purpose of this contract was to provide an annotated bibliography of methods used to assess quality of life. It was decided later in the project not to cover this in detail.

Jack Z. Yetiv, M.D., Ph.D.: "Adverse Medical Consequences of Unorthodox Cancer Treatments"

This report provided information on reported and suspected adverse effects of unconventional treatments, to complement the selectively positive information in the Lerner contract. The contract was let after receiving Lerner's draft, in which he stated that his emphasis was on the positive aspects, and he had not covered the "casualties of unconventional cancer therapies" thoroughly.

Other Sources

A paper prepared by Keith I. Block, M.D., an Advisory Panel member, and Charlotte Gyllenhall, Ph.D. ("Nutrition: An Essential Tool in Cancer Therapy"), was used as a primary source in chapter 3. Extensive conversations with Richard Jaffe, an attorney associated with several unconventional practitioners, provided much of the basis for the "freedom of choice" discussion in chapter 10 and for some of the ideas presented in chapter 9 concerning insurance coverage for unconventional cancer treatments.

A review of fifty case histories of patients in the Kelley program, as described in an unpublished manuscript by Nicholas Gonzalez, M.D., was carried out by members of the Advisory Panel at the request of OTA. The results are reported in chapter 3. Some Advisory Panel members also reviewed case histories of patients treated with a macrobiotic regimen, as reported by Vivien Newbold, M.D. This also is reported in chapter 3. To obtain information about laboratory testing of the herbs contained in Hoxsey's formulas and Essiac, OTA had searches of the published literature carried out by NAPRALERT, which maintains a data base on natural products.

Appendix B

Glossary of Terms and Abbreviations

List of Abbreviations

AAM	—Alliance for Alternative Medicine
ACCC	—Association of Community Cancer Centers
ACS	—American Cancer Society
ACSH	—American Council on Science and Health
ADS	—Agua del Sol
AIDS	—Acquired Immmodeficiency Syndrome
AMA	—American Medical Association
AQA	—American Quack Association
ASCO	—American Society for Clinical Oncology
BC/BS	—Blue Cross/Blue Shield
BCBSA	—Blue ***Cross*** and Blue Shield Association
BCBSNJ	—Blue Cross/Blue Shield of New Jersey
BCG	—bacillus Calmette-Guerin
BP	—Blocking Protein
BPF	—Blocking Protein Factor
CACR	—Center for Alternative Cancer Research
CAG	—Clinical Appraisal Group
Caltech	—California Institute of Technology
CANAH	—Coalition for Alternatives in Nutrition and Healthcare
CCS	—Cancer Control Society
CDC	—Centers for Disease Control (Public Health Service, DHHS)
CFCM	—Committee for Freedom of Choice in Medicine
CHAMPUS	—Civilian Health and Medical Program of the Uniformed Services
CIS	—Cancer Information Service (NCI)
CPT	—Current Procedural Terminology (4th edition)
CRS	—Cancer Response System (ACS)
CT	—computed tomography
DATTA	—Diagnostic and Therapeutic Technology Assessment program (AMA)
DHHS	—U.S. Department of Health and Human Services
DMF	—Drug Master File
DMSO	—dimethyl sulfoxide
DNA	—deoxyribonucleic acid
DNCP	—Diet, Nutrition, and Cancer Program (NCI)
D.O.	—doctor of osteopathy
DP	—Deblocking Protein
DPF	—Deblocking Protein Factor
ECaP	—Exceptional Cancer Patients
ELISA	—enzyme-linked immunosorbent assay
ERISA	—Employee Retirement Income Security Act
FACT	—Foundation for Advancement in Cancer Therapies
FAM	—Foundation for Alternative Medicine
FDA	—Food and Drug Administration (DHHS)
FDCA	—Federal Food, Drug, and Cosmetic Act
FTC	—Federal Trade Commission
FTCA	—Federal Trade Commission Act
GAO	—General Accounting Office (U.S. Congress)
GRAS	—generally recognized as safe
HCFA	—Health Care Financing Administration (DHHS)
hCG	—human chorionic gonadotropin
HIV	—human immunodeficiency virus
HNF	—Hans Nieper Foundation
HPB	—Health Protection Branch, Health and Welfare Canada
HTLV-III	—human T-cell lymphotropic virus, type III (formerly, human T-cell leukemia virus, type III) (see HIV)
IACVF	—International Association of Cancer Victors and Friends
IAT	—Immuno-Augmentative Therapy
IATPA	—IAT Patients' Association
ICD	—International Classification of Diseases (9th revision)
IL-2	—interleukin-2
IND	—Investigational New Drug
IRB	—Institutional Review Board
IRC	—Immunology Researching Centre, Inc. (Bahamas)
IRF	—Immunology Research Foundation (Great Neck, NY)
JCAHO	—Joint Commission on Accreditation of Health Care Organizations
LAV	—lymphadenopathy-associated virus
MAC	—Multispecialty Advisory Committee (BCBSNJ)
MCHSF	—Medicare Continuous History Sample File
M.D.	—medical doctor
MNP	—Medical Necessity Program (BCBSA)
MSKCC	—Memorial Sloan-Kettering Cancer Center
NACAA	—National Association of ConsumerAgency Administrators
NAPRALERT	—Natural Product Data Base
NCAHF	—National Council Against Health Fraud
NCI	—National Cancer Institute (NIH)
NDA	—new drug application
NDGA	—nordihydroguaiarectic acid
NHCAA	—National Health Care Anti-Fraud Association
NHF	—National Health Federation

NHL —non-Hodgkins lymphoma
NIH —National Institutes of Health (DHHS)
NK —natural killer (cells)
NRC —National Research Council (National Academy of Sciences)
OPMC —Office of Professional Medical Conduct (State of New York)
OTA —Office of Technology Assessment (U.S. Congress)
PAC —Pharmaceutical Advertising Council
PAHO —Pan American Health Organization
PC —***Progenitor cryptocides***
PDQ —Physician Data Query (NCI)
PDT —photodynamic therapy
PNI —psychoneuroimmunology
PRO —utilization and quality control peer review organization
RCT —randomized clinical trial
RDA —recommended daily allowance
Rico —Racketeer Influenced and Corrupt Organizations Act
SEER —Surveillance, Epidemiology, and End Results Program (NCI)
TA1 —Tumor Antibody 1
TA2 —Tumor Antibody 2
TC —Tumour Complement
TEC —Technology Evaluation and Coverage Program (BCBSA)
TIF —tumor induction factor
TNF —tumor necrosis factor
UCLA —University of California at Los Angeles
USCA —U.S. Court of Appeals
USP —U.S. Pharmacopoeia
USP DI —U.S. Pharmacopeial Dispensing Information
USPS —U.S. Postal Service

Glossary of Terms

Acupuncture: A treatment that involves piercing the skin with very fine needles at certain key "acupoints" on the body. Acupuncture is based on the theory that energy flows along specific pathways or "meridians" connecting the organs deep in the body with the acupoints on the surface of the body. The flow of energy is believed to be disrupted by disease, and may be restored to equilibrium by acupuncture.

Adjuvant: A substance added to a medical chug that enhances the effect of the active ingredient. In immunology, a substance added to a vaccine that non-specifically enhances its antigenicity. In cancer treatment, "adjuvant chemotherapy" refers to drug therapy used to complement surgical removal of the tumor.

Allopathy/allopathic practitioner: Terms used to refer to mainstream medicine its practitioners. The term was coined by Samuel Hahnemann, the founder of homeopathy, originally as a pejorative term, though it has largely lost that connotation.

Anthroposophy: A spiritual tradition encompassing all aspects of life, including medicine, founded by the Austrian-born clairvoyant Rudolf Steiner in the early 20th century.

Autogenous: Self-generated; originated within the body. As applied to bacterial vaccines, the term denotes those vaccines that are made for each specific patient from cultures originating from that patient, as opposed to stock vaccines which are made from standard cultures.

Autoimmune: Referring to a response of the immune system directed against the body's own tissue, an abnormal state (the immune system is designed to respond to foreign tissue) believed to contribute to a number of chronic diseases (e.g., rheumatoid arthritis, diabetes mellitus).

Behavioral treatments: Referring to treatments based on physical and mental activities, e.g., exercise, relaxation, qi gong.

Benign: Not malignant; in reference to tumors, lacking the capacity to invade normal tissue and metastasize to distant sites.

Biofeedback: A technique based on the theory that one can learn to regulate one's own internal state, including the autonomic nervous system, which had been thought to be beyond conscious control.

Biopsy: The removal and examination, usually microscopic, of tissue from the living body, performed to establish precise diagnosis.

Blinding: In randomized clinical trials, keeping secret which treatment is assigned to participants. When only the patient is kept unaware of his or her treatment assignment, the study is "single-blind." When the person administering treatment (e.g., the physician) also is unaware, the study is "double-blind." Additional layers of blinding can be added as, for example, when a third individual (usually the evaluator of outcomes) also is unaware of treatment assignments.

Brucellosis: A generalized infection involving the reticuloendothelial system caused by species of microorganism genus ***Brucella,*** that is contracted through contact with goats, cattle, pigs, and dogs.

Cachexia: In cancer, the progressive wasting that occurs in the late stages of disease, resulting from derangements in various metabolic processes.

Cancer: A tumor with the potential for invading neighboring tissue and/or metastasizing to distant sites, or one that has already done so. Cancers are categorized into major classes by their cell types. See also ***carcinoma, sarcoma, lymphoma,*** and ***leukemia.***

Carcinogen: An agent that causes cancer.

Carcinoma: A cancer arising from epithelial cells, including the external epithelia (mainly skin and linings of the gastrointestinal tract, lungs, and cervix)

and the internal epithelia that line various glands (e.g., breast, pancreas, thyroid). See ***cancer.***

Chemotherapy: The use of specific chemical agents to arrest the progress of, or eradicate, disease in the body.

Chiropractic: A system of treatment based on the theory that disease is produced by disruptions in the normal flow of a natural life force termed "Innate Intelligence. " This life force flows through the nervous system and is disrupted by displacements of the spinal vertebrae called subluxation. Chiropractic manipulation is intended to correct the subluxation allowing the uninterrupted flow of Innate Intelligence to return the body to full health. As practiced currently in the United States, most chiropractic is limited to treating skeletal abnormalities.

Chiropractor: A practitioner of chiropractic.

Chronic: Lingering, lasting, as opposed to acute. A term used to describe persistent disease.

Clinical trial: A scientific research activity undertaken to define prospectively the effect and value of prophylactic, diagnostic, or therapeutic agents, devices, regimens, procedures, etc., applied to human subjects.

Control group: In a randomized clinical trial, the group receiving no treatment or some treatment with which the group receiving experimental treatment is compared. The control treatment is generally a standard treatment, a placebo, or no treatment. Compare ***experimental group.***

Conventional: As used in this report, referring to ''mainstream' or ''orthodox' medical treatment. These terms are used interchangeably, with no intended distinctions among them.

Cure: (n.) A medical treatment that reliably relieves the patient of the disease. (v.) To heal, to make well, a restoration to health.

Device, medical: Any instrument, apparatus, or similar or related article that is intended to prevent, diagnose, mitigate, or treat disease or to affect the structure or function of the body.

Dimethyl Sulfoxide (DMSO): Analkyl sulfoxide, C_2H_6OS, a powerful solvent that can dissolve aromatic and unsaturated hydrocarbons, organic compounds, and many other substances. Its biological activities include the ability to penetrate plant and animal tissues and to preserve living cells during freezing. In mainstream medical treatment, it has been shown efficacious for one condition, interstitial cystitis. It is used in a number of unconventional cancer treatment, applied topically in conjunction with other agents.

Drug: Any chemical or biological substance that maybe applied to, ingested by, or injected into humans in order to prevent, treat, or diagnose disease or other medical conditions.

Effectiveness: Same as efficacy (see below) except that it refers to ". . . average or actual conditions of use. "

Efficacy: The probability of benefit to individuals in a defined population from a medical technology applied for a given medical problem under ideal conditions of use.

Encephalomyelitis: An inflammation of the brain and spinal cord that is caused by infection with any of a number of viruses.

Endogenous: Developing or originating within the organism, or arising from causes within the organism.

Enema: A rectal injection for the purpose of clearing out the bowel, or administering drugs or food.

Etiology: The cause or origin (of disease).

Experimental group: In a randomized clinical trial, the group receiving the treatment being evaluated for safety and efficacy. The experimental treatment may be anew technology, an existing technology applied to a new problem, or an accepted treatment about whose safety or efficacy there is doubt. Compare ***control group.***

Health fraud: False or unsupported claims for a medical treatment's effectiveness.

Health: The state of optimal physical, mental, and social well-being, and not merely the absence of disease and infirmity.

Herbalist: A practitioner who prescribes medicaments of herbal compounds; also, one versed in herbal lore.

Herbal treatments: Treatments based on the therapeutic use of plant products.

Homeopathy: A philosophy of treatment founded by Samuel Hahnemann (1755-1843), in which microdoses of medicines are believed to stimulate the body's vital force. Some of these medicines are not known to contain even one molecule of the original compound per dose, but are considered by the homeopath to be extremely powerful. The power of these doses is enhanced by "succession" (violent shaking) performed at various stages in their preparation.

Immune system: A specialized group of body cells and cell products that respond to foreign organisms and substances in the body. The cell products are largely immunoglobulins (antibodies), produced by specialized white blood cells known as lymphocytes. Some lymphocytes and various other cells of the immune system directly attack foreign organisms.

Immunity: The condition of being immune; an organism's capacity to resist disease. Immunity may be either innate or acquired. Innate immunity is natural or inherited. Acquired immunity may be active (resulting from either previous exposure to the disease-causing agent or vaccination) or passive (resulting from the transfer of preformed antibodies in immune serum or from mother to fetus).

Immunotherapy: Cancer treatment that produces antitumor effects primarily through the action of natural host defense mechanisms or by the administration of

natural mammalian substances. Also called biotherapy and biological therapy.

In vitro: Literally, "in glass," pertaining to a biological process or reaction taking place in an artificial environment, usually a laboratory. Sometimes used to include the growth of cells from multicellular organisms under cell culture conditions.

In vivo: Literally, "in the living," pertaining to a biological process or reaction taking place in a living organism. In biomedical research, used to describe experiments or processes in whole animals (e.g., mice, rats, humans), as opposed to those in a test tube or other experimental system.

IND application (Investigational New Drug application): An application submitted to FDA by any person or company for permission to conduct clinical research on an unapproved drug. If approved, the IND exempts the sponsor from the FDCA prohibition against shipping unapproved drugs in interstate commerce for the study or studies specifically described in the IND application.

Injunction: A prohibitive order issued by a court at the request of one party forbidding another party from committing some act.

Insurance fraud: Intentional misrepresentation of the facts in order to obtain reimbursement from an insurer.

Interstate commerce: Traffic, commercial trading, or the transportation of persons or property between States.

Intravenous: Within a vein or veins.

Laetrile: Trademark name for l-mandelonitrile-B-glucuronic acid.

Leukemias: Cancers of the blood-forming organs, characterized by abnormal proliferation and development of leukocytes (white blood cells) and their precursors in the blood and bone marrow. (See ***cancer.)***

Lymphomas: Cancers of cells of the immune system (i.e., the various types of lymphocytes). See ***cancer.***

Macrobiotics: A lifestyle and diet adapted from the Far East and popularized in America by Michio Kushi and others. Macrobiotics is not primarily a treatment for cancer, but it is adopted by some cancer patients. The principles of the diet consist of balancing the "yin" and "yang" energies of foods. Different types of cancer are considered either yin or yang and the macrobiotic program must be adapted to the particular type of cancer and to individual traits.

Malignant: Referring to tumors that are able to invade neighboring tissue and metastasize to distant sites in the body.

Medical malpractice: Professional misconduct or unreasonable lack of skill by a physician or other health care provider.

Metabolic treatment: Anon-specific term used by many unconventional practitioners to refer to a combination of unconventional approaches aimed at improving the physical and mental condition of cancer patients, sometimes including the concept of "detoxification."

Metastasis: The spread of a malignancy to distant body sites by cancer cells transported in blood or lymph circulation.

Microbe: A minute living organism, especially applied to those minute forms of life that are capable of causing disease in animals, including bacteria, protozoa, and fungi.

Microorganism: A minute living organism, usually microscopic, such as bacteria, viruses, molds, yeasts, rickettsiae, and protozoa.

Naprapathy: A system of treatment employing manipulation of connective tissue (ligaments, muscles, and joints) and dietary measures; said to facilitate the recuperative and regenerative processes of the body.

Naturopathy: The healing of disease through natural methods, making use of physical forces such as air, light, water, heat, massage, etc.

Neoplasm: A new growth of tissue in which the growth is abnormal, uncontrolled, and progressive. Malignant neoplasms are also called "tumors" or "cancer."

New Drug: According to the FDA standard it is defined in part as: "any drug . . . the composition of which is . such that such drug is not generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, as safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling thereof." (21 U.S.C. § 321(p)(l)).

Nontoxic: In general medical use, referring to treatments without adverse effects.

Nostrum: A medicine of secret composition recommended by its preparer but usually without scientific proof of its effectiveness.

Oncogene: A gene of which one or more mutant forms is associated with cancer formation.

Oncologist: A physician who specializes in the treatment of cancer, usually referring to medical oncology, which is a subspecialty of internal medicine.

Oral: Pertaining to the mouth, taken through or applied in the mouth as an oral medication.

Osteopathy: A system of treatment founded by Andrew Taylor Still (1828-1917) and based on the theory that the body is capable of making its own remedies against disease and other toxic conditions when it is in normal structural relationship and has favorable environmental conditions and adequate nutrition. It utilizes generally accepted physical, medicinal, and surgical methods of diagnosis and therapy, while placing chief emphasis on the importance of normal body mechanics and manipulative methods of detecting and correcting faulty structure.

Palliative treatment: Treatment designed to provide relief from a disease or condition (e.g., to provide comfort or reduce pain), but not to cure the disease or

condition.

Pathogen: A specific causative agent (e.g., a virus or bacterium) of a disease.

Pathogenesis: The mode of origin and development of a disease process.

Pathology: The scientific study of the cause of disease and of the associated structural and functional changes that are the result of disease.

Peptide: Compounds consisting of two or more amino acids linked together by a chemical process that produces one molecule of water for each joining of one amino acid to another. Peptides are the building blocks of proteins.

Pharmacologic treatments: Treatments based on the administration of chemical agents (other than biological chemicals).

Physician: An authorized practitioner of medicine, as one graduated from a college of medicine or osteopathy and licensed by the appropriate board.

Placebo effect: A beneficial effect of a medical technology that cannot be attributed to properties of the technology itself. Often considered psychologically-engendered well-being or improvement in a condition brought on by the belief of the patient that the technology itself is beneficial.

Placebo: A drug or procedure with no intrinsic therapeutic value. In a randomized clinical trial, a placebo is given to patients in control groups as a means to blind investigators and patients as to whether an individual is receiving the experimental or control treatment.

Pleomorphic: A term used in microbiology to refer to bacteria that change in size and shape during their life cycle (also called "cell wall deficient" bacteria).

Prognosis: A forecast as to the probable outcome of an attack of disease; the prospect as to recovery from a disease as indicated by the nature and symptoms of the case.

Prophylaxis: The prevention of disease and preservation of health.

Quackery: A slang term used to describe medical treatments that are falsely described to be effective.

Radiotherapy: The treatment of disease by ionizing radiation.

Random allocation: In a randomized clinical trial, allocation of individuals to treatment groups such that each individual has an equal probability of being assigned to any group.

Randomized clinical trial (RCT): An experiment designed to test the safety and efficacy of a medical technology in which people are randomly allocated to experimental or control groups, and outcomes are compared.

Recurrence: In cancer, the regrowth of tumor tissue after all evidence of it had apparently been eradicated either by surgery or other means (e.g., radiotherapy). A recurrence may occur at the site of the original tumor or elsewhere in the body, as metastatic disease.

Regression (or remission): In relation to cancer, regression refers generally to the shrinking of a tumor by other than surgical means. A complete regression occurs when a tumor that was at one time measurable disappears completely. Partial regression describes the condition where the measurable tumor is reduced by at least 50 percent in size.

Safety: A judgment of the acceptability of risk in a specified situation.

Sarcoma: A cancer of supporting tissue of the body (e.g., bone, blood vessels, fibrous tissue, muscle). See ***cancer.***

Spontaneous regression (or remission): In cancer, the disappearance (complete regression) or diminishing by at least 50 percent in size (partial regression) of a tumor without any identifiable cause (i.e., without medical intervention).

Staging: In oncology, an attempt to define the true extent of cancer in its three compartments, TNM. These refer to the primary tumor (T), regional nodes (N), and metastasis (M). Subscripts ranging from O to 4 are used to denote size and degree of involvement; O indicates undetectable, and 1,2,3, and 4 a progressive increase in size or involvement.

Subcutaneous: Beneath the skin.

Systemic: Pertaining to or affecting the body as a whole.

Terminal: In cancer prognosis, forecasting death due to the growth and progression of the cancer.

Third-party payer: Private insurers or government insurance programs that pay providers for medical care given to patients they insure, either directly or by reimbursing patients for payments they make.

Toxicity: Referring to medical treatments, the degree to which they produce unwanted, adverse effects.

Treatment IND: A provision of the Federal Food, Drug and Cosmetic Act that allows patients with life-threatening or serious diseases to obtain certain drugs that are in late stages of clinical testing, but have not yet been approved by FDA for marketing.

Tumor: A new growth of tissue in which the multiplication of cells is uncontrolled and progressive. Also called neoplasm.

Unapproved drug: A drug that has not been approved by the FDA for marketing in the United States.

Unconventional Cancer Treatment: As used in this report, unconventional cancer treatments include the wide variety of treatments that fall outside the bounds of mainstream medicine. Other terms used by ***proponents*** to describe all or some of these treatments include: alternative, complementary, non-toxic, holistic, natural, and non-invasive. Those used by the sharpest of ***critics*** include: unproven, questionable, dubious, quackery, and fraudulent. The term unorthodox is used at times by both proponents and critics.

Vaccine: A preparation of living, attenuated, or killed bacteria or viruses, fractions thereof, or synthesized antigens identical or similar to those found in the disease-causing organisms, that is administered to produce or increase immunity to a particular disease.

Visualization: The use of mental imagery to create positive beliefs that will activate the body's defenses against disease. In one type of visualization, patients are taught to see their cancer cells as vulnerable and disorganized, and their treatment as powerful and directed only at the cancer cells, sparing the healthy cells. They are also instructed to see their immune systems flushing away the cancer cells.

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Appendix C

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Index

Index