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Review article

Alternative pharmacological and biological treatments for cancer: Ten promising approaches

Ralph W. Moss, Ph.D.

There are well over 100 promising alternative treatments for cancer (1). How can clinicians and patients choose the best therapies? How can scientists know which methods are most promising to research? Clearly, one would like to base decisions on scientifically credible studies of such methods. But for a variety of reasons such tests have rarely been performed.

One major problem has been the difficulty of conducting clinical trials that will pass muster with a skeptical (if not downright hostile) Food and Drug Administration (FDA). The cost of such new drug development has been estimated at over $125 million per item, with a development time of up to ten years *(New York Times,* Feb. 9, 1988).

Such expenditures are tolerable for giant pharmaceutical companies, with their huge research and development budgets. In fact, the high regulatory barrier may actually benefit the largest companies. "These regulations favor companies with greater financial strength," said one spokesperson for the smaller drug companies. "They're eliminating competition" *(Business Week,* Jan. 17, 1977). The key point is that the most promising alternative approaches are found in the public domain, as either inexpensive natural substances or common chemical agents. They generally cannot be strongly patented. This means that the major pharmaceutical companies, who are always a major factor in the direction of cancer research, are rarely interested in investing the enormous sums required for full trials.

Developers of alternative methods often find themselves barred from interstate commerce under Title 21, article 355 of the U.S. Code, which states that unless a developer has presented "substantial evidence" of a drug's safety and efficacy, the FDA can deny approval for marketing. And this has in fact been the case with most alternative drugs and vaccines for cancer. Therefore, it is not surprising that many such products fail to obtain FDA approval for marketing and wind up in a kind of gray market, the "cancer underground."

Such difficulties have gone hand-in-hand with a long-standing prejudice of the dominant medical establishment. According to this prevalent view, alternative treatments for cancer should not even exist; they are an expression of "health fraud" or "quackery." Self-described "quackbusters," centered in aggressive groups such as the American Cancer Society's "Questionable Methods" subcommittee and the National Council Against Health Fraud (NCAHF), have expended considerable energy to convince the medical profession and the general public that alternative cancer treatments are automatically suspect. In some states, such as California, alternatives to surgery, radiation, and toxic chemotherapy are actually outlawed by statute.

At the federal level, the FDA, the Federal Trade Commission (FTC), Postal Service, and other agencies act separately or in concert to discourage the use of alternative treatments (2).

Frantic governmental and quasi-governmental activity has thus created a charged atmosphere around the evaluation of alternative cancer treatments, in which it has been exceptionally difficult to obtain dispassionate evaluations of any such method or modality. Not surprising, then, assessments of such treatments are almost all preliminary, and have to be patched together from limited laboratory experiments, uncontrolled clinical observations (often derided by orthodox physicians as "mere anecdotes"), and the arguments of passionate advocates and detractors. Meanwhile, doctors and patients earnestly crave *real* knowledge on which to base their life-and-death decisions concerning cancer treatment.

Since late 1991, however, a new element has been added to this picture. At the urging of retired Rep. Berkley Bedell (D-IA), Sen. Tom Harkin's (D-IA) Appropriations Subcommittee authorized the creation of an Office of Alternative Medicine (OAM) within the office of the director of the National Institutes of Health (NIH). The charge of this office was and is the serious evaluation, in a fair, honest, and competent way, of some of the most prominent of these alternative medical treatments.

OAM has proposed using a variety of research techniques to get the desired information. It takes as its starting point the declaration of Dr. Jay Moskowitz, deputy director of NIH in September 1992, that "not all alternative medical practices are amenable to traditional scientific evaluation, and some may require development of new methods to evaluate their efficacy and safety." In other words, one must use the right yardstick to obtain meaningful results.

These include standard *in vitro* and *in vivo* laboratory research, with the formation of regional and national centers (such as the AIDS center at Bastyr University funded by OAM in 1994). It includes "best case series" on particular treatments, as proposed by the National Cancer Institute, with both retrospective and prospective studies. Nor does it preclude using the so-called "gold standard" of research—the double-blind, placebo-controlled trials favored by FDA.

Priorities for research are still being established by the staff of the OAM, with the vigorous input of the Alternative Medical Program Advisory Panel (AMPAC), an 18-member body appointed in by Secretary of the Department of Health and Human Services, Donna Shalala, in May 1994. Members of AMPAC have played a very active role in suggesting areas, and specific items, for further investigation (3).

As indicated, there are a large variety of alternative approaches to cancer. These include techniques found in many of the most prominent alternative methodologies, including mind-body interventions; bioelectromagnetic applications; alternative systems, such as naturopathy, traditional Oriental medicine, ayurveda, homeopathy, anthroposophically extended medicine, etc.; manual healing methods; and a number of dietary approaches such as the Gerson, macrobiotic, and Kelley methods, specifically adapted to cancer. (These are discussed in a forthcoming report from the ad hoc advisory board of the OAM) (4).

In this article, we are not primarily concerned with these treatment modalities, promising as many of them are, but focus instead on eight of the most promising pharmacological and biological agents, as well as two commercially available herbal preparations (Essiac and Hoxsey). The ten treatments are discussed in alphabetical order.

Opportunities for Evaluation

Which cancer treatments most urgently need evaluation? Which ones are most likely to yield positive data? After a number of false starts and delays, such tests finally seem about to materialize. Shark cartilage, Revici's guided (non-toxic) chemotherapy, and Burzynski's antineoplastons are already in the OAM pipeline for evaluation, and others are on the way. While there is no hard-and-fast rule for what gets evaluated, some of the criteria being used in selecting treatments for evaluation inciude:

- *Therapeutic promise.* Available evidence suggests a likelihood that the compound or method may in fact be effective.
- *Wide use.* Because some treatments are now used by many people, public health considerations indicate that they should be vigorously investigated. Findings of any adverse effects should also be disseminated quickly, if only for public health reasons.
- *Subject of controversy.* Treatments that have been the subject of long-standing controversies need to have such controversy resolved.
- *Former use or use elsewhere.* Some products have been tested and well documented in the scientific literature in the past, or in foreign countries, but for various reasons have fallen by the wayside or failed to be accepted.

By these criteria, a number of alternative drugs, vaccines or herbal preparations appear ready for immediately evaluation. We shall discuss ten of the most promising below, although the reader should be aware that this list is in no way meant to exclude many other highly promising treatments:

Antineoplastons

Antineoplastons are peptide and amino acid derivative fractions, discovered by a Texas physician, Stanislaw R. Burzynski, M.D., Ph.D., when he was a graduate student in his native Poland. He named some of these fractions A2, A3, A5, A10, and AS2-1. These are non-toxic substances originally derived from normal human blood and urine, but subsequently synthesized. They are used to treat a variety of cancers as well as early-stage AIDS. (At the 1992 International Conference on AIDS Burzynski reported that some patients infected with human immunodeficiency virus responded to antineoplastons by a marked increase in certain white blood cells [CD4 + lymphocytes]; other observations included increases of energy and weight, and a decrease of opportunistic infections.)

Burzynski originally discovered antineoplastons when he compared normal blood to the blood of people with cancer and noted an anomalous streak on electrophoresis of the normal blood that was not present in that of cancer patients. Burzynski then switched to urine as the source (5) and chemically defined these antineoplastons after he moved to the Baylor College of Medicine in Houston in the 1970s (6). Burzynski assigns a profound biological role to these peptides. While other scientists regard them as "junk," he sees them as a newly discovered, natural form of anticancer protection, quite separate from the reticuloendothelial system.

Burzynski found that, when given as treatment, antineoplaston peptides are essentially nontoxic (7). He has reported considerable preliminary laboratory (8) and clinical work, showing tumor responses (shrinkages) in a number of difficult cases. Most of these involved subjects who had exhausted conventional treatments (9).

Although antineoplastons have been used against a wide variety of tumors, the greatest interest has been generated by reports of their effectiveness against otherwise incurable brain cancers, especially in children. Burzynski also reports that he has had the considerable success in treating (in descending order) prostate cancer, non-Hodgkin's lymphoma, pancreatic, breast, lung, and colon cancer.

Controversy has swirled around Burzynski since the late 1970s, when he left his position at the Baylor College of Medicine in a disagreement over an interdepartmental transfer, research freedom, and other issues. Since then, he has worked independently, supporting his research out of patient fees at his clinic, the Burzynski Research Institute.

Burzynski's work remains highly controversial in the United States, but is much less so in Europe and Asia. He has published scores of medical articles in peer-reviewed journals, especially in Europe. At the 18th International Congress of Chemotherapy in Stockholm on July 1, 1993, more than a dozen papers were presented by researchers from Brazil, Holland, Japan, Poland, and the United States in a special session on antineoplastons.

In October 1991, the National Cancer Institute conducted a "best case series" review and concluded that antitumor activity by antineoplastons had in fact been demonstrated by Burzynski in seven cases of incurable brain cancer. Consequently, NCI agreed that conducting confirmatory trials on antineoplastons would be worthwhile. At the same time, the attacks on Burzynski continued, in fact, increased. These are typified by a very negative article on Burzynski by Dr. Saul Green that appeared in the *Journal of the American Medical Association* in 1992, which failed to mention many of the positive studies on antineoplastons and relegated the NCI site visit to a footnote (10).

Despite a barrage of negative publicity, in late 1993 and early 1994, three sites opened enrollment for clinical trials on the use of antineoplastons in brain cancer: Memorial Sloan-Kettering in New York, the Mayo Clinic in Minnesota, and the Clinical Pharmacology Branch of NCI in Maryland. There are also four trials underway at the Burzynski Research Institute in Houston, with OAM participation.

Interest in antineoplastons also heightened when it was found that a substance called phenylacetate controls the expression of ras-oncogenes. Phenylacetate is one of the ingredients of Burzynski's formulation AS2-1, and in fact the National Cancer Institute learned of this substance by way of investigating Burzynski's research (11). And, indeed, the current theory at NCI of using ras-oncogene controllers as a way of inhibiting cancer growth is remarkably similar to Burzynski's earlier theory of urinary peptides as a natural defense system against cancer and other diseases.

Cartilage Products

The scientific investigation of the use of cartilage to improve health began in a serendipitous way. A graduate student wondered aloud whether cartilage could assist in wound healing. John F. Prudden, MD, at the time a surgeon at Columbia-Presbyterian Hospital in New York and an associate professor of clinical surgery at Columbia University, decided to settle the issue. He used a powdered and washed cartilage product. For example, some scientists subsequently showed that a type II collagen derived from chickens could relieve swollen and tender joints of patients with rheumatoid arthritis (12)—yet another victory for grandma's proverbial chicken soup!

Here, we shall focus on the anticancer properties of cruder cartilage products, including a powdered and cleansed form of beef cartilage that Prudden initially named Catrix (but has now renamed Vitacart) as well as various shark cartilage products, which go by such brand names as Cartilade, Benefin, etc.

A "60 Minutes" segment on shark cartilage in late February 1993, cited a seemingly positive 16-week clinical trial in Cuba. Since then, there has been tremendous public interest in cartilage treatments. An estimated 50,000 Americans are currently taking shark cartilage, either by mouth or via retention enemas, with an individual cost that can reach $7,000 per year. Shark cartilage is thus one of those treatments that deserves to be evaluated if only on the basis of its extensive use and the depth of the controversy over its alleged effects.

Charles Simone, M.D., a Lawrenceville, NJ oncologist who trained at the National Cancer Institute, was one of those who originally examined the results of the aforementioned Cuban study. He came away convinced that cartilage may indeed convey some benefits to cancer patients, and has obtained an Investigational New Drug (IND) license from FDA to conduct a preliminary trial of shark cartilage in adult patients with solid tumors.

As most people know, shark cartilage is an ingredient in a very old Chinese health product, shark fin soup. One modern hypothesis for its alleged effectiveness is an inhibiting effect of some cartilage constituent on new blood vessel formation. It has been shown that a tumor that cannot establish such a network, cannot grow any larger than the point of a pencil (13,14,15). One substance present in very small amounts in cartilage has been shown to inhibit angiogenesis, interfering with the ability of a tumor to create a network of new blood vessels. Critics reply that there may not be enough of this factor present in cartilage to account for the alleged anticancer effects.

One NCI researcher has proposed a possible mechanism for anticancer effect that involves a class of proteins produced in normal tissues such as cartilage and bone (16). Such proteins are called tissue inhibitors of metalloproteinases, or TIMPs. TIMPs appear to block the action of certain metal-containing enzymes that help tumor cells to invade surrounding tissue.

Dr. Prudden has published more than 60 papers on the use of cartilage. In 1985, he reported on the results of study in which 31 cancer patients were treated continually with Catrix. The overall response rate, measured as a greater than 50 percent reduction in tumor size, was reported as an unusually high 90 percent; 61 percent had complete disappearance of the tumors. Both oral and injectable forms of beef cartilage (Catrix) were used, but Prudden concluded that the oral route was, surprisingly, superior to injections.

Prudden provided data on 31 patients who "took Catrix consistently and followed instructions completely." Even if the number of patients who stopped treatment are included (approximately another 60 patients) then the recalculated response rate would still be 30 percent and the complete response rate 20 percent. It should also be noted that while cancer therapy studies usually deal with one type of cancer at a time, Prudden's patients had at least nine different types, which makes evaluation more difficult for conventionally trained scientists.

Clinical trials using Catrix in kidney (renal cell) cancer patients are currently underway at the Westchester Medical Center in Valhalla, NY as well as at the Royal Victoria Hospital in Montreal. Renal cell is a notoriously intractable tumor. Prudden has unofficially reported an initial response rate with Catrix in this tumor of around 25 percent (17).

Coley's Mixed Toxins

Like many of the other pharmacological and biological treatments, Coley's toxins have attracted considerable medical and political controversy. However, rather than being a new treatment, Coley's toxins were a breakthrough in cancer treatment that occurred at an "orthodox" institution, a discovery that was subsequently neglected.

More than 100 years ago, a bone surgeon at Memorial Hospital, New York, William B. Coley, MD, was investigating new approaches to curing cancer after his surgery failed to save a 1 9-year-old cancer patient. For various reasons, Coley chose to buttress a patient's immune system by giving him a bacterial infection that would cause a high fever and potently mobilize the patient's immune system to fight the cancer cells. This was a highly innovative and daring technique, and today, Coley is widely recognized as the first pioneer of immunotherapy. (A similar technique was used in Europe from the 1880's on.)

The preparations that Coley developed were a mixture of killed cultures of the bacteria *Streptococcus pyogenes* and *Serratia marcescens* (formerly called *Bacillus prodigiosus).* Although certainly not all patients responded to Coley's toxins, his treatment is reported to have shown dramatic curative effects on various cancers for many patients (18). These results have been documented by Coley's daughter, Helen Coley Nauts, in a series of many articles and monographs (19,20,21). Ms. Nauts founded the Cancer Research Institute in New York in 1953 to further "the immunological approaches to the diagnosis, treatment, and prevention of cancer."

Lloyd Old, MD, an immunologist at Memorial Sloan-Kettering Cancer Research Center and a colleague, wrote, "Those who have scrutinized Dr. Coley's records have little doubt that the bacterial products that came to be known as Coley's toxins were in some instances highly effective" (22). Ms. Nauts's monographs outline many remarkable successes using Coley's methods.

Over the years, Coley's innovative work led to other discoveries. For instance, in the course of work on Coley's toxins in the 1940's, M. J. Shear of NCI discovered lipopolysaccharide (LPS), a component of bacterial cell walls. By injecting LPS into mice previously treated with bacillus Calmette-Guerin (BCG), Old and colleagues discovered tumor necrosis factor (TNF) (23,24,25).

The original Coley formulas are rarely used even experimentally in the United States, although until the 1980's, they were still being researched at Temple University, Pennsylvania (26,27). In her 1990 paper, Havas pointed out that using purified LPS to evoke immune reactions is problematic because of its toxicity. She proposed returning to a cruder mixture, a mixed bacterial vaccine similar to Coley's toxins. The research reported in that paper showed the mixed bacterial vaccine to have anticancer and immunostimulatory properties at nontoxic levels in animals with tumors. The authors concluded that the vaccine "compares favorably with other biological response modifiers."

Outside the United States, Coley's toxins are being used in Beijing Children's Hospital, the People's Republic of China, and Germany (28). In 1994, science writer Wayne Martin reported that three doctors in the US, two doctors in Caracas, Venezuela, and two doctors in Guatemala City, Guatemala were using the treatment with some success (29).

Essiac

Essiac is an herbal treatment, widely used in Canada and the U.S. for the treatment of cancer. Reported to be primarily of Native American (Ojibwa) origin, it was first brought to public attention in 1922 by an Ontario nurse named Renee Caisse (Essiac is Caisse spelled backward). Caisse was impressed by the case of a local woman who claimed to have been cured of breast cancer many years earlier by a local Ojibwa healer.

After her own aunt was reputedly cured of breast cancer with this formula, Caisse set up a clinic in Bracebridge and treated thousands of patients before being shut down by the Canadian medical authorities in 1942. One problem was that Caisse never made the formula public during her long lifetime (1888-1978).

In 1982, a Canadian government report concluded, "No clinical evidence exists to support the claims that Essiac is an effective treatment for cancer." Nevertheless, the relevant government agency, Health and Welfare Canada (equivalent to FDA), agreed to make this medication legally available to advanced cancer patients under Canada's Emergency Drug Release Program. It is currently produced as a trademarked product in Canada. This and other versions of Essiac (such as Flor-Essence) are also widely available through health supplement stores in the United States.

Both trademarked Essiac and Flor-Essence claim to be the uniquely authentic Caisse formula. According to author Gary L. Glum, a Los Angeles chiropractor, authentic Essiac must contain four ingredients: (1) sheep sorrel *(Rumex acetosella);* (2) burdock *(Arctium lappa);* (3) slippery elm inner bark *(Ulmus fulva);* and (4) Turkey rhubarb *(Rheum palmatum)* (30). Flor-Essence adds a number of other ingredients, including watercress *(Nasturtium officinale).*

A brief discussion of the four main herbs follows:

• *Sheep sorrel.* The main ingredient in Essiac is said to be sheep sorrel. This is not to be confused with the more readily available vegetable garden sorrel, also known as "sour grass." Sheep sorrel contains vitamins, minerals, carotenoids, and chlorophyll, all of which are believed to have anticancer effects either directly or through immunological or antimutagenic activity (31). Sorrel was in fact the basis of a celebrated cancer "cure" in Virginia in the 1740s, and as *jiwisi* it was a noted remedy of the Algonquin Ojibwa (32). In folk tradition it is reputed to have many other medicinal qualities as well.

Sorrel also contains generous amounts of oxalic acid as well as emodin, which has been shown to have "significant antileukemia activity" (see discussion of buckthorn in the "Hoxsey Method" section, below).

• *Burdock root.* Burdock *(Arctium lappa) is* a Eurasian weed transplanted to North America. Its root (eaten as "gobo" in Japan) contains what Japanese scientists have called the "burdock factor" (33). This is reputed to act as a desmutagen, that is, a substance that reduces mutations in cells. Burdock also has been shown to inhibit the HIV virus, according to the World Health Organization

• *Slippery Elm Bark.* The inner bark of the slippery elm tree was tested by the National Cancer Institute without producing any sign of anticancer activity. Slippery elm lozenges, powdered bark, and slippery elm extracts are often available in health food stores and catalogs, with a wide range of curative and restorative claims made for them.

• *Turkey Rhubarb.* Also known as East Indian or China rhubarb, this graceful plant grows from 6 to 10 feet high, much larger than the ordinary garden rhubarb *(Rheum Raponticum).* Rhubarb comes originally from the mountains of Western and Northwestern China and has been used in Chinese medicine since at least 220 B.C. It was not grown in the West until 1732. Rhubarb is described in the standard herbal literature as an "astringent, tonic, stomachic, aperient"

(35). It is especially used in cases of dysentery and diarrhea. Rhubarb extract showed anticancer activity in the sarcoma 37 test system (36). It contains rhein, an anthraquinone, which has been shown to have antitumor effects (37). There is thus a reasonable supposition that Essiac may convey anticancer effects, although ,that remains to be proven with adequate studies.

Essiac is widely used throughout North America, although, unlike use of Hoxsey's formula, use of Essiac is not associated with any particular clinic (38).

Hoxsey Method

The Hoxsey treatment is among the oldest U.S. alternative therapies for cancer and among the most controversial.

Like Essiac (see above), it is mainly a mixture of herbs used by Native American Indians and early settlers. By coincidence, at least one herb (burdock) is included in both formulas.

Hoxsey was a colorful character, an uncredentialed layperson with a genius for medical marketing. He claimed that the formula had been developed by his grandfather after watching a pastured horse cure itself of cancer by eating selected herbs. This formula was then passed on to Hoxsey's father, a coal miner, and then to Hoxsey himself. Hoxsey opened several cancer treatment clinics across the Midwest and the South. He kept the formula secret until he was forced to reveal it by the FDA in 1950.

There are actually two Hoxsey remedies: an external salve and an herbal potion. The external medicine is an escharotic, a kind of burning paste composed of zinc chloride, antimony trisulfide, and bloodroot; its purpose is to corrode cancers. The paste is principally used for skin cancer (usually basal cell carcinomas), and many ambitious claims have been made for it. However, few reports on its efficacy (or lack thereof) exist in the peer-reviewed literature.

It is noteworthy that the orthodox treatment, Moh's micrographic surgery, bears a strong similarity to the Hoxsey external treatment (39). Moh's method consisted of the use of zinc chloride paste to "fix" the tumor in place; the tumor is then removed in a series of steps. It is still employed.

The internal medication, which is our primary concern here, is made up of various herbs added to a base of potassium iodide and cascara, a bark preparation. The principal herbs are pokeweed root, burdock root, barberry, buckthorn bark, stillingia root, and prickly ash. As historian Patricia Spain Ward, Ph.D. noted in a contract report to OTA (U.S. Congress Office of technology Assessment) for its *Unorthodox Cancer Treatments* project, many of these roots and barks are now known to have anticancer and immunostimulatory effects (40). The following items discuss three key ingredients:

• *Pokeweed.* Pokeweed root *(Phytolacca americana* or *decandra)* seems to have several modulatory effects on the immune system. For example, a form of *Phytolacca* stimulates production of two powerful cytokines, interleukin 1 (IL-1) and tumor necrosis factor (TNF) (41, 42). Although pokeweed root is poisonous, it apparently has been used in folk medicine without serious toxicity problems since the mid-18th century. As an interesting side note, the lieutenant governor of colonial New York, Cadwallader Colder (1688-1776) was convinced that poultices of this root would cure cancer and communicated this to Benjamin Franklin (43).

• *Buckthorn.* Buckthorn is a shrub that grows in swamps and damp places in the north and northeastern United States, as well as Europe. Like rhubarb, buckthorn bark is used as a purgative. Buckthorn contains emodin, which has shown antileukemia activity in the laboratory (44).

• *Burdock.* As noted, burdock has been shown to be bioactive in a number of experimental systems (45, 46, 47). That the two longest surviving herbal remedies for cancer—those of Hoxsey and Caisse— have burdock in common is provocative, since both formulas were long held in secret and it is unlikely that Hoxsey and Caisse communicated or even knew of each other's existence.

Although Hoxsey won a number of critical court battles, eventually U.S. authorities succeeded in shutting down his various clinics. The treatment is still available at the Bio-Medical Center in Tijuana, Mexico, which is headed by Hoxsey's former nurse assistant, Mildred Nelson. Hoxsey indicated that some of his herbal components were included in the mixture to necrotize tumors while others were included as purgatives, to carry away the waste.

It is noteworthy that, despite intense opposition, the Hoxsey formula has persisted as a cancer treatment for almost 100 years. Among numerous anecdotal accounts of its effectiveness, some are hard to dismiss out of hand; it therefore warrants serious investigation. Despite decades of controversy, however, no clinical trials have ever been performed by either supporters or detractors of the Hoxsey therapies. In fact, as Patricia Spain Ward noted in her OTA paper, the American Cancer Society listed Hoxsey's remedy in 1971 on its unproven methods list without citing any research basis for this listing. Since the Hoxsey formula contains a poisonous substance, pokeweed root *(Phytolacca Americana),* testing the widely used formula is also a public health concern.

Immunoaugmentative Therapy

Immunoaugmentative therapy (IAT), which was developed by Lawrence Burton, Ph.D., is "one of the most widely used unconventional cancer treatments," according to the Office of Technology Assessment (OTA)(48). It has also been one of the most bitterly contested. In fact, it was the attempt to achieve a fair evaluation of immunoaugmentative therapy that led some of its defenders to work for the establishment of OAM (49).

The process of manufacturing IAT is patented, but some details of it appear to have been kept secret. The secrecy issue seems to have diminished since Dr. Burton's death from heart disease in early 1993. Essentially, immunoaugmentative therapy is an experimental form of cancer immunotherapy consisting of daily injections of processed blood products. Several blood fractions recovered by means of centrifugation are used in an attempt to restore normal immune function to the person with cancer. These fractions are said to include the following substances:

• *deblocking protein*—an alpha-2 macroglobulin derived from the pooled blood serum of healthy donors;

• *tumor antibody 1 (TA1)*—a combination of alpha-2 macroglobulin with other immune proteins (IgG and IgA) derived from the pooled blood serum of healthy donors; and

• *tumor antibody 2 (IA2)*—also derived from healthy blood serum but differing in potency (and possibly in composition) from TA1.

Proponents of immunoaugmentative therapy hypothesize that the tumor antibodies attack the tumors while the deblocking proteins remove a "blocking factor" that prevents the patient's immune system from detecting the cancer.

Originally a New Yorker with a research laboratory at St. Vincent's Hospital and later a clinic in Great Neck, Long Island, Bur-

ton established a new base in Freeport, the Bahamas in the late 1970's. This followed his failure to obtain FDA approval for his blood fraction medications. This move followed nearly 20 years of work with tumor-inducing and tumor-inhibiting factors at various institutions. During the 1960's and 1970's, Burton and a colleague, Frank Friedman, published work on cancer inhibiting factors in mice (50). In one experiment, daily administration of these factors was said to eliminate palpable disease in 26 of 50 mice with leukemia. The treated animals appeared to survive significantly longer than the controls. In another experiment, Burton reported that 37 of 68 experimental animals survived for an average of 131 days without any evidence of leukemia, versus a 12-day average survival of untreated mice (51). Burton concluded that the study of the biological action and interaction of these components in mice suggests the existence of an inhibitory system involved in the genesis of tumors and capable of causing specific tumor cell breakdown.

In July, 1985, Burton's Freeport clinic was suddenly closed by the Bahamian health authorities and the Pan American Health Organization on charges of contamination with HIV (then called HTLV-III) and hepatitis virus. Despite alarming stories in the media, no patient has yet been found who became HIV positive or succumbed to AIDS because of Burton's treatment. Investigations by patient advocacy groups strongly suggested that there may never have been any HIV contamination (52). Some 500 patients were receiving 8 to 10 injections per day; during the year after the clinic was closed, several hundred all tested negative for HIV. Additional standard HIV tests of serum and blood supply used to prepare the treatment were all negative as well (53).

The Freeport clinic, which reopened in January 1986 through the actions of Burton's patients and some members of the U.S. Congress, remains open at present despite Burton's death. More than 5,000 patients have now received immunoaugmentative therapy in Freeport.

Yet in spite of the many patients treated and the many stories of remissions, extensions of life, and improvements in the quality of life, very little documentation exists of either the methods used or the results obtained with Burton's therapy. After the hostile reaction by the cancer establishment in the 1970s, Burton retaliated by withdrawing from his former colleagues and ignoring the basic requirements of scientific documentation. A standoff resulted, which OTA was unable to resolve. It is possible that the Freeport clinic, now led by R. J. Clement, MD, will be more willing to cooperate in concrete studies and that serious investigations of immunoaugmentative therapy can now be launched.

Iscador/Mistletoe

Iscador is a liquid extract from the mistletoe plant *(Viscum album)* that has been used to treat tumors for more than 60 years (54). A complex mixture, iscador has two properties that are thought to make it effective against tumors. Iscador is cytostatic and sometimes cytotoxic, that is, it can stop cell growth, sometimes even killing cells. In addition, iscador has immunostimulatory properties, affecting the immune system. Two protein components of the mistletoe extracts appear to be the major active ingredients, viscotoxins and lectins (55).

The mistletoe lectins have been studied in more detail than the viscotoxins. In general, lectins are a group of sugar-containing proteins that are able to bind specifically to the branching sugar molecules of complex proteins and lipids on the surface of cells. Certain lectins have both cell-killing and immunostimulatory activity. Their toxic effect occurs because they can stop protein synthesis in cells.

Viscotoxins can kill cells but do not act on the immune system. They act by,injuring cell membranes. Considering the toxic properties of both major active ingredients of mistletoe extracts, it is not surprising that mistletoe itself can be poisonous and that proponents of iscador provide cautions about how much to take.

One study examined a lectin from a proprietary mistletoe extract that has been reported to show ability to affect the immune system in rabbits (56). When a tissue culture of certain white blood cells was exposed to this lectin, increased secretion of certain immune system products resulted, including alpha interferon and interleukins 1 and 6. In turn, there was an increase in the number and activity of certain types of white blood cells. A corresponding increase was seen in cytokine levels in serum of patients after injection of lectin doses (57).

Both the cell-killing and the immunostimulatory activities of iscador could potentially affect tumor cells. Whether iscador is an appropriate treatment for cancer has been the subject of at least 46 published clinical studies (6 collective reports, 5 small historical studies, 9 large historical studies, 14 retrospective studies, 10 prospective studies, and 2 randomized studies), which were reviewed by Helmut Kiene (58). None of the studies fit the format of a controlled, randomized, double-blind clinical trial. Kiene points out that such studies would be difficult to do because visible local skin irritations appear early in mistletoe treatments; thus both patient and doctor would know about the treatment. (Also, "placebo" irritants might have immunostimulatory properties.)

Of 36 studies that Kiene decided were evaluable, he reported that 9 showed positive, statistically significant effects against diverse cancers, induding ovarian, cervical, breast, stomach (postoperative), colorectal, and bronchial cancers, and liver metastases. Usually the effect was to lengthen the survival time of the patient, commonly measured as median or average survival time; in one study, a significant reduction in the use of painkillers and psychopharmaceuticals was observed. The reviewer noted that the effect of mistletoe therapy tended to appear in situations involving patients with advanced stages of disease rather than patients with less advanced illness.

The antitumor effects observed in these studies with people are supported by studies with animal tumors. Furthermore, except for skin irritations, few uncomfortable side effects are reported by patients. This finding contrasts with the discomforts associated with more traditional anticancer radiation treatments and chemotherapy.

Much of the previous research was conducted in Germany, and the lead organization for a new study is also based there. NCI's Physicians' Data Query index identifies this study as a Phase III randomized trial of adjuvant treatment with INF-A (interferon alpha) versus INF-G (interferon gamma) versus mistletoe extract (iscador M) versus no further treatment following curative resection of high-risk stage I/IIB malignant melanoma. (EORTC-DKG-80-1, based at the Melanoma Cooperative Group of Hamburg, Germany). A three-volume compendium of research papers on iscador, including translations of some from German, is also available (59).

MTH-68/N

The MTH-68/N vaccine is a form of immunotherapy that employs a little-known biological product against viral diseases as well as various kinds of cancer. Developed by Laszlo K. Csatary, a Hungarian-American physician who currently resides in Ft. Lauderdale, FL, MTH-68/N therapy is based on the idea that certain attenuated, nonpathogenic viruses can be used to interfere with the growth of

cancer in humans and the activity of harmful viruses.

MTH-68/N is a modified attenuated strain of the Newcastle disease virus of chickens (a paramyxovirus). In poultry, it causes an acute, fever-causing, generally fatal disease. In humans, however, the worst it does is trigger an acute but transient conjunctivitis (pinkeye), but even this side effect is rare (60).

While Csatary was searching for a virus that would be harmless to humans but would attack cancer viruses, it came to his attention that a chicken farmer in Hungary with advanced metastatic gastric carcinoma had undergone a complete regression of his cancer after his flock experienced an epidemic of Newcastle disease. Csatary published his early observation in the British medical journal, *Lancet* (61). In 1982,1984, and 1985 he published study results and a general article on interference between pathogenic and nonpathogenic viruses (62,63,64). Researchers in Hungary, under the direction of Sandor Eckhardt, the 1990-1994 president of the International Union Against Cancer and the director of the Institute of Oncology, completed a multicenter, Phase II, double-blind, placebo-controlled clinical trial with terminal cancer patients (65).

According to the statistical analysis in internal reports on the Phase II study, "the number of cases with stabilization or regression was significantly higher in the MTH-68/N group; favorable response in subjective parameters, such as pain relief, occurred in a significantly higher percentage in the MTH68/N group; and performance status improved in the MTH-68/N group and significantly deteriorated in the placebo group."

Patients in Phase II received MTH-68/N by nasal drops or by inhalation. The researchers say that the treatment has proved to be nontoxic and devoid of side effects. Currently, the Hungarian research team is still awaiting financial backing for Phase 3 trials.

A report published in 1993 provides more details concerning the Phase II study (66). The study subjects had advanced cancers with multiple and widely distributed metastases. The duration of the protocol was six months, but those patients who had reacted favorably to treatment were continued on therapy. Further evaluation about survival was done after 1 and 2 years.

There were 59 patients in the study—33 in the MTH-68/N group and 26 in the placebo group. Their tumor types included lung, pancreas, kidney, sigmoid colon, and stomach cancer. In the MTH-68/N group, 2 patients experienced complete remissions, 5 experienced partial remission, 1 had moderate remission, and 10 had stabilization, for a total of 18 positive responses. Median survival time was significantly extended beyond that of the placebo group, which had only 2 stabilizations.

In addition, 26 subjects in the MTH-68/N group versus only 7 in the placebo group had either unchanged or increased weight. In the MTH-68/N group, 15 subjects had a sense of better well-being, 13 reported increased appetite, and 11 reported decreased pain; no one in the placebo group reported these effects.

Csatary is currently negotiating with an American biotechnology company to speed development in the United States, and he has expressed willingness to have the Office of Alternative Medicine conduct clinical trials of his product. He does not treat patients in the United States.

Csatary's own explanation of how MTH-68/N works is based on his belief that many human cancers are of viral origin.

Three possible mechanisms of antitumor action by the nonpathogenic avian viruses include direct cytolysis (cell killing), tumor-specific immune enhancement, and cytokine stimulation. Thus, the avian viruses may modify tumor cells and enhance tumor-specific immunity (67). Or they may selectively kill cancer cells. Alternately, they may stimulate a wide variety of cytokines (68,69), such as TNF (70), interferons (71), and interleukins (72).

In 1994, scientists published a report on the treatment of neuroblastoma with Newcastle disease virus (NDV) in the *Journal of the National Cancer Institute (JNCI)* (73). They announced the "complete regression of human neuroblastoma" in animals using NDV.

Although a rare cancer, neuroblastoma is the most common extracranial solid tumor in children. When this type of human cancer cell was transplanted into 11 "nude mice," a kind of rodent bred to accept human tumor grafts, they grew quickly. However, when a strain of NDV was injected directly into these lesions, "it caused all 11 tumors to regress completely (no palpable or visible tumor remained)," while rapid tumor growth continued in the control animals. The NDV-treated mice were then observed for 12 months, during which time, the Chicago scientists say, only one tumor reappeared. "A second virus treatment on day 23 led to complete regression of this tumor."

The Chicago researchers credit Dr. Csatary for the initial work on NDV and also acknowledge that in the Budapest trial there were good results in about a quarter of the patients tested. There was also a lead editorial in the *JNCI* about this promising approach.

Revici's Guided Chemotherapy

Emanuel Revici, a Romanian-born physician, is still practicing in New York City in his late nineties. (His license was suspended in November, 1993, but that decision is being challenged in the courts.) Revici has developed an approach to illness (particularly cancers) that he calls biologically guided chemotherapy (74,75). The basis of Revici's approach is a concept that disease involves a biological dualism. While in a healthy body there is a balance between anabolism (constructive metabolic processes in which new substances are built) and catabolism (destructive metabolic processes in which substances are broken down). But in a diseased body their imbalance results in diseases that are either primarily anabolic or catabolic.

Correspondingly, the way the diseased body responds to treatment differs depending on the type of imbalance. In their choices of therapies, physicians must therefore be guided by which condition predominates.

Revici ascribes the effects of tumor cells to lipid imbalances. If fatty acids predominate—a catabolic condition—the tumor tissues are described as having an electrolytic imbalance and an alkaline environment. If, instead, sterols predominate, as in anabolic conditions, there is a reduction in cell membrane permeability, according to Revici.

The patients whom Revici determines to have a predominance of fatty acids are treated with sterols and other agents with positive electrical charges that can theoretically counteract the negatively charged fatty acids. But if on the other hand sterols are predominant, treatment is with fatty acids and other agents that can increase the metabolic activity of fatty acids.

The determination of anabolic (rich in sterols) or catabolic (rich in fatty acids) character is based on a series of medical tests and judgments about body type. For example, a lean individual would be more likely to have a catabolic condition, and a rounded individual, an anabolic one; Revici also considers females more likely to have an anabolic character, and males, a catabolic one. Based on the various tests, an individualized chemotherapy program is designed for each patient with cancer. (This individualization makes it harder to conduct controlled studies of treatment effectiveness.)

Along with Revici's choice of type of lipid to administer, he may incorporate other materials, such as selenium, in his lipid envelope. According to his theory, the additional agent will be delivered ("guided") directly to the tumor site because of the site's affinity for the selected lipid carrier. Because of this specificity, lower systemic drug toxicity is expected.

OAM has expressed interest in conducting a field evaluation of Revici's approach as a cancer treatment. Besides anecdotal reports concerning Revici's patients, one independent clinical trial was already conducted by Joseph Maisin, director of the Cancer Institute of the University of Louvain, Belgium. Although the results were never published, Maisin is reported to have written to Revici that dramatic improvements occurred in 75 percent of 12 terminal cancer patients. These improvements included tumor regression, disappearance of metastases, and cessation of hemorrhage.

Revici has applied his dualistic theory to other conditions besides cancer. He first developed therapies for different kinds of pain. Among the other conditions he is reported to have addressed are itching, insomnia, vertigo, migraine, radiation burns, osteoarthritis, rheumatoid arthritis, convulsions, postoperative bleeding, AIDS, ileitis, colitis, and drug addiction.

714X

The ideas of French-born Gaston Naessens are a controversial area at the edge of modern medicine. Naessens, a microbiologist whose formal education was interrupted by World War II before he could earn an advanced degree, has proposed a theory that cancer cells are starved for nitrogen ("nitrogen traps") and will immobilize the body's immune system in order to obtain it. Naessen's main therapeutic idea is to provide nitrogen to the tumor in a mixture with camphor he calls 714X, thereby loosening the malignancy's grip on the immune system. A reactivated immune system can then be unleashed to attack the tumor.

714X is injected directly into the perilymphatic area in the right side of the abdomen. The kind of camphor used has an enormous attraction to the tumor. In addition, certain mineral salts in 714X help reliquidify a sluggish, gelatinous lymph system, while the camphor helps deliver the nitrogen. This treatment is said to be helpful in the palliative treatment of AIDS.

Naessens does not regard himself as primarily a drug developer. In fact, 714X was a by-product of more fundamental biological work carried out by Naessens since the late 1940's on a pleomorphic entity found in normal blood, which he calls the "somatid." Naessens invented a special kind of dark-field microscope to study the "life cycle" of this entity, which he called a Somatoscope. The prototype Somatoscope is in Naessens's laboratory in Rock Forest, P.Q. Because Naessens was frequently accused of being secretive about this one-of-a-kind Somatoscope, since 1991 he has marketed a special condenser for ordinary light microscopes that helps scientists see many of the same effects as the more elaborate instrument.

The Somatoscope uses a novel combination of incandescent light, which has a wave length of 3,600 angstroms, and an ultra-violet light, with a wave length of 2,200 angstroms. Naessens claims that the Somatoscope can visualize living things at up to 30,000X, magnifications clearly unattainable through ordinary light microscopes. In addition, the resolution is 150 angstroms, far sharper than any ordinary light microscope. (An angstrom is one-hundred-millionth of a centimeter.) With this remarkable instrument, he is able to monitor the health status of patients by evaluating the status of the variable (pleomorphic) particles that he has described in his viewings with the Somatoscope (76).

In 1989, Naessens was prosecuted in Sherbrooke, P.Q. for negligent homicide in the death of a woman who took 714X instead of conventional chemotherapy, as well as 64 counts of practicing medicine without a license. These charges carried a virtual life sentence. Naessens was acquitted on all counts, however, after many people testified not only to his character, but also to the beneficial results they obtained by using 714X. Some of the individuals claiming "cures" for cancer and AIDS are quoted in an account of the trial and its aftermath by author Christopher Bird (77).

Many Americans, including former Iowa Congressman Berkley Bedell (78), have used 714X as their primary unconventional treatment for cancer. The product has penetrated a number of alternative clinics that concentrate on other treatments. Stories are circulating of dramatic improvements or, with AIDS, of conversion from HIV positive to HIV negative. However, Naessens does not generally attempt to publish in peer-reviewed scientific literature, because he feels that research as unorthodox as his own is highly unlikely to find acceptance in such publications.

Naessens's ideas, and 714X in particular, are among the most provocative concepts in all of alternative medicine. But without serious and impartial scientific evaluation, including best case reviews, prospective field trials and possibly double-blind, placebo-controlled studies, it will be difficult to reach any definitive conclusions about this work.

Future Research Opportunities

Even orthodox scientists now admit that the fight against cancer is in serious trouble (79,80). Few successful treatments for adult, solid tumors have emerged from the 23-year war on cancer. In general, alternative biological and pharmacological treatments provide a rich area for the investigation of innovative cancer treatments. The fact that most of these treatments are non-toxic is a major additional incentive to speed up their evaluation.

Key Issues and Specific Recommendations

Exciting new non-toxic cancer treatments continue to emerge, and the above list is in no way meant to be restrictive or all-inclusive. At the current time, further research under OAM supervision would certainly be helpful for all ten of these treatments. Historical prejudices and economic considerations have barred the fair evaluation of all but a few of these treatments so far. But some evaluative work has now begun (on cartilage, Burzynski, Revici) and more is anticipated. Members of the OAM's Pharmacological and Biological Panel have identified a number of key regulatory issues that directly relate to the treatments discussed in this article.

- Changes in regulations for FDA approval should be made if alternative pharmacological and biological treatments are to have a fair hearing. OAM and FDA have now begun to work well together. But in order to prepare for innovative approaches, the director of OAM should work together with his or her counterpart at FDA to develop a memorandum of understanding so that proposed trials that have been approved by OAM can proceed more quickly.
- FDA, as well as state authorities, including medical licensing boards, should be urged to declare a *moratorium* on seizures, raids, Import Alerts, and licensing actions against physicians, researchers, and health care providers whose work has been chosen by OAM

for evaluation.

• In choosing specific treatments for testing, priority should be given to drugs and vaccines that address major causes of preventable death in the United States: cardiovascular disease, cancer, and AIDS. Priority should also be given to testing treatments that particularly show promise for safety and low costs. To gain public recognition and credibility, it is important that OAM achieve some clear successes.

These ten treatments clearly offer realistic possibilities of success. For over a million Americans a year who develop cancer, such breakthroughs can come none too soon.

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