

UN SOUND METHODS OF CANCER TREATMENT.

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"Things are seldom what they seem, skim milk masquerades as cream."

Gilbert and Sullivan, "HMS Pinafore"

DEFINITION AND MAGNITUDE OF THE PROBLEM

Earlier editions of "Cancer: Principles and Practice of Oncology" entitled this chapter "Unproven Methods of Cancer Treatment." However, the term "unproven" is nonjudgmental and is, at best, a euphemism for the unsound therapies that are described in this chapter. After all, many of the newer methods of cancer treatment described in the previous chapter are, in some sense, "unproven" in that their precise role in clinical treatment remains uncertain. The distinguishing characteristics of unsound methods of cancer treatment (whether one wishes to label them unproven, unorthodox, nontraditional, or alternative therapies) are:

- 1) promotion without sufficient preclinical data to justify use in patients, and
- 2) unmethodical treatment of patients that is incapable of detecting either meaningful responses or therapy-related side effects.

Not surprisingly, purveyors of unsound methods generally offer "non-toxic" or "natural" approaches to cancer treatment. Somewhat surprisingly, and as will be discussed in greater detail later, these unorthodox practitioners are largely physicians who escape regulatory control by the Food and Drug Administration and offer their particular treatment approach to well-educated patients with early-stage disease. At a time when 50% of the serious cancers diagnosed in the United States are curable with existing therapies and access to scientifically sound experimental trials has been considerably simplified with computerized

information systems, it seems inconsistent that unsound methods of cancer treatment should continue to be a significant public health problem. And yet, the problem remains enormous.

Until recently, accurate estimates of the magnitude of the use of unsound cancer remedies were difficult. In 1984, the Subcommittee on Health and Long-Term Care of the U.S. House of Representatives concluded that Americans spent \$10 billion on unsound and unscientific remedies (1), with some \$4-5 billion being spent annually on useless cancer treatments. The cost in human terms is impossible to estimate.

One survey found that 13% of in-patients treated at a large urban cancer center had used or were using an unorthodox treatment regimen in addition to therapy prescribed by their oncologists (2). Although this represents a highly selected in-patient population at a university referral center, this estimate of the frequency of use of unsound treatments is supported by a more recent Harris telephone survey of over 6000 American households. The study, undertaken for the Division of Consumer Affairs of the Food and Drug Administration in 1986, reports that 15% of all cancer patients had used one or more questionable cancer treatments (3). This sample estimate, applied to the six million Americans who are alive today with a previous diagnosis of cancer, would project that approximately one million Americans have experimented with one or more unsound cancer treatments.

What factors contribute to the continuing appeal of "alternative" cancer treatments over time? An interesting and perhaps predictable component to cancer quackery has always been an element of faddism.

Indeed, it is notable that the popularity of different methods of unsound cancer treatment has often paralleled advances in orthodox clinical cancer medicine. In the 1940s and 1950s, an era when radiation therapy was beginning to improve control of local-regional disease, cancer quackery became device-oriented. This was a time when cancer patients were treated with the oscilloclast (a device that supposedly retuned disharmonic electrons and restored health) and the orgone energy accumulator (purportedly capable of concentrating a visible and ubiquitous cosmic energy into depleted erythrocytes). During the 1960s and 1970s, a period when chemotherapy was beginning to become accepted as an effective treatment for patients with advanced cancer, useless drugs were offered by nonscientific practitioners. This was the era that saw the use of krebiozen and laetrile in literally thousands of cancer patients, and when the shiboleth "freedom of choice" became a banner under which cancer patients demanded access to organized quackery.

There have been two recent fundamental shifts in the practice of unsound cancer treatment. The first, and most predictable, is a new focus on treatments that might be called "biological." Since the beginning of the 1980s, thousands of cancer patients have paid millions of dollars for treatment with "antineoplastons" (proteins derived from urine and said to be capable of differentiating tumors) or with Dr. Lawrence Burton's "immunoaugmentative therapy" (falsely represented as being able to boost immune response). Differentiating agents and immunotherapy are among the most promising leads in mainstream cancer treatment, and the biological trend in unsound cancer therapy in the 1980s continues the device orientation of the 1940s-1950s and the drug orientation of the 1960s-1970s.

In each case, the unsound practitioner echoes the most promising theories of the day in offering his own peculiar brand of optimism. This optimism is derived from the promise that, in addition to being scientifically avant garde, the alternative therapist promises safer, more natural, less toxic, yet uniquely effective treatment.

The second most recent and fundamental shift in alternative medicine involves the perception of cancer and other diseases as symptoms of metabolic imbalance rather than illnesses in and of themselves. It is a lifestyle orientation to cancer that holds that the disease can be effectively prevented and treated by changes in diet, supplements of enzymes and vitamins, or avoidance of stress, pollutants and impurities. This is the world of "metabolic therapy," where laetrile is no longer a drug, but reborn as "vitamin B-17."

In addition, because metabolic therapy holds that the cancer is merely a symptom of more fundamental underlying processes, tumor progression does not necessarily indicate treatment failure. Instead, the effectiveness of treatment can be monitored by subjective feelings, by blood assays available only to the practitioner, or through other irrelevant observations, such as iridology (anatomic diagnosis by examination of the iris). The result of all of these unsound approaches is the same: patients spend time and money on useless therapies. The potential for greater harm is obvious: cancer patients who seek out and obtain unsound therapy may not receive treatments of proven efficacy or appropriate experimental treatment approaches based in sound science. In addition, as will be described later in this chapter, some of the

most popular unsound treatments are potentially harmful in themselves. A list of unsound therapies is given in Table 1, and detailed statements on each approach are available from the American Cancer Society.

It is useful, from an historical perspective, to understand how quackery affected drug regulation in the United States before reviewing the evolution of past and present unsound cancer treatments.

TREATMENT REGULATION

The Food and Drug Administration (FDA) is responsible for regulating drug availability in the United States. Indeed, the FDA has the ultimate authority to approve or disapprove new treatments in cancer and other diseases. It is interesting that much of the FDA's current regulatory authority came from an obvious hoax in cancer therapy at the turn of the century--the so-called "golden age of quackery" (4).

The case involved Dr. O. A. Johnson of Kansas City, Missouri, and his "Mild Combination Treatment" for cancer. As shown in Figure 1, prospective patients were invited to send for Dr. Johnson's books, "Cancer and Its Cure" and "My 125-page Testimonial Book"--titles that have a contemporary ring in today's world of unsound cancer treatments. Those who were unable to visit the doctor were asked to fill out a symptom sheet so that cures could be "effected at home." Recognizing that the Mild Combination Treatment was fraudulent, the Bureau of Chemistry (forerunner of today's FDA) prosecuted Dr. Johnson under the Food and Drug Act of 1906. The case eventually reached the Supreme Court, and was decided in favor of Dr. Johnson. Justice Oliver Wendell Holmes, writing the majority opinion, interpreted existing laws to pertain only to drug labeling and

not therapeutic claims. As long as the treatment materials were properly labeled, Dr. Johnson could not be prosecuted for "mistaken praise" of the Mild Combination Treatment! (4)

President Taft and Congress responded by amending the Food and Drug Act, finally making "false and fraudulent" therapeutic claims a criminal offense. However, proof of fraudulence was often difficult in practice; and in 1938 Congress passed a new Food and Drug Law that required proof of safety before a drug could be marketed. The new law strengthened FDA's ability to cope with fraudulent cancer therapists, and the subsequent years saw a series of successful criminal prosecutions. As will be discussed later, it was during this era that the Koch therapy, Hoxsey's herbal tonic, and Krebiozen became subjects of highly visible public trials that also resulted in seizures of drug supplies and injunctions against further drug distribution. By 1961, FDA Commissioner George Larrick could state, "The Food and Drug Administration has had considerable success in combatting quackery in the courts. There have been some heavy fines and some prison sentences. Such actions have had a strong deterrent effect." (5)

In 1962, however, the FDA's responsibilities and priorities changed with the passage of the Kefauver-Harris amendments to the 1938 Food and Drug Act. These amendments required evidence of drug efficacy as well as safety before marketing. As a result, the FDA increasingly turned its attention to the control of legitimate treatment, and between 1962 and 1987, over 7,000 previously available prescription drugs were removed from the U.S. market. During the same interval, the FDA's commitment to combatting quackery decreased proportionately; less than 0.001% of the FDA budget is currently committed to combatting health fraud.

THE ERA OF UNSOUND DEVICES

As discussed earlier, the period between 1940 and 1950 saw the use of a number of fraudulent devices in the treatment of cancer. One of the more interesting therapists was Dr. William Reich, a Viennese colleague of Sigmund Freud. Reich's studies of character analysis and sexuality during the 1930s were considered seminal to the new discipline of psychoanalysis.

Between 1936 and 1939, Reich's research took him to Norway, where he claimed discovery of orgone, a visible and ubiquitous cosmic energy that he described as "the most powerful force in the universe." In 1940, Reich emigrated to the United States, where he purchased a 300-acre estate in Rangeley, Maine, which he named, appropriately enough, Organon. The estate eventually housed the "Orgone Energy Observatory," the William Reich Foundation, laboratories, and its own printing facilities (6).

It was in Rangeley where Reich designed and built "orgone energy accumulators," treatment devices resembling telephone booths constructed of metal, wood and asbestos board. Specialized, cone-shaped instruments were also designed to treat the head. Hundreds of these devices were leased throughout the United States at the then-remarkable cost of \$250 per month. Treatment was simple and consisted of sitting in the box or under the cone in order to absorb orgone energy. Treatment response was judged by blood tests performed in Reich's own laboratories. Volume I of the 1942 edition of The International Journal of Sexual Economy and Orgone Research has a strangely contemporary tone in describing some of the four blood tests for cancer: a culture test, a biological resistance test, a disintegration test, and a blue margin test. This battery of

studies was purported to be capable of distinguishing between healthy and "cancerous" blood and was said to be able to detect cancer before the development of a tumor.

Reich had thus developed not only his own theories of cancer etiology (orgone depletion in erythrocytes) but also a completely self-contained system for diagnosis, treatment, and prevention of cancer (7,8). It was an unimpeachable and self-fulfilling system that anticipated many common characteristics of unsound cancer therapists today.

However, as described in the previous section on the role of the FDA, this was an era of organized opposition to cancer quackery. The FDA consulted a group of independent clinicians and physicists who examined several orgone accumulators and concluded that orgone energy could be neither accumulated nor measured and that Dr. Reich's principles were without scientific merit or clinical utility. In 1954, a Federal injunction was issued against Dr. Reich and his foundation demanding recall of orgone accumulators and banning interstate advertisements in Dr. Reich's pamphlets and magazines.

Needless to say, proponents of the orgone energy theories charged that the FDA investigation interfered with freedom of the press and was part of an organized Government effort to prevent effective and nontoxic cancer treatments from being widely distributed (9). Dr. Reich was held in criminal contempt of the FDA injunction when he continued to lease and distribute orgone accumulators, claiming that courts and juries had no jurisdiction in matters of "natural law" (4). Despite an appeal to the Supreme Court, Dr. Reich was sentenced to two years in prison, where

he died in 1957. Although orgone energy devices are not part of the contemporary scene of cancer quackery, there are several common themes (a charismatic "scientist" with an appealing--albeit unsupportable--theory of cancer and its treatment, using unverifiable measures of success, whose faithful proponents believe that orthodox medicine desires to suppress innovation) that remain all too familiar.

At the same time on the west coast of the United States, Dr. Albert Abrams was pioneering other devices--equally unsound in principle and profitable in practice--for the diagnosis and treatment of cancer. Abrams' diagnostic technique involved analysis of patient blood specimens in a "radioscope"--a tuning apparatus capable of detecting radio frequencies associated with disease. After a blood specimen was dried on filter paper and inserted into the machine, the patient was required to hold metal plates connected to the radioscope while the operator completed an examination with a plastic wand. This examination was described as sufficiently sensitive to "inform the doctor whether or not the patient has cancer, or a tendency towards cancer, long before there has been any visible disturbance of tissue" (10). To treat what the radioscope diagnosed, Dr. Abrams developed the oscilloclast, a device that was said to be capable of restoring electronic vibrations in diseased tissue. Eventually, the fraud blossomed into a mail-order business sponsored by the Electronic Medical Foundation. Radioscopes were "perfected" to diagnose blood specimens mailed in on postcards by practitioners who rented an oscilloclast directly from Dr. Abrams. A diagnosis was promptly returned with recommended oscilloclast treatment settings. At the height of its popularity in 1950, oscilloclasts were

rented to more than 3,000 practitioners for a \$250 deposit and \$5 per month. As a result, Abrams was able to "endow" his Electronic Medical Foundation with some \$3 million (11).

However, a comprehensive investigation by the FDA demonstrated that the radioscope was incapable of distinguishing colored water from blood. The radioscope diagnosis of a specimen from an 11-week-old rooster was sinus infection and bad teeth (12). In 1958, after a series of appeals, the Electronic Medical Foundation was prohibited from interstate shipment of the devices. In 1962, the Foundation was dissolved. The story has an ironic twist in that the officers of the Electronic Medical Foundation subsequently founded the National Health Federation, an organization established to represent, protect, and promote alternative medicine in the United States. During the ensuing years, the National Health Federation would become increasingly organized supporters of the Hoxsey therapy, Krebiozen, and Laetrile.

THE ERA OF UNSOUND DRUGS

As discussed earlier, the popularity of individual unsound cancer treatments has varied over time, often paralleling advances in bona fide cancer medicine. The 1950s saw the beginning of not only the first successful use of cancer chemotherapy but also an era of promotion of fraudulent drugs.

The Hoxsey Treatment

One of the most popular health scams of the 1950s was the Hoxsey method of cancer treatment. In his 1956 book, "You Don't Have to Die," Harry Hoxsey described his approach as "essentially chemotherapy" for

"the systemic treatment of cancer" (13). The Hoxsey method was the prescription of two medicines: 1) the "pink medicine" (consisting of potassium iodide and pepsin) and 2) the "black medicine" (consisting of cascara in an extract of licorice, red clover, burdock root, stillingia root, berberis root, poke root, and the bark of the buckthorn and prickly ash) (14). This complex of plant products was attributed to Hoxsey's great-grandfather, who observed that his horse was cured of cancer after grazing on these same plants.

Hoxsey initially peddled his medicines from state to state and was convicted of practicing medicine without a license in Illinois and Iowa. He finally established clinics in Texas and Pennsylvania, where patients were examined, uniformly diagnosed as having cancer, and routinely offered treatment at a cost of \$400. At the height of its popularity in the late-1950s, more than 10,000 "cancer" patients were receiving Hoxsey's medicines (4).

Because of the treatment's popularity, there were many contemporary attempts to validate antitumor activity by independent review. In 1957, a site visit by the University of British Columbia to Hoxsey's Texas clinic concluded: "The medications are of no value in the treatment of cancer. We have found that the methods of diagnosis are inadequate, that treatments do not affect the progress of disease, that no serious attempt is made to evaluate results and that no significant research has been done." (15) This was followed by a detailed FDA examination of 400 cases of cancer "cured" by Hoxsey's regimen. Patients were found to fall into one of three categories: 1) those who never had a diagnosis of cancer, 2) those who had been previously cured of cancer

by conventional therapy, or 3) those (the majority) who had cancer that had not responded to the regimen (16). In short, no cures could be documented and no evidence of antitumor activity was found.

These reviews led to a series of highly public trials during which Hoxsey proponents countered the prosecution by lobbying Congress with a prayer campaign against the FDA. After ten years of litigation, the Hoxsey cancer treatment was finally banned from U.S. sales, although by that time over \$50 million had been spent on the drugs (17). As will be discussed later, the medicines continue to be offered for cancer treatment in Mexico.

Krebiozen

The growing popularity of Krebiozen in the late-1950s and early-1960s, following the invalidation of Harry Hoxsey's herbal medicines, began a new era in unsound cancer treatments. Unlike Hoxsey's folksy, midwestern tonics, Krebiozen and subsequent popular unsound remedies had a pseudo-scientific ring of authenticity and were increasingly promoted by more convincing proponents with the support of an organized constituency.

Krebiozen was initially manufactured as an antihypertensive by Dr. Stevan Durovic, a Yugoslavian physician who claimed to produce the drug by extracting the serum of horses injected with sterile extracts of Actinomyces bovis, a pathogenic fungus that causes lumpy jaw disease in animals. The original two grams of Krebiozen (comprising an estimated 200,000 doses) were purportedly produced from 2000 horses in Argentina and brought into the United States in Durovic's suitcase in 1949. In the U.S., Dr. Durovic met Andrew Ivy, M.D., Ph.D., Professor Emeritus

at the University of Illinois. Dr. Ivy became convinced that Krebiozen had antitumor activity following an experiment in which Durovic demonstrated disease "improvement" in seven of twelve animals treated with the drug (18). These results were never reproduced. Instead, Ivy, who was a respected scientist, began treating a series of patients after deciding that the drug was nontoxic by administering it to himself.

In 1951, the results of Krebiozen treatment in 22 cancer patients were announced at a press conference at the Drake Hotel in Chicago. The results of the trial were never submitted for publication. Instead, pamphlets published by the newly organized Krebiozen Research Foundation were distributed to the press at the time of the press conference claiming improvement in most patients treated. Although eight patients had died during the course of the trial, death was said not to be due to progressive cancer, and the fact that two additional patients had died in the interval between publication of the pamphlet and the press conference was omitted. Following Dr. Ivy's announcement, small quantities of Krebiozen were provided to several medical centers to allow them to reproduce results of the initial clinical trial. During the subsequent 12 years, independent investigators were unable to confirm that Krebiozen had any antitumor activity. However, this did not stop the Krebiozen Research Foundation from issuing reports and independently publishing monographs claiming impressive treatment responses in individual patients.

Between 1951 and 1963, Krebiozen was distributed by the Krebiozen Research Foundation to thousands of general practitioners throughout the United States. Physicians could receive an injectable ampule of

Krebiozen for a "research donation" of \$9 and use it in any way they saw fit. Business was brisk. The initial 200,000 doses were rapidly depleted, and in 1960 Dr. Durovic manufactured an additional 100,000 ampules from horse serum and horse meat. It was claimed that, like the original batch of Krebiozen, the treatment material contained lipopolysaccharides consisting of galacturonic acid, glucosamine, arabinose and xylose, combined with glycerol.

In 1962, the Kefauver-Harris Amendment to the Food and Drug Act required sponsors of investigational drugs to submit plans for the rational clinical development of new agents. Although Dr. Durovic submitted such a plan for Krebiozen to the FDA in June of 1963, he withdrew the package without review a month afterwards, making interstate shipment of Krebiozen illegal. A number of concurrent observations led to subsequent criminal proceedings. In 1963, FDA chemists analyzed samples of Krebiozen submitted by Drs. Ivy and Durovic. The white powder was found to be creatine, a simple organic acid widely distributed in muscle tissues and inactive as an antitumor agent. Analysis of pre-1960 ampules of Krebiozen revealed nothing but mineral oil, while those vials manufactured after 1960 contained mineral oil and trace quantities of methyl hydantoin, a soluble form of creatine.

Independent analysis of the clinical results of Krebiozen treatment was equally revealing. In 1962, the Krebiozen Research Foundation selected its 504 best responses (from over 4000 patients on whom records were available) to the National Cancer Institute (NCI) for independent review and analysis. Because these cases were inadequately documented for careful review, FDA officials spent considerable effort confirming

diagnoses, and reconstructing treatment duration, dose, and response. This information was submitted to an independent 24-member panel of experts appointed by the NCI. In 1963, that committee reported that review of all 504 cases established that Krebiozen had no antitumor activity. From the NCI's perspective, the case was closed and there was no justification to pursue clinical trials (19). In addition, the FDA undertook its own independent analysis of an additional 4307 cases submitted by the Krebiozen Research Foundation. Again, no convincing evidence for antitumor activity could be demonstrated.

In short, Krebiozen had been promoted for the treatment of thousands of cancer patients at a cost of millions of dollars. The treatment materials were falsely labeled. Moreover, although indiscriminate prescription made retrospective review of the thousands of available records particularly time-consuming and expensive, there was no evidence of reproducible antitumor activity in any malignancy.

In 1964, Dr. Ivy, Dr. Durovic, and the Krebiozen Research Foundation were indicted on 49 counts of violation of the Food, Drug and Cosmetic Act, including mail fraud, mislabeling of drugs, and conspiracy to defraud the public. Although the defendants were found innocent after a highly public nine-month trial (20), the interstate distribution of Krebiozen was stopped.

This decision was followed by a series of demonstrations by Krebiozen supporters who felt that the Government, industry, and organized medicine had worked in concert to deny the public an effective and nontoxic cancer treatment. Proponents blocked the FDA Commissioner's office and lobbied Congress to reverse the FDA decision. Eventually, eleven Senators would

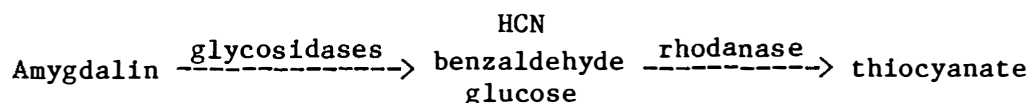
demand an impartial trial of Krebiozen. Dr. Durovic offered to sell the NCI bulk Krebiozen for such a clinical trial for \$170,000 per gram; the same quantity of pure creatine from chemical suppliers was available for thirty cents. However, interest in Krebiozen evaporated when Dr. Durovic unexpectedly left the United States for Switzerland, after withdrawing large amounts of cash from Foundation bank accounts. At the time, he was under investigation by the Internal Revenue Service for nonpayment of taxes on \$904,907 of unreported income. Dr. Ivy renamed Krebiozen "Carcalon"--Greek for a natural substance that slows down a cancerous process (21)--and continued to prescribe the drug from his Chicago office. At the request of the Illinois State Medical Society, the Governor appointed the Illinois Krebiozen Committee to oversee continued "controlled scientific testing of Krebiozen" by Dr. Ivy. The Committee never gave a report, and at the time of Dr. Ivy's death in 1977 there was still no evidence that Krebiozen was useful in the treatment of cancer.

Laetrile

Laetrile is a generic term for a group of cyanogenic glucosides that can be isolated from a number of natural sources, including the pits of edible fruits such as apricots, cherries, pears, apples, and peaches (22,23). The term was initially coined by E. T. Krebs, "because this apricot-kernel preparation was laevorotary to polarized light and because amygdalin was chemically a malonittrile" (24). The principal constituent of Laetrile is amygdalin, a compound first isolated in 1830 (25) and chemically synthesized in 1924 (26). As early as 1935 it was found that the beta-glycosidic linkage in amygdalin could be hydrolyzed by emulsin (an enzyme found in almonds) or specific beta-glucoridases to release one molecule of hydrogen cyanide and benzaldehyde and two molecules of glucose.

In the 1920s, Dr. Ernest Krebs, Sr., was the first to use oral amygdalin in the treatment of cancer. The preparation proved toxic, however, and it was not until 1952 that Krebs' son, Dr. E. T. Krebs, reported development of a "safe" parenteral formulation.

Laetrile's purported mechanism of action is shown below. It was hypothesized that beta-glucosidases would activate amygdalin to glucose, benzaldehyde, and toxic hydrogen cyanide. Hydrogen cyanide could be itself detoxified by rhodanese (thiosulfurtransferase), which would convert HCN to inactive thiocyanate (27).



In order to explain amygdalin's specific antitumor effects and lack of toxicity, proponents further postulated that cancer cells have high intracellular levels of beta-glucosidase and low levels of rhodanase, while the opposite occurs in normal tissues.

There are a number of critical flaws to this theory. First, normal and malignant tissues appear to have comparable levels of rhodanase (28) and tumor tissues lack beta-glucosidase activity (29). Indeed, there appears to be little detectable in vivo beta-glucosidase activity, so that virtually all of a parenteral amygdalin dose is excreted intact in the urine (23). Moreover, laetrile itself is inactive both in vitro and in vivo against murine and human tumors in a number of preclinical assays, even when beta-glycosidase is administered concurrently (30-33). Indeed, control animals in comparative studies show improved survival, suggesting that amygdalin is toxic without being active against disease.

Because beta-glycosidase is not found in mammalian tissues, up to 10 grams of amygdalin can be administered intravenously without toxicity (34). However, intestinal flora have significant beta-glucosidase activity and are capable of releasing cyanide from amygdalin. Cyanide toxicity can occur following oral Laetrile, and death from cyanide poisoning has been reported following such treatment (35). Moreover, although cyanide is proposed as the active component to Laetrile, cyanide itself has been tested as a potential antitumor agent and appears to be more toxic to normal than malignant tissues (36-38).

Thus, there is no evidence for selective activation of amygdalin by malignant tissues, preferential inactivation of hydrogen cyanide by normal tissues, or usefulness of hydrogen cyanide as a chemotherapeutic agent. The drug has proved inactive in every in vivo and in vitro system in which it was tested. And yet Laetrile became the most popular and celebrated unsound cancer therapy of contemporary medicine. What explains the Laetrile phenomenon?

As Wallace Janssen has noted, by the mid-1950s the Laetrile business was controlled by Andrew McNaughton, an international entrepreneur with a flair for manipulating the press (4). In 1961, McNaughton founded Bioenzymes International, Ltd., and began the manufacture of Laetrile in both Mexico and Canada. In 1963, a strongly pro-Laetrile paperback book, "Laetrile--Control for Cancer, The Authorized Story," was published with an introduction by McNaughton (39). Several of the chapters were reprinted in contemporary newspapers and magazines, and so began an intense public interest in and demand for the drug. However, with neither preclinical nor clinical evidence that Laetrile was useful in the treatment of cancer,

the FDA began a series of actions against Dr. Krebs and the McNaughton Foundation. The Canadian FDA followed by prohibiting distribution of Laetrile in Canada. Manufacture and distribution continued in Mexico, where apricot pits were largely imported from the California fruit-packing industry.

In 1970, the McNaughton Foundation of Canada submitted an investigational new drug application (INDA) to the U.S. FDA. The INDA was granted, but the FDA withdrew its approval a month later. Dr. Charles Edwards, then Commissioner of the FDA, cited "serious preclinical and clinical deficiencies" in the application (40). For example, while chemical analysis of Canadian Laetrile in the 1960s found amygdalin contents between 87% and 98%, Mexican production suffered from problems in quality control (41). FDA analysis of Laetrile from Mexican laboratories indicated that a 500 mg tablet might contain from 42 to 450 mg of amygdalin, while the parenteral product was 14-87% pure. Indeed, vials of injectable Laetrile were found to be contaminated with bacteria, fungus, and isopropyl alcohol (42). However, the FDA's reversal only strengthened the public's opinion that the Establishment was intent on keeping a useful product away from patients. An article in the Harvard Political Review ignored available evidence and concluded that "vested interests have prevented the use of an inexpensive and effective cancer cure." (43) At the same time, the legal prosecution of the ultra-conservative physician Dr. John Richardson under a California law that made prescription of Laetrile a felony galvanized the John Birch Society. Laetrile proponents established the International Association for Cancer Victims and Friends in 1963 and in 1972 John-Bircher Robert Bradford founded the Committee for Freedom of Choice in Cancer Therapy. Together with the National Health

Foundation, these organizations mounted an effective campaign to "legalize" Laetrile on the premise that the patient and physician should have ultimate authority in choosing treatment and that the Government should not regulate medical practice. As Lerner notes in assessing the Laetrile phenomenon, this was a time when anti-establishment groups and ultraconservatives united in the name of "freedom of choice" (44).

Their efforts at the state level were highly successful. In a 1977 New England Journal of Medicine editorial entitled "Laetrilomania," Dr. F. J. Ingelfinger summarized contemporary developments: "In Alaska, Laetrile may be prescribed by doctors, and an Oklahoma judge legalized importation of drug from Mexico. Indiana, if the physician-Governor signs the bill passed by his legislature, would become the first state to approve the manufacture and sale of the substance as well as its use. Bills that prohibit interference with the sale or use of laetrile are well on their way in Arizona, Florida, Massachusetts, and Minnesota" (45).

During the next year, additional legislation to approve Laetrile at the state level would follow the celebrated case of Rutherford vs. the United States. In this 1978 case, Glen Rutherford enjoined the FDA from interfering with his constitutional right to obtain nontoxic therapy (Laetrile) for his terminal malignancy. Both the U.S. District Court in Oklahoma and the Court of Appeals ignored the fact that Rutherford's "terminal" rectal polyp had been surgically cured. Instead, they ruled that safety and efficacy have no meaning in the treatment of terminally ill patients and that the designation of terminal illness could be made by any licensed physician. The FDA was directed to provide regulations for the distribution of Laetrile to any terminal cancer patient who

desired it (46). Although this decision was eventually overturned by the Supreme Court, Laetrile gained additional political credibility and 23 states moved to legalize Laetrile therapy.

Despite widespread Laetrile usage, evidence that the drug was effective remained unconvincing. By 1978 it was estimated that more than 70,000 Americans had been treated with Laetrile (47). A small retrospective analysis of Laetrile treatment response was undertaken by the California Cancer Commission in 1953 (48); no antitumor activity was found in 44 patients with a variety of tumors. By far the largest retrospective analysis of Laetrile efficacy was undertaken by the National Cancer Institute in 1978 (47). Case reports of patients who might have benefited from Laetrile were solicited from 385,000 physicians, 70,000 health professionals, and pro-Laetrile groups. Only 93 cases were submitted, of which 67 were evaluable. Of these, six patients were felt to have had an objective treatment response (2 lymphoma, 2 adenocarcinoma, 1 carcinoid, 1 squamous cell lung cancer). The authors admitted that the design of the study made it impossible to rule out intentional or unintentional submission of inaccurate information, but concluded that if Laetrile has antitumor activity, it must be vanishingly small. The proper denominator for the six responses is not the 67 cases selected for best response but the 70,000 patients known to have been treated with the drug.

The issue of Laetrile's usefulness in cancer treatment remained unsettled. Some prominent physicians urged legalization as a way to "make forbidden fruit less tempting" (45) while others urged prospective clinical trials (49). In 1978, the NCI submitted its own investigational new drug application for a clinical trial of amygdalin to the FDA. The

NCI assured quality control in the production of the drug as well as prospective, well-designed and well-implemented clinical trials.

In a small Phase I study, a single patient developed cyanide toxicity after eating almonds during Laetrile treatment (almonds not only contain small quantities of amygdalin but also have beta-glycosidase activity) (50). In the larger Phase II trial, no responses were seen in 178 patients with a variety of cancers (51). The resolution of Laetrile's activity as an anticancer drug came 30 years and 70,000 patients too late.

UN SOUND CANCER TREATMENTS POPULAR TODAY

As discussed at the beginning of this chapter, there have been two fundamental developments in the contemporary practice of unsound cancer medicine. The first is a predictable shift towards treatments that might be considered biological, while the second is the development of the concept that cancer is a symptom of underlying metabolic disturbances that can be prevented and treated by diet, vitamins, and stress avoidance. Two of the most popular unsound biological treatments are immunoaugmentative therapy (IAT) and antineoplastons.

Immunoaugmentative Therapy (IAT)

IAT is a scientifically unsupportable treatment that is dispensed by the Immunology Researching Center in Freeport, Bahamas. The Center was established in 1977 by Dr. Lawrence Burton, a Ph.D. zoologist, after his failure to receive approval for clinical studies of IAT in the U.S. from the FDA (52). The treatment is based on the theory that cancer develops because of "immunoincompetence," which Dr. Burton can measure and restore using a series of protein fractions derived from the blood of patients and healthy donors.

Patients receiving IAT first undergo a series of "immunocompetence" blood tests that are computer-analyzed to select an individual patient's treatment regimen. The treatment itself consists of four "immune serum protein fractions": 1) "blocking protein," 2) "tumor antibody," 3) "tumor complement," and 4) "deblocking protein." Based on the computer analysis of the patient's immune profile, some or all of these fractions may be prescribed as daily subcutaneous injections. Stabilization of the immune system usually requires several weeks on the island, after which patients leave with a cache of sera and computer projections for further treatment (53). The initial treatment costs approximately \$10,000, and patients are required to make follow-up visits for immune system "tune-ups." (53) The clinic also provides patients with assistance in filing claims for third-party reimbursement.

In 1978, a year after the clinic was established, the Bahamian government requested a review of IAT by a committee of physician-scientists from the Pan American Health Organization. This panel found neither a scientific rationale for IAT nor clinical evidence for its efficacy and unanimously recommended that the Center be closed (54). Despite these findings, the clinic remained open (for the treatment of non-Bahamians only) and over 3000 patients, the majority of whom are Americans with cancer, have received IAT for cancer treatment or prevention. Because of political pressures at the state level, IAT was approved for the treatment of cancer in Florida and Oklahoma in 1981 (55,56). In addition, there have been unsuccessful Congressional proposals to exempt IAT from FDA control (57). As with Laetrile in the previous decade, an unsound cancer treatment was essentially legalized by individual states without regard to either therapeutic effectiveness or potential toxicity.

However, subsequent independent analysis of IAT treatment materials has shown them to be devoid of purported content or biological activity (Table 2). In each case, analysis of the IAT treatment reagents revealed diluted blood proteins, the major component of which was albumin (58). Specific immunoglobulins, macroglobulins, and complement activity said to be essential to the activity of the regimen were undetectable. Of additional concern was the finding that treatment materials were uniformly contaminated with bacteria and hepatitis (59), and an epidemic of nocardia abscess formation was reported at IAT injection sites (60). Even more worrisome was Dr. Burton's use of IAT in the treatment of AIDS, a disease that he ascribes to the immunodepressant effects of sexual lubricants (61). Since the IAT labs pool blood specimens prior to processing into treatment reagents, contamination of reagents with HIV is possible. Indeed, of 72 vials of IAT treatment materials available to the NCI for analysis, 37 (51%) were positive for antibodies to HIV (58), and the Centers for Disease Control was subsequently able to culture viable AIDS virus from Dr. Burton's treatment materials (62).

Thus, IAT is without scientific rationale or documented clinical activity. Rather, patients are treated with a series of inert blood products capable of transmitting bacterial infection, hepatitis, and AIDS. Because of these findings, in July 1985 the IAT clinic was closed as an international hazard to public health. After six months of demonstrations in Freeport and Washington, the clinic reopened. However, IAT remains an unsound and potentially harmful approach to the treatment of cancer and AIDS.

Antiplastons

Antiplastons is another "biological" therapy, offered by Dr. Stanislaw Burzynski at the Burzynski Research Institute in Houston, Texas. The treatment is based on the theory that medium-sized peptides normally present in urine are capable to controlling tumor growth and differentiation of cancer cells in vivo. In the early 1970s, Dr. Burzynski was a member of the faculty at the Baylor College of Medicine. During this time he used gel filtration techniques to isolate peptides from normal urine that inhibited in vitro growth of a number of human cell lines (63,64).

In 1977, Dr. Burzynski left Baylor to establish the Burzynski Research Institute. There, the initial peptide fraction, called antineoplaston A, was subfractionated into Antineoplaston A₁, A₂, A₃, A₄, A₅, A₁₀, and AS2-1 (65). Each fraction is said to be composed of low molecular weight peptides in the 2-5000 dalton range. The active component in each of these peptides has recently been identified as 3-[N-phenylacetaminopiperidine]-2,6-dione (65), a substance that is not known to occur in urine and has no known antitumor activity. In treating cancer patients, the dosage of each antineoplaston fraction is determined individually by first "measuring" pretreatment levels of antineoplastons in serum and urine. Dr. Burzynski claims that this ambient antineoplaston profile is a valuable aid in cancer diagnosis and also uses the assay to monitor response to antineoplaston therapy (66).

The period of "full dose" antineoplaston treatment may require from six weeks to more than a year (67). Therapy is administered via Hickman catheter, although newly available capsules for oral administration

"appear to produce better results in some forms of cancers" (67). The cost of each treatment (exclusive of monitoring and laboratory testing) is \$45.00, regardless of dose, and the therapy is claimed to be nontoxic. The clinic accepts full responsibility for billing third-party insurers, although a cash deposit of \$5000 has been requested from patients at the beginning of therapy (68).

The results of Phase I clinical trials using antineoplastons have been reported only as paid supplements in a single European journal. Although those trials are small (typically 15-20 patients), activity, including complete responses, is claimed in carcinoma of the lung, prostate, stomach, colon, breast, and bladder (69-72). Independent confirmation of these results, however, has not occurred. A site visit to the Burzynski Research Institute by the Canadian Ministry of Health in 1982 found no evidence of therapeutic efficacy, and medical claims for antineoplaston treatments were subsequently disallowed (73). In 1985, a follow-up of 36 antineoplaston-treated patients followed by 25 Canadian physicians found no evidence of partial or complete responses. Indeed, 34 of the 36 patients had died, and the only two survivors had had prior curative therapy (74). Moreover, antineoplaston preparations have no antitumor activity over a wide range of doses in tumor-bearing experimental animals and lethal toxicity was observed at highest treatment levels (75). Thus, current evidence does not substantiate the Burzynski Research Institute's claim that "the use of antineoplastons has gained, and continues to gain, recognition as a logical and likely basis for cancer control and perhaps a future cure. Antineoplastons are non-toxic to the patient, and this is a major factor for patients

when choosing this as a treatment" (67). Unfortunately, the treatments also appear to be ineffective.

METABOLIC THERAPIES

Current "metabolic" approaches to the treatment of cancer represent a wide spectrum of alternative interventions, including enzyme therapy, cellular therapy, dietary manipulation, vitamin treatment (including B-17, i.e., Laetrile, and megavitamins), and detoxification with enzymes or hydrogen peroxide. In each case, cancer is viewed as a symptom of a more basic and underlying metabolic imbalance. Thus, the metabolic therapist believes that cancer can be both prevented and treated with metabolic interventions. The idea is not new. In the early-1900s, Dr. William Koch prescribed a regimen of cancer treatment that was based on the theory that malignancies were nothing more than a protective response to toxic compounds generated within the body (76). Cancer could be treated by oxidizing these toxic compounds with Koch's "anti-toxin" preparation in combination with diet and enema therapy. Although Koch's antitoxin was, in essence, distilled water (Koch actually labeled the drug one part glyoxylide to one trillion parts water), the treatment was enormously popular and remains available today (4).

Indeed, as shown in Table 2, there has been a renaissance of interest in the metabolic and holistic therapy of cancer. Treatments offered at these centers vary widely, depending on the philosophy of the program. For example, the International Health Institute was established by dentist William Kelley, who believes that cancer is caused by pancreatic enzyme deficiency. He developed the Kelley

Enzyme Test, or the "self test for cancer." For a "donation" of \$50.00, patients are provided a Nutritional Lifestyle Program and the procedure for the enzyme test. Patients are instructed to take 6-8 pancreatic tablets after each meal for four weeks. The analysis then runs as follows: If, at the end of this time:

- A. You feel worse, have a loss of appetite, nausea, headache, goopy, sick, toxic or in general listless, you can be assured there is a cancerous condition present in your body.
- B. You feel better--have more energy and a brighter happier outlook, you can be assured there is a precancerous condition in your body.
- C. You feel no different, you can be reasonably assured there is not a cancerous condition present in your body. (77)

Overall, not very reassuring, although the Institute's nutritional program explains "how to avoid cancer or how to proceed if you're a victim." The program might include a low-protein diet (buttermilk allowed), mineral supplements (for example, blackstrap molasses), yogurt enemas, and induced sweating.

Some of the clinics offer more "traditional" alternative treatments. For example, the Biomedical Center in Tijuana still uses herbal tonics based on Hoxsey's original methods. Most of the clinics have evolved with the times, however. Diet, an important component of many metabolic therapies, is especially emphasized by the East West Center for Macrobiotics and the Kushi Foundation. The emphasis here is on the traditional oriental philosophy of yin-yang, where cancers of "yin" organs (colon, stomach, bladder) are treated with "yang" foods (cooked vegetables, fruit, fish) and cancer of "yang" organs (lung, liver) are treated with "yin" food (raw vegetables, no fruit, no fish) (78-80). Kushi recommends that

patients avoid meat, dairy products, sweets, processed foods, hot spices, and "toxic and unnatural" conventional cancer treatments (81). Because the macrobiotic diet is deficient in calories, vitamins D and C, and iron, nutritional deficiencies have been reported in both children and adults (82-84), and there is no evidence that this approach is useful as a cancer treatment (85-88).

Others, most notably Dr. Linus Pauling, have espoused nutritional supplementation as primary cancer treatment. It was Ewan Cameron who, in the mid-1960s, hypothesized that vitamin C might inhibit tumor cell invasion and metastasis. The theory, also called the "orthomolecular treatment" of cancer, is predicated on the notion that vitamin C augments collagen production or stabilization and decreases tumor cell production of enzymes, such as hyaluronidase, required for basement membrane invasion (89,90). An initial clinical trial of high-dose vitamin C (10 grams daily) did appear to improve survival, at least when compared to historic controls (91). However, because of the problems inherent in this kind of retrospective analysis, the NCI supported two successive trials at the Mayo Clinic. The first, a standard Phase II study, used vitamin C therapy in patients who had disease refractory to standard therapy; no evidence of tumor progression or subjective benefit was observed (92). The second study was a randomized, double-blind, placebo-controlled trial of high-dose vitamin C in patients who had had no prior therapy; again, no evidence of tumor regression was observed (93). Interestingly, vitamin C can prevent development of carcinogen-induced malignancies in some animal models (94). As discussed in the chapter on prevention, the NCI is supporting chemoprevention trials of vitamin C. However, available evidence now indicates that ascorbic acid has no role in primary cancer treatment.

However, nutritional and megavitamin therapy for the treatment of cancer and other diseases has developed into a profitable health-fraud industry in the U.S. (87,95). Here, practitioners can obtain degrees in "nutrition" by mail: \$1000 for a bachelor's degree, \$2000 for both bachelors and masters degrees, and \$4000 for bachelor, masters, and Ph.D. degrees (96,97). Some diploma mills even provide a computer program that will prescribe specious nutritional supplements based on the patient's dietary history. In addition to high-dose vitamin C, these "Health and Wellness" clinics might prescribe:

- Megadose vitamin A (3000-300,000 unit/day) for "immune stimulation" and "epithelial integrity" (88). These doses of vitamin A are not known to have such effects and may, in fact, be associated with significant toxicity. Indeed, the ingestion of 5000-10,000 units of vitamin A for 30 days can cause increased intracranial pressure, fetal abnormalities, and hepatic and renal toxicity (98,99).
- Megadoses of vitamin E (up to 3200 IU/day) as an "antioxidant" (100). Vitamin E has no known use in cancer treatment. Although doses of 300 IU or less a day are considered nontoxic, increased triglycerides are seen at 600 IU/day (101), depression and fatigue at 900 IU/day (102), and nausea, diarrhea, headache, and blurred vision at 3200 IU/day (103). Double-blind studies have shown no effect of vitamin E on work performance or libido (101), and high doses in experimental animals can cause teratogenesis, depressed bone calcification, and testicular atrophy (104).
- Vitamin B-15 ("pangamic acid," "15" or "pangamate"). "Vitamin B-15" is not known to be a vitamin at all. Prescribed as a dietary supplement in health stores, analysis reveals that preparations consist of

dimethylglycine hydrochloride (DMG) or diisopropylamine dichloreacetate (DIPA) (105). Both compounds are, indeed, known carcinogens of no nutritional value (106,107). Although pangamic acid is illegal in the U.S. as either a drug or a vitamin, it remains freely available in health stores because the FDA is unable to trace the thousands of "B-15" retailers (88,108).

The majority of the metabolic clinics shown in Table 3, including American Biologics, Centro Medico Del Mar (the Contreras clinic), Fairfield Medical Center, The Manner Clinic, and the Gerson Clinic offer a combined program of diet, vitamin therapy (sometimes including Laetrile), and detoxification with wheatgrass therapy or coffee enemas. Again, the underlying principle for these approaches is the theory that reversing the metabolic imbalances that "actually caused" the malignancy will control or cure the disease. For example, the portal delivery of caffeine to liver by coffee enema is thought to increase bile production, alkalize the intestine and detoxify impurities (109,110). Yet, there are certain internal inconsistencies to the theory; for example, drinking coffee is absolutely prohibited during treatment. The Centro Medico Del Mar of Tijuana, established by Dr. Ernesto Contreras, also offers orthodox treatment in addition to its metabolic program of Laetrile, cell therapy, interferon, and enzyme enemas. However, laboratory tests, chemotherapy, and surgery are not included in the \$3,500 base price of Dr. Contreras' three-week program. Other practitioners, such as Hans Nieper of Germany, routinely include standard anticancer chemotherapy as part of a metabolic program that includes tumor vaccines, vitamin A, anavit (enzymes extracted from pineapple), squalin (shark liver extract), carnivora (venus fly trap

extract), Laetrile, and selenium and zinc (minerals that supposedly promote "tissue healing"). Should the tumor respond to effective drugs, practitioner and patient can ascribe the regression to the chemotherapy or any other aspect of the program.

Metabolic therapists offer not only an unsound cancer treatment but also compound the problem with unsound methods of cancer diagnosis. One such technique is iridology, the science of reading the iris to diagnose disease (111,112). As shown in Figure 2, the iridologist studies a homunculus superimposed within the iris, and from the physiologic black stripes therein is able to make organ-specific diagnoses. Because the technique is purported to be more sensitive than standard diagnostic imaging techniques, the iridologist claims to be able to detect preclinical or subclinical disease. Of course, this can then be conveniently "cured" (i.e., reversal of iris changes) with a medically useless intervention. Indeed, double-blind studies in which both ophthalmologists and iridologists have examined photographs from patients and healthy controls have shown the technique to be without merit (113,114). Still, iridology is a common technique for diagnosing disease and following therapeutic response in homeopathic and metabolic clinics.

THE SIMONTON METHOD--AN UNPROVEN ADJUNCT TO CANCER TREATMENT

There is one unproven (as opposed to unsound) method that deserves mention in this chapter, if only because of its current popularity. The Simonton method of relaxation and imagery is basically a self-help program designed to be used in conjunction with standard medical treatment (115). The program is described in detail in Dr. O. Simonton's best-selling

book, "Getting Well Again. A Step by Step Self-Help Guide to Overcoming Cancer for Patients and Their Families" (116). The techniques are simple and largely easily self-taught, including a program of relaxation and mental imagery performed three times daily, drawing analysis, identification and reduction of stress, exercise, counseling or group therapy, and a "sensible diet." Since the book was first published in 1978, "Getting Well Again" has gone through over 20 editions, and Stephanie Matthews-Simonton has recently authored another popular text, "The Healing Family" (117), which describes how family members can participate in the Simonton method. There is nothing here that is patently unsound, but is it of any use?

Dr. Simonton first became interested in the psychological factors that might influence treatment response during his training in radiation oncology. In 1975, he and Stephanie Matthews-Simonton published a study in The Journal of Transpersonal Psychology in which 152 patients were examined for their "attitude" profile at the time of completing radiotherapy for a variety of cancers. This attitude was then retrospectively correlated with treatment responses (118). Not surprisingly, patients who had had a good response to radiotherapy were optimistic; those with progressive disease had a sense of hopelessness. Despite the obvious problems with this kind of analysis, the Simontons conjectured that stress, depression, and hopelessness might actually contribute directly (independent of other behavior such as smoking or alcohol consumption) to the development of cancer. For example, in "Getting Well Again" the Simontons note that a number of studies have temporally linked the development of cancer to severe psychologic trauma, such as the loss of a loved one (119-122).

In a leap of faith, the Simonton's hypothesized that positive thinking and stress reduction might be useful as therapy and established the Cancer Counseling and Research Center (recently renamed the Simonton Cancer Center) in Fort Worth, Texas, to teach and administer their program. The Center conducts regular counseling and training workshops for both patients and professionals. A ten-day "Phase I" program of group therapy, training in relaxation and imagery, and counseling, intended primarily for patients, is offered at the Simonton's Southern California clinic and costs \$1900 for tuition, exclusive of food and lodging. In addition, more extensive "Phase II" workshops are conducted to instruct professionals in the Simonton techniques; more than 4000 such counselors have been trained (123). Finally, the Simontons have produced a series of audio-tape cassettes describing the program that can be purchased by mail (124).

In today's climate of "self-help" or "how-to" literature, the Simontons' techniques have become enormously popular, and there are certain appealing facets to the program. It is relatively inexpensive and recommended only as an adjunct to proven therapy. An American Cancer Society review notes other potentially positive aspects to the method: it gives the patient a sense of control, promotes relaxation and well-being, and causes no known deleterious effects (125). R. M. Mack, a physician with metastatic lung cancer, has detailed the usefulness of Simonton's techniques in a deeply personal note in The New England Journal of Medicine (126), and equal praise has appeared in other journals as well (127-130).

However, the literature on mind-set and cancer is much more confused than the Simontons would have us believe. For example, "Getting Well Again" limits its discussion to studies in which development of cancer has followed bereavement and asks the reader to accept that depression and carcinogenesis are causally linked. Alternative explanations are not discussed. For example, a patient under stress may be more likely to visit a doctor--behavior that might lead to early detection (131). Moreover, as Wellisch and Yager discuss in their excellent review, "Is There a Cancer-Prone Personality," the studies that link depression and disease use faulty personality measurements, have inherent selection bias, and are statistically imprecise (132). Indeed, there is an equal body of evidence to suggest that no relationship between psychologic attitude and cancer exists (133-135). For example, a controlled study demonstrated no correlation between psychologic attributes and development of breast cancer (134). A 24-year follow-up comparison of a large number of World War II veterans discharged because of "psychoneurosis" showed no increase in cancer incidence compared with controls (136). A carefully controlled 22-year study of 191 chronically depressed patients demonstrated an incidence of cancer equal to age-matched controls (137). A recent, well-controlled, prospective study indicated that attitude appears to have no effect on time-to-recurrence or survival of patients with Stage II breast cancer or high-risk melanoma (138). Indeed, there are animal studies that suggest that stress has a protective effect in carcinogenesis and can inhibit the growth of implanted experimental tumors (139). By ignoring this information, the Simontons fail to acknowledge that this is an area of controversy (140); indeed, although some of these studies have appeared since the first printing of "Getting Well Again," the book has remained

unrevised through more than 20 printings. Friedlander has written a balanced review of the Simonton hypothesis and concludes, correctly, that the method is unproven (141). Only well-designed negative studies can show if it is unsound.

PATIENT CHARACTERISTICS AND THE ROLE OF HEALTH PROVIDERS

Logic might suggest that patients who adopt unsound methods of cancer treatment might be unsophisticated consumers with diseases for which there is no effective standard therapy. However, analysis in this area once again defies logic. In one important review of contemporary popularity of unsound cancer treatments, Cassileth and coworkers compared 304 cancer in-patients at the University of Pennsylvania Cancer Center to 356 cancer patients under the care of 138 alternative practitioners at 19 clinics (2). In decreasing order of popularity, unsound or unproven cancer treatments included metabolic therapy (161 patients), diet (134 patients), megavitamins (92 patients), imagery (89 patients), spiritual healing (71 patients), and immunotherapy (57 patients). Practitioners of unsound therapies were likely to be physicians (60%) and 18% had subspecialty boards. Insurance covered some costs of treatment in a third of the patients being treated.

When compared to patients being treated with standard therapy, those adopting unsound or unproven (imagery) approaches were more likely to be white ($p < 0.00001$) and better educated ($p < 0.00001$). Of these, patients who selected imagery were the most educated, with 79% having some college education. This finding is also supported by the recent FDA telephone survey of 6000 American households in which higher

levels of education were the single best predictor of likelihood to adopt an unsound treatment approach (3). Another surprising finding of the Cassileth study is that patients who opted for unsound therapy were more likely to be asymptomatic and have earlier (and perhaps more conventionally curable) stages of disease. Importantly, of the 325 patients concomitantly receiving both standard and unsound treatments, 40% discontinued standard therapy in favor of the unorthodox approach. One expected finding is that patients who opted for non-traditional care were distrustful of the medical establishment.

There are some important lessons for health professionals in this analysis. Patients who seek out alternative or unsound cancer therapies are intelligent and inquisitive and unlikely to be persuaded that an approach is useless simply because the proponent lacks scientific credentials or has not published in peer-reviewed journals. The clinician needs to understand and be able to discuss the seemingly attractive, although useless, treatments patients hear about through the media or from well-intentioned friends. Various sources of updated information on unsound remedies exist. The American Cancer Society and the American Society of Clinical Oncology (ASCO) both maintain committees that critically review and publish the facts on questionable treatments. Other organizations, such as the National Council Against Health Fraud (Box 1276, Loma Linda, CA 92354), the Center for Medical Consumers and Health Care Information (237 Thompson Street, New York, NY 10012), the Consumer Product Safety Commission (Food & Drug Administration, Rockville, MD 20892) and the National Consumer League (1028 Connecticut Ave., N.W., Washington, DC 20036), have additional consumer-oriented information.

However, the most important protection against health fraud is the practitioner's willingness to discuss the disease and available treatments in an open and supportive fashion (142,143). The NCI's Physician Data Query (PDQ) computer data base on current state-of-the-art (Phase III) and scientifically sound experimental (Phase I and II) therapies is a useful resource in guiding patients to best available care. In addition, a recent NCI booklet, "What Are Clinical Trials All About?", is a helpful educational tool that explains how bona fide clinical studies are performed and gives patients the information they need to know to learn if a trial is logical and well run (144). In today's world of "alternative" treatments, education has replaced legislation as the first defense against unsound cancer therapy.

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TABLE 2

RESULTS OF ANALYSIS OF IMMUNOAUGMENTATIVE THERAPY TREATMENT MATERIALS (58)

Fraction	Source*	Purported Function*	Protein Content mg/mL	Comments
Blocking protein	Necrotic tumors	"Controls rate of tumor antibody production to protect liver."	3.2	Protein content principally albumin by high-performance liquid chromatography and gel electrophoresis
Tumor antibody	Human blood (from donors who do not have cancer)	"Contains alpha-2 macroglobulin, IgG, IgM and IgA"	0.020	Alpha ₂ -macroglobulin undetectable (<85 mg/dL); IgG < 1.18 mg/dL; IgM < 1.50 mg/dL; IgA < 1.47 mg/dL
Tumor complement	Tumor donors' blood	"Tumor complement is complement C ₃ ... activates tumor antibody	0.01	Complement C ₃ < 1.29 mg/dL; complement C ₄ < 0.25 mg/dL; CH ₅₀ = 0 (total complement activity)
Deblocking protein	Human blood (from donors who do not have cancer)	"Deblocking protein is alpha ₂ macroglobulin. Combines with blocking protein to activate tumor antibody."	0.42	Alpha ₂ -macroglobulin < 85 mg/dL

*As detailed by Dr. Burton in reference 53.

FIGURE LEGENDS

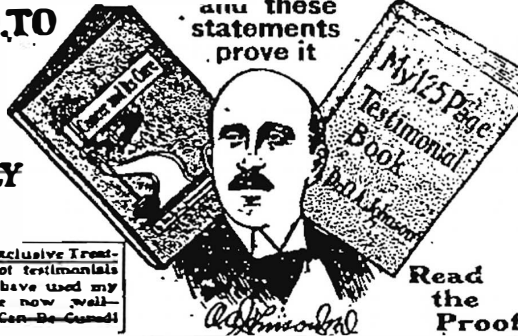
- Figure 1. A 1908 advertisement of Dr. Johnson's Mild Combination Cancer Treatment. Litigation involving this reached the Supreme Court and resulted in important changes in U.S. drug regulation. [Courtesy of the U.S. Food and Drug Administration History Office]
- Figure 2. The iridology homunculus. Metabolic and holistic practitioners commonly use changes in the iris to diagnose organ-specific cancer and follow "disease response." While inexpensive and non-invasive, iridology is also useless. [Adapted from reference 112]

Fig 1

CANCER CAN BE CURED

I WANT TO SEND TO ALL SUFFERERS FROM CANCER, THESE TWO BIG BOOKS ABSOLUTELY FREE

and these statements prove it



Read the Proof

Back of Every Statement I make is the story of a living Hundred who have Used My Mid Combination Treatment.

Ten years of successful practice—in the Exclusive Treatment of Cancer—backed by the scores of testimonials I am able to furnish—from those who have used my Mid Combination Treatment—and are now well—should give me the right to say—Cancer Can Be Cured!

I have no stronger evidence to offer than the actual living proof of those who have suffered and are now well. Read their statements and if you want more proof write for the two large books

[PROOF FROM MISSOURI]

[PROOF FROM KANSAS]

[PROOF FROM OREGON]

Have Hope

My Professional Advice Free

Highly effective, reliable and comfortable treatment of cancer. I have been successful in curing many cases of cancer, and I am now able to furnish testimonials from those who have used my Mid Combination Treatment—and are now well—should give me the right to say—Cancer Can Be Cured!

Many cases of cancer have been cured by my Mid Combination Treatment. I have been successful in curing many cases of cancer, and I am now able to furnish testimonials from those who have used my Mid Combination Treatment—and are now well—should give me the right to say—Cancer Can Be Cured!

WRITE TODAY FOR TWO FREE BOOKS: CANCER AND ITS CURE AND MY 125-PAGE TESTIMONIAL BOOK

DR. JOHNSON REMEDY CO. Dr. O. A. Johnson, President, Kansas City, Mo.
13TH AND GRAND AVENUE

Fig 2

