



Chapter 5

Pharmacologic and Biologic Treatments

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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’ 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

¹Peptides 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 funding 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 justify 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-phenylacetylarnin o-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 anti-tumor 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

²Burzynski 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 “non-toxic” (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 anti-cancer effect) is included in each of these papers.

A particular difficulty with these papers is that some important terms--e.g., "complete 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.

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

⁴In 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 Thiotepe. 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 patient in '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 Bersagel, 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 tumor 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 Niehans' 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 freshly 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.

⁵Anaphylaxis 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 DMSO* (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 hemolysis (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, unresectable (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 0 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 in patients 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 0 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), sarcasinase, 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 first 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," primarily 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).

⁶Laetrile 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 (100,585,644,697,768,779,800,811). 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 below.

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 CD₁F₁ 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 effect.

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 determining 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 “degraded product” (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 auto-

genous 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

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

⁸The 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.”

⁹Since 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 primordial, 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

¹⁰Human 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 tumors 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 conven-

tional 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 Wisconsin¹¹ that collects and distributes some of Nieper's papers in the United States. These papers, some of which are translated from German, are

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

distributed by that library as mimeographed type-scripts, 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-called 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.A.M.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 1961, 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 describes 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 abnormal 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 determining 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/cm²), and has a low specific gravity. Patients whose urine measures below 6.0 to 6.2 in pH and below 68 dynes/cm² 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/cm²—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 preparations 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 (I). 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, methylthioglycolate, 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.M.A.* 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 tumor regressions 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 10 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 first 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 first 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 immunosuppressed, 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 first 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).